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Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

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**ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY**

Cancels & replaces the same document of 14 February 2012

**SIDS Initial Assessment Profiles agreed in the course of the OECD HPV Chemicals Programme
from 1993 to 2011**

**Series on Testing & Assessment
No. 166**

The complete document is available in pdf format only.

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OECD Environment, Health and Safety Publications

Series on Testing and Assessment

No. 166

SIDS Initial Assessment Profiles agreed in the course of the
OECD HPV Chemicals Programme from 1993-2011



INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among **FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD**

Environment Directorate

ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT

Paris 2012

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This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

OECD works with member countries and other stakeholders to cooperatively assess the hazards of industrial chemicals to generate OECD-agreed assessments that are available to the public and that can be used for priority setting, risk assessment and other activities within national or regional programmes. Further, this cooperative work allows member countries and the chemical industry to share the burden of evaluating chemicals and avoid duplication, which in turn increases efficiencies, decreases costs and minimizes the need for animal testing.

This document presents a collection of SIDS Initial Assessment Profiles (SIAP) presenting hazard conclusions for human health and for the environment for chemicals assessed in the OECD HPV Chemicals Programme between 1993 (1st SIDS Initial Assessment Meeting) and 2011 (32nd SIDS Initial Assessment Meeting).

Each SIAP, together with the full evaluation report once finalised, can be retrieved in the OECD Existing Chemicals database (www.oecd.org/env/existingchemicals/data).

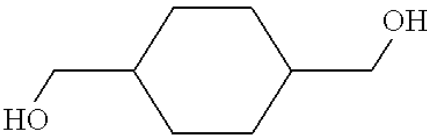
The collection of SIAPs has been divided in six parts, following a chronological order, to keep individual parts to a manageable size. For each part of the document, the corresponding SIDS Initial Assessment Meeting (SIAM) number and the year of the meeting have been indicated below.

		Year
PART 1	SIAM 1 to SIAM 5	1993-1996
PART 2	SIAM 6 to SIAM 10	1997-2000
PART 3	SIAM 11 to SIAM 15	2000-2002
PART 4	SIAM 16 to SIAM 20	2003-2005
PART 5	SIAM 21 to SIAM 25	2005-2007
PART 6	SIAM 26 to SIAM 32	2008-2011

The 32nd SIDS Initial Assessment Meeting was the last one under the OECD HPV Chemicals Assessment Programme before launching the OECD Cooperative Chemicals Assessment Programme (www.oecd.org/env/hazard).

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	105-08-8
Chemical Name	1,4-Cyclohexanedimethanol
Structural Formula	<i>cis and trans form</i> 

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Following uptake of 1,4-Cyclo[¹⁴C] hexanedimethanol (70% trans, 30% cis-isomers) via oral gavage in Sprague-Dawley rats, it is converted into the cyclohexanedicarboxylic acid and the 4-hydroxymethylcyclohexanecarboxylic acid. 1,4-Cyclohexanedimethanol was rapidly absorbed, and 95% was excreted in urine. The *cis-trans* ratio remained as it was. The elimination half life of this chemical in plasma was approximately 3 min.

The acute oral LD₅₀ of 1,4-Cyclohexanedimethanol in rats ranged between 3200 and 6400 mg/kg bw. Slight prostration and vasodilatation were noted in treated animals. For acute dermal toxicity [OECD TG 402] the LD₅₀ in rats was >2000 mg/kg bw. No clinical signs were reported. No human data on acute toxicity are available. No studies are available for acute inhalation toxicity.

No reliable skin/eye irritation or skin sensitization data are available.

In a repeated dose oral toxicity study in rats according to the OECD TG 408, 1,4-Cyclohexanedimethanol was administered via drinking water to 12 males and 10 females per dose at 0, 256, 479, 861 mg/kg (males) and 0, 440, 754, 1754 mg/kg (females) for 13 weeks. Death (one male and one female) and clinical effects like bloody or brown/red discolored urine, softened or reduced feces, and reductions in body weights were observed in males and females at 861 and 1754 mg/kg bw respectively. The mean body weight for male rats was significantly lower for 861 mg/kg bw treated group when compared to that of control group ($p < 0.05$). Based on clinical effects, the NOAELs of the study were considered to be 479 mg/kg bw for males and 754 mg/kg bw for females.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium*, 1,4-Cyclohexanedimethanol was negative both with and without metabolic activation [OECD TG 471 and 471-like]. An *in vitro* chromosomal aberration test in Chinese hamster lung (CHL/IU) cells was negative with and without metabolic activation [OECD TG 473]. In addition, this chemical did not induce significant increase in cells with chromosome aberrations or polyploidy, or endoreduplication in the rat bone marrow cells *in vivo* according to the OECD TG 475. The available information from genetic toxicity tests suggests that 1,4-Cyclohexanedimethanol is not genotoxic *in vitro/in vivo*.

No data are available for the carcinogenicity of 1,4-Cyclohexanedimethanol.

The reproductive toxicity of 1, 4-Cyclohexanedimethanol has been investigated in a reproductive and developmental toxicity screening test in rats [OECD TG421]. In this study, 1,4-Cyclohexanedimethanol was administered via drinking water to 12 males and 12 females per dose at 0, 256, 479, 861 mg/kg (males) and 0, 385, 854, 1360 mg/kg (females) for 13 weeks. 4 of 11 male rats exposed to 861 mg/kg bw had reduced sperm motility without statistical significance compared to the control group (the mean percent value was 69% for treated group and 90% for control group). However, this decrease did not induce any difference in fertility. Brown/red discoloured urine was observed in 5 of 12 male and 6 of 12 females dosed at 861 and 1360 mg/kg bw respectively. The NOAELs for this effect were considered to be middle dose (479 mg/kg bw for males and 854 mg/kg bw for females). The mean body weight for litters from dams on day 0 post partum and of pup survival from Day 0 to Day

4 (75.8% for treated group and 97.6% for control group) were lower than those for control group at 1360 mg/kg bw. There was no effect observed upon haematological, clinical biochemistry or histopathological examination at any dose. Based on decreases in sperm motility and survival of pups from dams, the LOAEL and NOAEL for reproductive/developmental toxicity were considered to be 1360 and 854 mg/kg bw, respectively. Fetotoxicity and maternal toxicity were only observed at the highest dose of 1360 mg/kg. This dose is in excess of the 1000 mg/kg bw limit dose recommended in the OECD TG 421. Overall, 1,4-Cyclohexanedimethanol is considered not to be a reproductive/developmental toxicant.

Environment

1,4-Cyclohexanedimethanol is a white solid with a melting point of 43°C (*cis*) and 67°C (*trans*), a boiling point of 286 °C (*cis*) and 283 °C (*trans*) and a measured vapour pressure of 0.041 Pa at 25 °C. The calculated *n*-octanol-water partition coefficient ($\log K_{ow}$) is 1.49, and the water solubility is 920,000 mg/L at 20 °C.

1,4-Cyclohexanedimethanol did not hydrolyze under acidic, neutral or basic conditions after a 5-day period at 50 °C. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.5 days. 1,4-Cyclohexanedimethanol attained significant degradation (98% in 19 days) in an inherent biodegradation test conducted according to OECD test guideline 302B. No information is available on the ready biodegradability of the chemical.

Level III fugacity model with equal and continuous distributions to air, water and soil compartments suggests that 1,4-Cyclohexanedimethanol will distribute mainly to the soil (70 %) and water (29.8%) compartments with minor distribution to the air (0.081%) and sediments compartment (0.07 %). If released only to the water compartment, 1,4-Cyclohexanedimethanol stays in the water compartment (99.8 %) with negligible amounts in other compartments. A Henry law's constant of 4.13×10^{-9} Pa.m³/mole at 25 °C suggests that volatilization of 1,4-Cyclohexanedimethanol from the water phase is expected to be moderate. A K_{oc} of 10 was estimated based on the $\log K_{ow}$.

Bioaccumulation potential is expected to be low based on the $\log K_{ow}$ of 1.49, which is supported by an estimated BCF value with BCFWIN v. 2.17 of 2.8.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Oryzias latipes</i>];	96 h LC ₅₀ > 100 mg/L nominal concentration
Fish [<i>Pimephales promelas</i>];	96 h LC ₅₀ > 120 mg/L nominal concentration
Invertebrate [<i>Daphnia magna</i>]	48 h LC ₅₀ > 100 mg/L nominal concentration
Algae [<i>Pseudokirchneriella subcapitata</i>]	72 h ErC ₅₀ > 120 mg/L nominal concentration
Algae [<i>Pseudokirchneriella subcapitata</i>]	72 h EbC ₅₀ > 120 mg/L nominal concentration

1,4-Cyclohexanedimethanol is of low acute toxicity to aquatic organisms (fish, aquatic invertebrate and algae).

Exposure

1,4-Cyclohexanedimethanol is commercially produced with an annual production volume of 11,000 tonnes in the Republic of Korea (2007). Worldwide production volume is not available. 1,4-Cyclohexanedimethanol is used for polyester films and protective coatings. The substance is an intermediate reactant, promoting reduction of reaction time in esterification for polymers industry and any left over from the process will be collected.

No monitoring data for effluents or surface water are available from the production and processing sites in the sponsor country. Occupational exposures are expected to be minimal due to the processing in closed system and personal protective equipments.

1,4-Cyclohexanedimethanol is used as intermediate reactant, and there is therefore no known inclusion of the substance in final products. Therefore, the possibility of exposure for consumer is negligible.

**RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED**

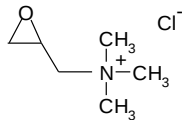
Human health:

The substance is of low priority for further work due to its low hazard potential.

Environment:

1,4-Cyclohexanedimethanol is currently of low priority for further work due to its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3033-77-0
Chemical Name	2,3-epoxypropyltrimethylammonium chloride (EPTAC)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No toxicokinetics studies are available. An *in vitro* skin penetration study on the related substance CHPTAC ((3-chloro, 2-hydroxypropyl)trimethylammonium chloride, CAS No 3327-22-8) showed a maximum penetration rate of 0.685 % in human skin. Accounting for the amount retained in the stratum corneum the average absorbed ranged between 0.1-15 %.

EPTAC is harmful via oral exposure (LD₅₀ (rat) = 1088 mg/kg in a valid study) and via dermal exposure (LD₅₀ (rabbit) = 1500 – 3000 mg/kg in a study of limited validity). Based on limited data, the LC₅₀ (inhalation) is greater than 8.17 mg/l for 7 hours (>5 mg/l in a 4-h period) and is therefore not considered harmful via inhalation. Due to lack of good quality study no definite conclusion can be drawn for the acute toxicity via inhalation route. EPTAC is a severe eye irritant. EPTAC is not corrosive or a skin irritant, except under extended duration of exposure. However, a study showed that EPTAC irritated skin over a longer time period. It is a skin sensitiser, based on the results of a guinea pig maximisation test and human patch tests.

In a 28-day oral repeat dose test conducted according to OECD TG 407 and to GLP, the LOAEL was determined to be 3.16 mg/kg/day, the lowest dose tested, based on slight morphological changes in the kidneys of rats. No NOAEL could be derived. Effects on the reproductive organs and haematological changes were observed at dose levels of 10 mg/kg/day and above. Changes in clinical chemistry were also observed, although most of these were reversible after a 4-week recovery period.

EPTAC gave positive results in both *in vitro* and *in vivo* mutagenicity studies. In addition to causing point mutations in bacteria, EPTAC has clastogenic or aneugenic potential in mammalian cells. Effects observed in the 28-day repeat dose test indicate that EPTAC may also be a germ cell mutagen. Overall, EPTAC is an *in vitro* and *in vivo* genotoxicant.

A 2-year dermal carcinogenicity study was conducted in mice. At a dose level of 1% (equivalent to approximately 50 mg/kg/application), EPTAC was found to be a local carcinogen and there were also indications that it produced systemic tumours (e.g. lung or mammary tumours). However, the systemic tumors may have occurred as a consequence of oral exposure due to licking of fur. The evidence shows that EPTAC is a genotoxic carcinogen.

No studies on reproductive or developmental toxicity are available. A 28-day oral study in rats showed effects on the gonads of both sexes and a NOAEL of 10 mg/kg/day based on severe morphological effects on the reproductive organs, i.e., atrophy of the testes and ovaries, which can be used as an indication of toxicity to reproduction. EPTAC may represent a hazard to fertility. As EPTAC is a genotoxic carcinogen, exposure should be controlled to be as low as reasonably possible, and therefore testing on reproductive toxicity is not considered warranted.

Environment

Pure EPTAC is a solid at 20°C and 1013 hPa, but is typically produced, supplied and used as an aqueous solution at a concentration of 70 – 75 % by weight. The temperature range where EPTAC melts and simultaneously decomposes is

118 to 126 °C. It is highly soluble in water (852.0 ± 16.7 g/l at 20°C), has low vapour pressure ($< 10^{-3}$ Pa at 22 – 80°C) and low $\log K_{ow}$ (< -1.3). Under aqueous conditions, EPTAC hydrolyses to DIOL (2,3-dihydroxypropyltrimethylammonium chloride) with half-lives of 5.5, 5 and 14 days at 25°C and pH 4, 7 and 9 respectively. In a further test under conditions more relevant to the environment, the half-life for hydrolysis of EPTAC was 177 days at 12°C and pH 7.8.

No valid ready biodegradation studies are available for EPTAC and therefore EPTAC can not be regarded as readily biodegradable. In an inherent biodegradation test conducted according to OECD TG 302B, using non-adapted sludge, EPTAC was not inherently biodegradable. In an STP simulation test conducted according to OECD 303A, the mean primary degradation was 15 ± 9.7 %, from which the removal rate constant for EPTAC was calculated to be 0.035 h^{-1} . Based on the very low $\log K_{ow}$, EPTAC is not expected to bioaccumulate. Calculation of the adsorption coefficient, $\log K_{oc}$, from $\log K_{ow}$ is not appropriate for cationic substances such as EPTAC. An adsorption study using activated sludge, conducted according to ISO Guideline 18749, gave approximately the same removal rate (7 %) in the test vessel as in the abiotic control (no sludge, 4 %) and the sterile control (sterile sludge, 6 %). Removal was therefore due mainly to abiotic degradation, but with contributions from adsorption and biodegradation. Based on these data, $K_{p, \text{sludge}}$ was calculated to be 25.6 l/kg, and K_{oc} was estimated as 51.2 assuming an organic carbon content of 50%. Measured concentrations of EPTAC in sludge from the OECD TG 303A STP simulation study allowed a K_{oc} of 53.8 to be determined ($K_{p, \text{sludge}}$ 26.9 l/kg, assuming an organic carbon content of 50%), which is equivalent to $\log K_{oc} = 1.73$.

No measured data are available on photodegradation rate in air, but a half-life of 8.57 hr, based on reaction with OH radicals, has been calculated by using EPIWIN v3.2. A Henry Law's Constant of $< 1.78 \times 10^{-7} \text{ Pa.m}^3/\text{mol}$, calculated from measured vapour pressure and water solubility values, indicates that EPTAC does not volatilise from water. According to fugacity modelling (EQC)EPTAC will partition almost totally to water compartment.

Acute ecotoxicity values for EPTAC are available from tests conducted according to OECD Guidelines:

Fish: LC_{50} (96-h, *Brachydanio rerio*) = 1992 mg/l (nominal)

Invertebrates: EC_{50} (48-h, *Daphnia magna*) = 16.4 mg/l (nominal)

Algae: E_rC_{50} (72-h, *Scenedesmus subspicatus*) > 1000 mg/l (nominal)

A 21-day *Daphnia* reproduction test conducted according to OECD Guideline 211 gave a NOEC of 0.16 mg/l. The E_rC_{10} from the *Scenedesmus subspicatus* study was 814 mg/l; NOEC 580 mg/l (nominal).

EPTAC is of low toxicity to activated sludge, with an EC_{50} > 2000 mg/l (highest test concentration) (nominal). An EC_{10} of 443 mg/l was derived in the same study.

Exposure

Production of EPTAC takes place at 2 locations in the European Union, therefore total production volume data are confidential. Total consumption, taking into account imports and exports, was 6153 tonnes in 2001, although significant decreases were seen in 2002 and 2003, with the 2003 total being 3937 tonnes. 99 % of the volume consumed was used for the cationisation of starch. The remaining 1 % was used for cationisation of other substrates such as guar, protein and cellulose. The downstream application of cationic starch is in the production of paper and board. Other cationised substrates may be used in personal care products and cosmetics.

Due to the nature of the processes used, some conversion of EPTAC to CHPTAC can occur after cationisation and it is typical that finished starch product and waste water from the process contain both substances.

The most likely route of occupational exposure is via the dermal route, although EPTAC is handled using appropriate personal protective equipment to minimise exposure. Measured dermal exposure data are not available. Inhalation exposure is not expected since the substance has very low vapour pressure and is not used as an aerosol.

Exposure to consumers may occur from any residues in products containing cationised substrates. Typically, these include books, copy paper and newspaper, food-grade paper board, and personal care products. The most likely route of exposure to consumers is via the dermal route from handling and use of these products. Ingestion of EPTAC from contact of food is considered unlikely as the packaging would need to be moistened for migration to occur, and spoiled food would not usually be eaten. However the calculated exposure levels are based on reasonable worst case estimations and are considered negligible based on measured residue concentrations in starch and consideration of the processing of the cationised starch.

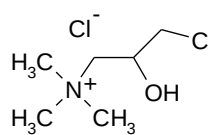
EPTAC may be released into the environment in aqueous effluents and contaminated sewage sludge from production, cationisation and further downstream use of cationic starches containing residues. A rough estimation of total aquatic releases to WWTPs from use of EPTAC in EU is 522 kg/d. However, there are high variations between release volumes of different sites. No release to the atmosphere is anticipated.

**RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED**

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health, for the following end points: severe eye irritation, sensitisation, repeated dose toxicity, reproductive toxicity, mutagenicity and carcinogenicity. Based on a full risk assessment conducted under the EU Existing Substances Regulation 793/93 risk reduction measures are required for occupational exposure. Countries outside the EU are invited to perform an exposure assessment, and if necessary a risk assessment for human health.

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (chronic toxicity below 1 mg/l and acute toxicity between 1-100 mg/l to aquatic invertebrates and not readily biodegradable). Concern has been identified in a risk assessment performed in the context of the EU Existing Substances Regulation (793/93/ECC) for surface water receiving effluents from some starch cationisation sites. Countries outside the EU may wish to perform an exposure assessment, and if necessary a risk assessment for the environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3327-22-8
Chemical Name	(3-Chloro-2-hydroxypropyl)trimethylammonium chloride (CHPTAC)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

The present SIAP is a stand-alone document but refers extensively to the related substance EPTAC (2,3-epoxypropyltrimethylammonium chloride, CAS 3033-77-0), for which a separate SIAP is available. Conversion of CHPTAC to EPTAC is the first stage of its use as a starch cationisation agent.

Human Health

No toxicokinetics studies are available. An *in vitro* skin penetration study showed a maximum penetration rate of 0.685 % in human skin.

CHPTAC is not acutely toxic, with an LD₅₀ (oral) of 2170 mg/kg and an LD₅₀ (dermal) of >2348 mg/kg in rats. The available LC₅₀ inhalation study is inadequate and no conclusions can be drawn. It is not sensitizing and is not irritating to skin. A 65% aqueous solution of CHPTAC produced mild eye irritation effects that were not sufficient to warrant classification, although more severe effects may be produced if pure test substance were used.

A 28-day oral repeated dose test was conducted in accordance with GLP and OECD guidelines, with the exception of the number of dose levels. The single treatment level of 1085 mg/kg/day produced slight morphological changes in the kidneys of rats. The LOAEL was therefore determined to be 1085 mg/kg/day. No NOAEL could be derived since effects were seen at the only dose tested. The observed effects were similar to those seen in a test with the related substance EPTAC (2,3-epoxypropyltrimethylammonium chloride, CAS 3033-77-0), for which a separate SIAP is available, and may reflect conversion of CHPTAC to EPTAC *in vivo*.

CHPTAC gave positive results in all *in vitro* mutagenicity tests conducted using bacterial and mammalian cells. CHPTAC gave a negative result in a valid *in vivo* mouse micronucleus test conducted according to OECD Guideline 474, however, because of the contradictory findings between *in vitro* and *in vivo* results, there are remaining uncertainties.

A dermal carcinogenicity study was conducted in mice. Males were treated for 105 weeks and females for 89 weeks. Based on the results of this test it was concluded that CHPTAC is not a local carcinogen in mice following dermal administration, but may be a systemic carcinogen based on an increased incidence of bronchiolo-alveolar tumours. However, the systemic tumors may have occurred as a consequence of oral exposure due to licking of fur.

No studies on reproductive or developmental toxicity are available. A 28-day oral study in rats at a single dose level of 1085 mg/kg bw/day showed no evidence of effects on the gonads.

Environment

Pure CHPTAC is a solid at 20°C and 1013 hPa, but is typically produced, supplied and used as an aqueous solution at a concentration of 50 – 70 % by weight. CHPTAC's melting point is 180.5 °C and boiling point's range is 190 °C - 209 °C. It is highly soluble in water (835.2 ± 9.9 g/l at 20°C), has low vapour pressure (< 10⁻³ Pa at 20 – 150°C) and low log K_{ow} (< -1.5). Under aqueous conditions, CHPTAC undergoes abiotic degradation for form EPTAC with half-lives of > 1 year, 27 days and < 1 day at 25°C at pH 4, 7, and 8.7 respectively. The conversion is not a true hydrolysis reaction (it is a base-catalysed cyclisation), but further true hydrolysis to produce DIOL (2,3-dihydroxypropyltrimethylammonium chloride) occurs to some extent. In a second hydrolysis test under conditions more relevant to the environment, the half-lives for degradation of CHPTAC were 279, 21 and 5.3 days at 12°C and pH 7.0, 7.8 and 8.4 respectively.

In standard OECD studies (a modified Sturm test, OECD TG 301B, and an STP simulation study, OECD 303A), CHPTAC was not readily biodegradable, although there was some evidence of removal in other non-standard tests. The mean primary degradation of CHPTAC was $28 \pm 14.3\%$ in the OECD 303A simulation study, from which the removal rate constant was calculated to be 0.065 h^{-1} , which is close to the value of 0.1 h^{-1} applicable to substances considered as inherently biodegradable. Some evidence of inherent biodegradability is available from a test conducted using a method comparable to OECD 302A, but the conditions used were highly favourable for biodegradation compared with other inherent tests. Based on the very low $\log K_{ow}$, CHPTAC is not expected to bioaccumulate. Calculation of the adsorption coefficient, $\log K_{oc}$, from $\log K_{ow}$ is not appropriate for cationic substances such as CHPTAC. An adsorption study using activated sludge, conducted according to ISO Guideline 18749, gave approximately the same removal rate (22 %) in the test vessel as in the abiotic control (no sludge, 22 %) and the sterile control (sterile sludge, 27 %), therefore it was not possible to determine the adsorption coefficient in sludge from this study. Measured concentrations of CHPTAC in sludge from the OECD 303A STP simulation study allowed a K_{oc} of 68.8 l/kg to be determined, assuming an organic carbon content of 50%, which is equivalent to $\log K_{oc} = 1.84$.

No measured data are available on photodegradation in air, but a half-life of 7.1 hr, based on reaction with OH radicals has been calculated by EPIWIN v3.2. A Henry Law's Constant of $< 2.25 \times 10^{-7} \text{ Pa.m}^3/\text{mol}$, calculated from measured vapour pressure and water solubility values, indicates that CHPTAC does not volatilise from water. According to fugacity modelling (EQC) CHPTAC will partition almost totally to the water compartment.

Acute ecotoxicity values for CHPTAC are available from tests conducted according to OECD Guidelines:

Fish: LC_{50} (96-h, *Brachydanio rerio*) = 4128 mg/l (nominal)

Invertebrates: EC_{50} (48-h, *Daphnia magna*) = 164 mg/l (nominal)

Algae: E_rC_{50} (72-h, *Scenedesmus subspicatus*) > 10,000 mg/l

A 21-day *Daphnia* reproduction test conducted according to OECD TG 211 gave a NOEC of 0.51 mg/l (immobilization). EC_{50} based on immobilization was lower (1.03 mg/l) than the EC_{50} based on reproduction (1.52 - 4.56 mg/l). The E_rC_{10} from the *Scenedesmu subspicatus* study was 3200 mg/l; NOEC of < 100 mg/l was reported in a screening test.

CHPTAC is of low toxicity to activated sludge, with an EC_{50} >2000 mg/l (highest test concentration). An EC_{10} of 1032 mg/l was derived in the same study.

Exposure

Production of CHPTAC takes place at 4 locations in the EU, and was 22,847 tonnes in 1999. It is produced from epichlorohydrin and an amine. Total consumption, taking into account imports and exports, was 23,695 tonnes in 2001. 95 % of the volume consumed was used for the cationisation of starch. The remaining 5 % was used in the synthesis of carnitine salts and for cationisation of other substrates such as guar, protein and cellulose. The downstream application of cationic starch is in the production of paper and board. Other cationised substrates may be used in personal care products and cosmetics.

During starch cationisation, it is EPTAC that acts as the reagent, therefore CHPTAC is converted to EPTAC prior to use. Due to the nature of the processes used, some conversion of EPTAC to CHPTAC can occur after cationisation and it is typical that finished starch product and waste water from the process contain both substances.

The most likely route of occupational exposure is via the dermal route, although CHPTAC is handled using appropriate personal protective equipment to minimise exposure. Measured dermal exposure data are not available. Inhalation exposure is not expected since the substance has very low vapour pressure and is not used as an aerosol.

Exposure to consumers may occur from any residues in products containing cationised substrates. Typically, these include books, copy paper and newspaper, food-grade paper board, and personal care products. The most likely route of exposure to consumers is via the dermal route from handling and use of these products. Ingestion of CHPTAC from contact of food is considered unlikely as the packaging would need to be moistened for migration to occur, and spoiled food would not usually be eaten. However the calculated exposure levels are based on reasonable worst case estimations and are considered negligible based on measured residue concentrations in starch and consideration of the processing of the cationised starch.

CHPTAC may be released into the environment in aqueous effluents and contaminated sewage sludge from production, cationisation and further downstream use of cationic starches containing residues. No release to the atmosphere is anticipated.

**RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED**

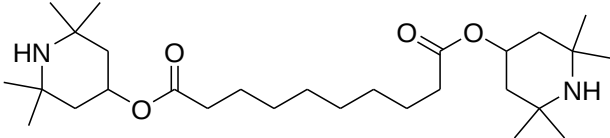
Human Health:

The chemical is a candidate for further work due to properties indicating a hazard for human health for the following endpoint: carcinogenicity. Due to the genotoxic carcinogens (epichlorohydrin and EPTAC) present in the production and use of CHPTAC, stringent exposure control measures should be in place. Provided adequate risk management measures are in place to protect workers then further testing is not considered necessary. Within the EU a full risk assessment concluded that risk reduction measures were required for occupational exposure. Countries outside the EU are invited to perform an exposure assessment, and if necessary a risk assessment for human health.

Environment:

The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (chronic toxicity to aquatic invertebrates below 1 mg/l and lack of ready biodegradation). Concern has been identified in a risk assessment performed in the context of the EU Existing Substances Regulation (793/93/ECC) for surface water receiving effluents from some starch cationisation sites. Countries outside the EU may wish to perform an exposure assessment, and if necessary a risk assessment for the environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	52829-07-9
Chemical Names	Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No ADME studies were available. However, based on the amphiphilic properties of bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (further referred as bis-TMPS), the substance is expected to be well absorbed from the gastrointestinal tract and consequently bioavailable to some extent. Based on toxicodynamic data, metabolic degradation by Phase I hydrolysis is assumed, generating 2,2,6,6-Tetramethylpiperidin-4-ol (HTMP) and decanedioic acid as the main metabolites, leading to phase II reactions and rapid urinary and/or biliary elimination. Based on the results of the reproductive toxicity study, bis-TMPS or its metabolite(s) might be excreted via breast milk.

Bis-TMPS is of low acute oral and dermal toxicity. In rats, the oral LD₅₀-value was 3700 mg/kg bw. The substance caused salivation, diarrhoea and diuresis in all treated animals and a dose dependent decrease in body weight gain. The dermal LD₅₀ in rats exceeded 3170 mg/kg bw after 24 hours of exposure. The substance caused some unspecific clinical signs in all animals. Bis-TMPS showed substantial acute inhalation toxicity with an acute inhalation LC₅₀ value of 500 mg/m³ (0.5 mg/L) in rats after a 4-hour exposure. Dyspnoea, salivation, trismus, tremor and sedation were observed in a dose dependent intensity in all treated animals.

Bis-TMPS showed minimal skin irritation in rabbits after 24 hours of exposure in a study lacking details regarding the application procedure of the test substance. Bis-TMPS caused serious eye damage in rabbits in a study conducted equivalent to OECD TG 405.

Based on the available information from two guinea pig studies (a maximization test equivalent to OECD TG 406 and a photosensitizing test), bis-TMPS is not considered to possess skin sensitizing properties.

In all repeated dose oral toxicity studies in rats and dogs, administration of bis-TMPS was associated with decreased body weight gain. In a study similar to OECD TG 407, bis-TMPS was administered to rats via gavage to 10 animals/sex/dose at 0, 50, 200 or 600 mg/kg bw/day for 28-days. A NOAEL for oral toxicity in rats of 50 mg/kg bw/day was derived based on decreased body weight gain and gross pathology (distensions of small intestine in some male and female animals). In a further repeated dose oral toxicity study (similar to OECD TG 408) in Sprague-Dawley rats, bis-TMPS was administered via the diet to 20 animals/sex/dose at 0, 26, 80 or 261 (males) and at 0, 29, 90 or 277 (females) mg/kg bw/day for 90 days. The NOAEL for males was 80 mg/kg bw/day and the LOAEL for females was 29 mg/kg bw/day (lowest dose tested) based on decreased body weight gain. In a repeated dose oral toxicity study (similar to OECD TG 408) in dogs, bis-TMPS was administered via the diet to 4 animals/sex/dose at 0, 27, 69 or 150 (males) and at 0, 27, 78 or 155 (females) mg/kg bw/day for 90-days. A NOAEL of 69-78 mg/kg bw/day was derived based on decreased body weight gain and liver hypertrophy.

In an Ames test (similar to OECD TG 471) with multiple strains of *Salmonella thyphimurium*, bis-TMPS was negative with and without metabolic activation. An *in vitro* chromosomal aberration test following OECD TG 473 with human lymphocytes was negative with and without metabolic activation. Based on these results, bis-TMPS is considered not to be mutagenic/genotoxic *in vitro*.

No data on carcinogenicity were available.

A one-generation reproduction toxicity study following OECD TG 415 was performed with male and female rats (24/sex/dose) at 0, 3, 30 or 300 mg/kg bw/day (gavage). Males were exposed 10 weeks before mating, during mating and up to termination (after delivery of litters). Females were exposed two weeks before mating, during post-coitum and during 20 to 22 days of lactation. Decreased body weight gain and food consumption as well as increased spleen (males only) and uterus weights were observed in parental animals at 300 mg/kg bw/day, thus the NOAEL for parental toxicity was established to be 30 mg/kg bw. The NOAEL for reproductive toxicity (fertility) was derived to be ≥ 300 mg/kg bw due to the absence of effects. The NOAEL for developmental toxicity was established at 30 mg/kg bw based on slightly reduced pup weight during lactation, which was not associated with any other developmental adverse effect. Bis-TMPs is not considered to be a specific developmental toxicant since the only finding in pups was marginal decrease in body weight at the end of lactation. This finding is not unexpected since such bodyweight effects were consistently seen in repeated dose toxicity studies.

In *in vitro* toxicodynamic studies, bis-TMPS was shown to block calcium channels and to act as an antagonist at the nicotinic acetylcholine receptors. In an investigational study in rats (5 weeks intraperitoneal), histopathological examinations revealed lesions in cardiomyocytes. However, no adverse effects in terms of neuro- or cardiotoxicity could be observed when bis-TMPs was orally applied.

Environment

Bis-TMPS is a white crystalline solid with a melting point of 210°C (calculated) and a vapor pressure of 5×10^{-8} Pa (calculated). It decomposes at 425°C. The substance has a solubility in water of 18.8 mg/l at pH 7.5 (measured, 22°C) and a log Kow of 6.5. Bis-TMPS is predominantly protonated (positively charged) at environmentally relevant pH conditions. With the PALLAS program (v.3.0) pKa values of 9.6 and 10.2 have been calculated. At pH <9 the charged ionic species predominates. A log Kow of 6.5 (KOWWIN v.1.67) and 7.3 (ACD/Labs v.8.14) has been calculated for the neutral species. When considering the pH-dependency of the protonation the octanol/water distribution coefficient of bis-TMPS at 25°C is 3.22, 3.24, and 3.64 for pH 6, 7 and 8 respectively (ACD/Labs v.8.14). However, since the substance occurs as charged species in aqueous media at environmentally relevant pH, all results for physico-chemical properties and environmental fate that were obtained by QSAR modeling have to be regarded with caution because the calculations only consider the uncharged species which predominates only under high pH conditions (pH > 10).

In a modified Sturm test performed according to Directive 84/449/EEC C.5 (not GLP; corresponds to OECD TG 301 B with CO₂-evolution monitoring) bis-TMPS was not readily biodegradable. 10-24% of the test substance was degraded after 28 days. Based on abiotic hydrolysis testing according to the OECD TG 111 (GLP), bis-TMPS is not stable in water and is hydrolyzed, depending on pH conditions to form 2,2',6,6'-tetramethylpiperidin-4-ol (HTMP; CAS 2403-88-5), decan-1,10-dioic acid (CAS 111-20-6) (and the possible intermediary 9-(2,2,6,6-tetramethylpiperidin-4-yloxy)carbonyl nonanoic acid). A half-life of 206 days at pH 4, 57 days at pH 7 and 2 days at pH 9 was determined for bis-TMPS at 25°C. One of the hydrolysis products of bis-TMPS, 2,2',6,6'-tetramethylpiperidin-4-ol (HTMP) has been evaluated under the OECD HPV Chemicals Programme at SIAM 14 (March 2002). The calculated half-life of bis-TMPS for the reaction with hydroxyl radicals in air is 0.847 hours and the overall OH rate constant is 151.67×10^{-12} cm³/molecule-sec.

An OECD TG 106 adsorption/desorption study was performed with ¹⁴C-labelled bis-TMPS at three concentration levels (4-5, 20-23, and 40-50 mg/L) for seven European soils and one soil-like mature compost. Apparent K_{oc} (L/kg) values for adsorption were in the range of 800-16000 (log app. K_{oc} 3-4) which indicates strong binding to soil. It was concluded that not only the organic carbon but also the clay content of the soils determined adsorption. Because significant degradation of bis-TMPS occurred, actual K_{oc} values can be expected to be even higher and the reported K_{oc} values can be considered worst case

with respect to leaching. Desorption occurred maximally for 17%.

No measured data on bioaccumulation is available for bis-TMPS. At environmentally relevant pH conditions the substance is almost completely ionised. A BCF in the range between 17.2 (pH 6) and 45.1 (pH 8) is calculated by using pH-dependent log D_{ow} values of 3.22 and 3.64. Therefore, bis-TMPS is not expected to accumulate in biota.

Based on fugacity modeling (Level I and III) uncharged bis-TMPS will partition primarily into soil and sediment. Surface water is considered to be a minor target compartment for the neutral species and partitioning into air is negligible. However, partitioning into water may be underestimated by fugacity calculations, since the chemical occurs as a protonated cationic species under neutral pH conditions.

Aquatic toxicity testing has resulted in a 96-h LC_{50} in fish (*Oncorhynchus mykiss* and *Lepomis macrochirus*) of 4.3 mg/l (measured concentration), a 24-h EC_{50} in aquatic invertebrates (*Daphnia magna*) of 17 mg/l (nominal concentration), and a 72-h EC_{50} in aquatic plants (*Scenedesmus subspicatus*) of 1.9 mg/l (NOEC = < 1.23 mg/l; nominal concentrations), based on growth rate. A 21-d EC_{50} in aquatic invertebrates (*Daphnia magna*) of 1.31 mg/l (NOEC for reproduction = 0.23 mg/l; measured concentration). The 3-h EC_{50} of bis-TMPS was found to be above 100 mg/l in a 3-hour activated sludge study.

Exposure

The estimation of the global production of bis-TMPS is 11,000 tonnes per year where 6,500 tonnes per year is estimated to be produced in Europe. Bis-TMPS is used to prevent or slow down spontaneous changes in and ageing of polymers; it belongs to the hindered amine light stabilisers (HALS), the most important chemicals used in light stabilisation for polymers. The substance is used in concentrations between 0.1 and 0.5% – depending on the substrate, processing conditions and application – for industrial applications demanding particularly high light stability. Bis-TMPS is incorporated in thermoplastics by extrusion compounding and is not reacted with the polymer but may be degraded partially by photochemical reactions during service life of the product. Compounding with plastics is done in closed systems.

Synthesis of bis-TMPS takes place in dedicated equipment. It is estimated that workers, during production and industrial use, can be exposed, in particular during filling activities, weighing, cleaning and maintenance work. If emission occurs into the workplace atmosphere, appropriate protective equipments are in place (e.g. local exhaust ventilation, gloves, eye protection and protective clothing). From the synthesis process, the substance is obtained in the form of a melt that is transferred in a closed system to a melt granulation tower to yield the test substance shaped as granules. The granulate form of the test substance reduces the possible exposure concentration of inhalable dust significantly compared to powder (particle size < 100 μm : 3-5 %). Therefore exposure of workers is expected to be minimal. Estimated workplace exposure by inhalation of bis-TMPS is 0.01-0.1 mg/m^3 (for granules) and 1-10 mg/m^3 (powder). Consumers may be exposed when they are in contact with the end products. However, as the concentration of the substance is relatively low (maximum 0.5 %) and as the substance is mostly immobilized in the polymer matrix, consumer exposure is regarded as negligible.

Exposure of the environment may occur during production and industrial use of the substance and by leaching waste at landfills. Emission to wastewater from contact of extruded plastics with cooling water and cleaning of equipment at sites of industrial production and use is considered the most relevant route of exposure of the environment. The measured emission factor for crude waste water from production of bis-TMPS is 3.53×10^{-4} . Local emission to wastewater from compounding with polyolefins for a representative scenario has been estimated to be 1.08×10^{-2} kg/day for a production of 50,000 tonnes polyolefin per year. Therefore, exposure of the environment from production and industrial use of bis-TMPS is considered to be very low.

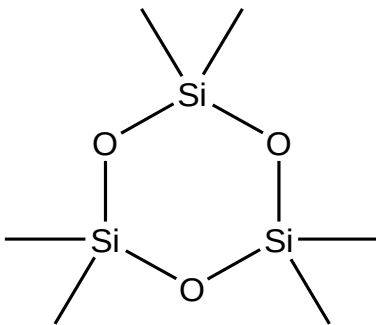
**RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED****Human health:**

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (serious eye damage, acute inhalation toxicity and reduced bodyweight gain after repeated exposure and in pups during lactation). However, based on data presented by the Sponsor Country, relating to production by one producer in one OECD country, which accounts for 27% of global production, exposure to humans is anticipated to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor Country.

Environment:

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to aquatic organisms between 1 and 100 mg/l, non-ready biodegradability and relatively slow hydrolysis). However, based on data presented by the Sponsor Country, relating to production by one producer in one OECD country, which accounts for 27% of global production, exposure to the environment is considered to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor Country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	541-05-9
Chemical Name	Hexamethylcyclotrisiloxane (D3)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No data are available on absorption, distribution, metabolism or excretion. The oral LD50 of D3 in rats is greater than 15,400 mg/kg bw. Undiluted D3 was not irritating to rabbit's eyes in a study with one rabbit. Repeated dermal application of undiluted D3 in a single rabbit resulted in minimal skin irritation (slight redness). No experimental data are available for skin sensitization.

Two inhalation exposure studies and one repeated-dose oral toxicity study were conducted with D3. The oral study, although not conducted according to an OECD guideline, was designed to investigate whether D3 increases liver weight similar to other oligomeric cyclosiloxanes. Test article-related increases in liver weights were seen in the male rats as low as 100 mg/kg-bw/day and in female rats at dose levels of 400 mg/kg-bw/day and above. In a combined repeated-dose/reproductive/developmental toxicity study conducted according to OECD TG 422, Sprague-Dawley rats were exposed to D3 vapor via inhalation at 100, 500 or 2500 ppm (approximately 0.61, 4.5 or 22.8 mg/L) for up to 29 days for 6 hrs/day, 7 days/week. Decreased body weight gains and food consumption, increased liver weights and incidence of centrilobular hepatocellular hypertrophy (both sexes), increased kidney weights and decreased seminal vesicle weight (with an increased incidence of atrophy) in males were seen at 2500 ppm (22.8 mg/L). Males showed protein droplet nephropathy with markedly increased incidence at 500 and 2500 ppm (4.5 and 22.8 mg/L). Decreased serum glucose was observed at 500 ppm (4.5 mg/L) and above. Serum cholesterol was increased in females at the highest concentration. The LOAEC was considered to be 0.61 mg/L (100 ppm) (the lowest dose tested) based on kidney findings in males.

Sprague-Dawley rats (5/sex/dose at 0.084 and 0.945 mg/L; 10/sex/dose at 9.041 mg/L) were exposed to D3 aerosols via nose-only inhalation for 6 hrs/day, 7 days/week for 4 weeks. Mortality was noted in males and females at 9.041 mg/L. Symptoms prior to death were dyspnea, ataxia, reduced reflexes and piloerection. Hemorrhagic encrustation of the nose was seen at 0.945 mg/L and above. Slight inflammatory changes were seen in the nasal cavity at the highest concentration. Microscopically, aggregation of macrophages and perivascular round cell infiltration was seen in the lungs of high exposure animals. These changes are consistent with respiratory tract irritation. Complete recovery for the local effects was not achieved during the 4-week recovery period. The NOAEC for local effects was considered to be 0.084 mg/L. A NOAEC for systemic toxicity was considered to be 0.945 mg/L based on the mortality and clinical signs.

D3 tested negative in bacterial cells (*Salmonella typhimurium* and *Escherichia coli*) and yeast (*Saccharomyces*

cerevisiae) and in some mammalian cells in vitro. D3 was slightly cytotoxic in the L5178Y Fischer mouse lymphoma cell line at concentrations of 0.016 and 1 mg/ml in the absence and presence of metabolic activation, respectively. However, D3 gave equivocal or weak positive results in tests for sister chromatid exchange, DNA repair and chromosomal aberrations (L5178Y mouse lymphoma cell line) at a concentration of about 1 mg/ml or higher. D3 tested negative in an in vivo cytogenetic assay in CD® rats. In the rat bone marrow cytogenetic assay, male and female rats were injected D3 intraperitoneally up to 1080 mg/kg-bw. Although it cannot be confirmed that D3 reached the bone marrow in the cytogenetic assay, D3 was tested at a high enough level that further attempts to increase the dose to demonstrate that D3 did reach the bone marrow would have resulted in death of the rat. Appropriate positive and negative controls were included and the expected responses were observed. D3 did not increase the frequency of chromosomal aberrations or chromosomal breaks in bone marrow cells. D3 is not expected to be genotoxic in vitro or in vivo. Carcinogenicity data are not available.

In the combined repeated-dose/reproductive/developmental toxicity screening study described above, D3 vapor caused an adverse effect on fertility following inhalation exposure, with decreased litter size and number of implantation sites at a concentration of 2500 ppm (22.8 mg/L), the highest concentration tested. No external abnormalities were observed in the pups. Mean litter weight was decreased at 22.8 mg/L. The litter weight decreases at the high dose level are probably due to the reduced litter size and not treatment-related manifestation of developmental toxicity. A NOAEC of 500 ppm (4.5 mg/L) and LOAEC of 2500 ppm (22.8 mg/L) for reproductive/developmental toxicity were determined based on the decreased litter size and implantation sites. The maternal NOAEC and LOAEC were 500 ppm (4.5 mg/L) and 2500 ppm (22.8 mg/L) based on the decrease in body weights.

Environment

The EPISuite program developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain siloxanes in their molecular structure; therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported below; the estimated values reported here are assigned a reliability code of 4.

D3 is a solid material at room temperature with a melting point of 64°C, a boiling point of 135.1°C at 1013 hPa, and an extrapolated vapor pressure of 6.71 hPa at 25°C. The water solubility of D3 is 1.6 mg/L at 25°C. The measured log Kow is 3.85 and the modeled EPISuite log Kow is 4.47. Rapid hydrolysis of D3 makes measurement of the D3 water solubility and octanol/water partition coefficient problematic and the values may not be accurate.

D3 is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions. At pH 4, 7, and 9 (25 °C), the half-lives were 2, 23 and 0.4 minutes respectively. D3 initially hydrolyzes to hexamethyltrisiloxanediol followed by final hydrolysis to dimethylsilanediol (DMSD). In the atmosphere, indirect photooxidation by reaction with hydroxyl radicals is predicted to occur with a half life of 21 days. D3 is hydrolytically unstable therefore reaction with water vapor is likely the predominant degradation process for D3 in air. D3 is not readily biodegradable; an OECD TG 310 study resulted in 0.06% biodegradation after 28 days.

Level III fugacity modeling, using loading rates of 1000 kg/h each to air, soil and water shows the following percent distribution: air = 60.5%; soil = 34.5%; water = 4.9%; sediment = 0%.

In a 14-day study using rainbow trout, a BCF value of 100 ± 49 for D3 was calculated based upon parent D3 analysis in water and fish. Some morbidity and one case of mortality were observed among the ten fish. The impact of the diminished health of the fish on the reported BCF is unknown. This study utilized closed (except for an overflow) flow-through test vessels. It is expected that fish were exposed to the hydrolysis products in addition to D3.

Dimethylsilanediol is the final hydrolysis product of D3, but is not usually isolated because of its tendency to condense and form higher molecular weight oligomers. Dimethylsilanediol can be kept in a stable state only under special acid- and base- free conditions. Thus, most measured physicochemical properties of DMSD are not available; only measured water solubility of 1×10^6 mg/L at 25°C. Furthermore, due to these properties, current estimation models are not capable of calculating physicochemical or environmental fate values with any degree of accuracy. Thus, modeled data are not provided for DMSD because estimated physicochemical properties coupled with uncertainty associated with the modeling of this chemical class, could result in an assessment of an unrealistic scenario.

The adsorption of DMSD onto surfaces and its tendency to polymerize itself are important properties of this chemical. In the environment, DMSD is expected to be found in water and air and to be adsorbed by soil and sediment, but is

still subject to hydrolysis. Unbound DMSD in air, water, and soil is expected to degrade photolytically to silica and carbon dioxide. DMSD has been shown to biodegrade to methylsilanetriol, carbon dioxide, and silica.

Due to rapid hydrolysis, aquatic toxicity tests invariably expose test organisms to a mixture of D3 and very soluble hydrolysis products. No mortalities were observed in a 96-h flow-through rainbow trout study with 10 renewals per day of the test solution when fish were exposed at the limit of water solubility (1.6 mg/L). Similarly no effects were seen in a 48-h, flow-through *Daphnia magna* study when daphnids were exposed at the limit of water solubility. In a 72-h algal (*Pseudokirchneriella subcapitata*) study, closed-bottle with zero headspace, the EC50 of D3 was >1.6 mg/L (nominal) for biomass and growth rate.

Exposure

D3 is used solely as an industrial intermediate in the Sponsor country. It is sold to industrial customers for the manufacture of other chemicals (siloxanes). The substance is reacted during use and loses its chemical identity. The use pattern is the same in the USA, Europe and Japan. In 2001, the North America production volume of D3 was 207 tonnes (455,000 lbs), European production volume was 3221 tonnes (7,100,000 lbs.) and in Japan the production volume was 236 tonnes (520,000 lbs).

There are no intentional releases to the environment. Throughout the world, D3 is produced in closed reactors and transferred by hard piping to storage tanks to exclude moisture until it is intentionally reacted. D3 may be stored at the manufacturing site in tanks or trailers. This method of manufacture of D3 minimizes the potential that workers will be exposed to the compound. D3 may be sampled by chemical operators for analysis and both the chemical operators and analytical technicians have the potential for dermal and inhalation exposure to D3 during the sampling.

Consumer exposure directly to D3 is not expected since it is not used in consumer products. However, D3 is an impurity in siloxane polymers and other cyclosiloxanes used in consumer products.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (repeated-dose toxicity and effects on fertility). Based on exposure data presented by the Sponsor country, (closed system, site limited intermediate) and relating to use pattern in three world areas (North America, Europe and Japan) this chemical is currently of low priority for further work. These properties should nevertheless be noted by chemical safety professionals and users. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical is currently of low priority for further work because of its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	67-68-5
Chemical Names	<u>Dimethyl sulfoxide</u>
Structural Formula	$\begin{array}{c} \text{O} \\ \\ \text{H}_3\text{C}-\text{S}-\text{CH}_3 \end{array}$

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No data is available on the absorption of DMSO by inhalation exposure. However, its physico-chemical properties (low molecular size, high polarity and water solubility) suggest that DMSO is significantly absorbed by the inhalation route. DMSO appears to be readily absorbed through the skin. An *in vitro* permeability rate of 176 g/m².hour has been reported for human skin. Maximal serum concentration of DMSO occurred at 4 to 8 hours following skin contact in humans, and at 2 hours in rats. DMSO is also well absorbed after oral exposure. Peak plasma concentration of DMSO was attained at 4 hours after oral dosing in humans and at 0.5 hours in rats. DMSO is widely distributed to all body tissues. Higher concentrations of DMSO were found in the kidney, spleen, lung, heart and testes of rats given an oral dose, while higher levels were noted in the spleen, liver and lungs following a dermal dose. In humans, the plasma DMSO clearance half-life was about 11 to 14 hours, and 20 hours after dermal and oral dosing, respectively. A shorter clearance half-life of 6 hours was observed in rats after both routes of exposure. Metabolism of DMSO takes place primarily in the liver and kidneys. The principal metabolite is dimethyl sulfone (DMSO₂). Peak plasma levels of DMSO₂ in humans were observed at 72 to 96 hours after dosing, and then declined with a half-life of about 60 to 72 hours. DMSO is excreted unchanged or as the metabolite DMSO₂ in the urine. In the human, about 13 and 18% of a dermal dose, and 51% and 10% of an oral dose were accounted for by urinary excretion of DMSO and DMSO₂, respectively.

DMSO is of low acute toxicity. In non-guideline studies, LD₅₀ in rats are generally higher than 20,000 mg/kg bw and 40,000 mg/kg bw by the oral and dermal routes, respectively. In an acute inhalation study performed following the OECD TG 403, the LC₅₀ in rats was higher than 5000 mg/m³ for a 4-hour exposure.

A skin irritation assay performed in rabbit according to the OECD TG 404 revealed no more than a very slight or well-defined erythema, which disappeared in 3 days. In humans, repeated application of DMSO solution for up to several months could induce transient erythema, burning, stinging and itching, which returned to normal after discontinuation of treatment. In one study in humans, occlusive exposure to DMSO caused cell death of the outer epidermis, followed by rapid regeneration.

DMSO is slightly irritating for the eye. In studies performed following the OECD TG 405 or the EEC method B.5, a slight to moderate conjunctival irritation, which cleared in 3 days, was observed in the eyes of rabbits. A repeated instillation (100% DMSO, 3 times/day for 6 months) in the eyes of rabbits induced only a temporary lacrimation but did not show any changes in the iris, cornea, lens, retina, conjunctiva and lids. In humans, the instillation of solutions containing 50 to 100% DMSO has caused transient sensation of burning which was reversible within 24 hours.

DMSO is not a skin sensitizer. Sensitization tests performed in guinea pigs and mice following methods comparable to the OECD TG 406 were uniformly negative. A skin sensitization assay performed in humans was also negative.

DMSO is of low toxicity by repeated administration. According to the results of a 13-week inhalation toxicity study compliant with the OECD TG 413, the No Adverse Effects Concentration (NOAEC) for DMSO could be established at *ca.* 1000 mg/m³ for respiratory tract irritation and *ca.* 2800 mg/m³ (the highest concentration tested) for systemic toxicity. Other non-guideline repeated dose toxicity studies performed by different routes of administration and with several mammalian species have also shown that DMSO produced only slight systemic toxicity. With the exception of a decrease of the body weight gain and some hematological effects (which could be secondary to an increased diuresis) at very high dose levels, the most common finding observed in these studies is changes of the refractive power of the lens. These ocular changes were observed following repeated oral application of DMSO at doses of around 3000 mg/kg bw/d in rats for 18 months and 1000 mg/kg bw/d in dogs for 2 years. Following repeated dermal application, the same effects were observed at doses of around 1000 mg/kg bw/d in rabbits for 30 days, in dogs for 118 days and in pigs for 18 weeks. Similar ocular changes were not observed in monkeys following dermal application at doses of up to 9000 mg/kg bw/d for 18 months (dose levels that caused marked ocular toxicity in sensitive species). Clinical signs of systemic toxicity and the alterations of the lens were also never observed or reported in clinical and epidemiological studies performed in humans, even after exposure to a high dose level (1000 mg/kg/d for 3 months) or for a long period of time (up to 19 months). Overall, primates appear to be much less sensitive to DMSO ocular toxicity, and the ocular changes observed in rats, rabbits, dogs or pigs are not considered relevant for human health. Then, it is possible to estimate that the No Observed Adverse Effect Levels (NOAELs) by oral or dermal routes would be close to 1000 mg/kg bw/d.

In studies performed with methods compliant or comparable to OECD guidelines, no genotoxic activity was observed for DMSO in gene mutation assays in *Salmonella typhimurium*, an *in vitro* cytogenetics assay in CHO cells and an *in vivo* micronucleus assay in rats. With few exceptions, a large battery of additional *in vitro* and *in vivo* non-guideline studies confirmed the lack of genotoxic potential.

There is no valid carcinogenicity study conducted with DMSO.

DMSO is not a reproductive toxicant. In a Reproduction/Developmental Toxicity Screening Test performed following the OECD TG 421, the NOAEL for parental toxicity, reproductive performance (mating and fertility) and toxic effects on the progeny was considered to be 1000 mg/kg/day. In addition, no effect was observed on the estrus cycle, the sperm parameters (count, motility and morphology) and the reproductive organs of male and female rats after a 90-day inhalation exposure to DMSO concentrations up to 2800 mg/m³. In developmental toxicity studies performed according to the OECD TG 414, oral administration of DMSO to pregnant female rats or rabbits during the period of organogenesis was not teratogenic. The NOAELs for maternal toxicity were 1000 and 300 mg/kg bw/d in rats and rabbits, respectively, and the NOAELs for embryo/foetotoxicity were 1000 mg/kg bw/d in both species.

Environment

DMSO is a liquid (density 1.1) with no color but in some cases a light characteristic sulfur odor due to traces of the raw material dimethyl sulfide. DMSO has a melting point of 18.5°C and a boiling point of 189°C (at 1,013 hPa). Its log K_{ow} is of -1.35 (measured). DMSO has a vapor pressure of 0.81 hPa at 25°C and a Henry law's constant of 1.17*10⁵ mol.kg⁻¹.atm⁻¹. DMSO is miscible in all proportion with water and with most of the common organic solvents such as alcohols, esters, ketones, ethers, chlorinated solvents and aromatics. DMSO is stable in water and is not expected to volatilize. DMSO Log K_{oc} is estimated to be equal to 0.64. This value suggests that DMSO is mobile in soil. DMSO is not expected to adsorb to suspended solids, sediments and soils. In atmosphere, DMSO is not susceptible to direct photolysis by sunlight. Calculations indicate DMSO half-life values, for reaction with OH radicals, from *ca* 2 to 6 h.

Distribution modeling using Mackay Fugacity model Level III, for equal release in the environment (*i.e.*

1000 kg/h), indicates that the main target compartment will be soil (60.4%) and water (39.5%) with the remainder partitioning between air (0.0334%) and sediment (0.0723%). DMSO is not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor lower than 4.

One readily biodegradation test performed following the norm AFNOR NF T 90-312 concluded that DMSO is readily biodegradable. Nevertheless, based on literature data and weight-of-evidence approach, better expectation is to consider DMSO as inherently biodegradable. For instance, 500 mg/L DMSO were entirely biodegraded within *ca.* 37h with aerobic settling sludge obtained from the activated sludge process at an opto-electronic plant, under optimized pH/temperature conditions. In a test report following OECD TG 303A, it has been validated that more than 90% DMSO was biodegraded at a concentration of 65 mg/L after 32 days of exposure.

Acute toxicity studies, carried out for some of them according to guidelines similar to OECD guidelines, reveal 48-hour EC₅₀'s ranging from 24,600 to 58,200 mg/L for daphnid (*Daphnia magna*) and 96-hour LC₅₀'s ranging from 32,300 to 43,000 mg/L for fish according to the species considered (*eg.* *Ictalurus punctatus*, *Lepomis cyanellus*). Modeling calculation for algae indicates 96-hour EC₅₀ value of about 400 mg/L. On this basis DMSO can be considered non-toxic for aquatic compartment.

Exposure

The worldwide consumption of DMSO is estimated for the year 2004 between 30,000 T and 40,000 T. The production sites are located, one in Europe, one in Japan, one in the United States and several sites (3-4) of smaller size in China. With its high polarity combined with a high electric constant, DMSO is known to be an excellent solvent for polar or polarizable organic compounds, and also many acids, alkalis and mineral salts. DMSO is used industrially, and not exclusively, as a reaction, polymerization, clean-up and pharmaceutical solvents, paint and varnish removers, analytical reagent, in the manufacture of synthetic fibers, industrial cleaners and pesticides and in the electronic industry. DMSO is also used as a preservative for organ transplantation and for the treatment for the symptoms of interstitial cystitis. There is a well-known phenomenon of use of DMSO by patients for other than the treatment of interstitial cystitis purposes, primarily to treat sprains, bruises, minor burns and arthritis. It should be noted, that only a medical purity grade DMSO is safe, and the technical grade DMSO should not be used for the curative dermal applications. In addition, DMSO enhances the permeability of skin to other substances. Fifty percent of the DMSO applications are in the pharmaceutical and agrochemical industries, 25% in the electronics, 10% in fine chemistry and 15% in other applications.

DMSO naturally occurs in natural water. DMSO is produced and released into seawater by phytoplankton, as is dimethylsulfide (DMS). DMS, which is estimated to comprise 90% of the reduced sulfur flux from the ocean to the atmosphere, is subsequently oxidized to DMSO and then sulfur dioxide and sulfate as part of the global atmospheric sulfur cycle. A representative surface sample of seawater from the North Pacific contained 0.49 ppb of DMSO. However, its occurrence in seawater is restricted to the zone where light penetrates (the euphotic zone < 100 m depth). DMSO also occurs in rain (*ca.* 5 nmol/L) from marine air masses, suggesting that DMSO participates in the transfer of sulphur between ocean and atmosphere

DMSO production and use may result in its release to the environment through various waste streams. As already mentioned, DMSO is used in many industries. Therefore, the anthropogenic environmental sources are numerous.

Comprehensive surveys of wastewater identified DMSO in discharges of industrial sites with highest effluent concentration of 1266 ppb in the laundry industry. In fact, DMSO concentrations are variable in the environment ranging from no quantified concentrations to *ca.* a thousand of ppb, depending on the sampling site (*eg.* below the LOQ in leachate plumes under sanitary landfills; 10-80 ppb in kraft mills effluent.).

Occupational exposure to DMSO is most likely via the inhalation and/or dermal routes of exposure. However, manufacturing and distribution processes utilize closed system engineering practices to eliminate/reduce potential exposure to DMSO. In addition, adequate ventilation and chemical-specific personal protective equipment (PPE) is utilized for additional protection. The American Industrial

Hygiene Association (AIHA) has established a Workplace Environmental Exposure Level (WEEL) 8-hr time-weighted average (TWA) of 250 ppm.

Environmental monitoring data indicate that the general population may be exposed to DMSO *via* inhalation of ambient air and ingestion of food and drinking water contaminated with DMSO. Exposure through dermal contact with a small number of consumer products containing DMSO is also a possibility. The SPIN database for Substances in Preparations in Nordic Countries lists a few uses of DMSO in consumer preparations for products registered in Sweden, but no record was found for DMSO in the U.S. National Institutes of Health Household Products database.

**RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED**

Human health: DMSO is currently of low priority for further work for the Human health due to its low hazard profile.

Environment: DMSO is currently of low priority for further work for the environment due to its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	7697-37-2
Chemical Names	Nitric acid
Structural Formula	HNO ₃

SUMMARY CONCLUSIONS OF THE SIAR**Supporting Chemical Rationale**

The nitrate salts, sodium nitrate (CAS No. 7631-99-4), potassium nitrate (CAS No. 7757-79-1) and ammonium nitrate (CAS No. 6484-52-2), are used as supporting chemicals to assess toxicity of nitric acid. The nitrates category was presented and agreed upon at SIAM 25. Nitric acid is a strong acid with a pKa of -1.4. The toxicological effect of nitric acid is related to severe corrosive effects at the point of contact. Nitric acid almost completely (93% at 0.1 M) ionizes into the nitrate ion NO₃⁻ and the hydronium ion H₃O⁺ under environmental conditions. Many aquatic and mammalian toxicity tests with nitric acid are precluded due to its pH effects. The nitrate salts are soluble in water and dissociate into the nitrate ion and the corresponding cations in biological fluids and aquatic environments. The cations sodium, potassium and ammonia are not expected to play a significant toxicological role at low doses. Therefore, the data from these salts are used as read across to fill data gaps in this assessment.

Human Health

In rats, the 4-hr LC₁₀ for red fuming nitric acid (RFNA) was ≤ 8 ppm (~21 mg/m³). Widespread inflammation of the upper respiratory tract, rhinitis, tracheitis and pneumonitis were seen in the rats sacrificed shortly following exposure. Respiratory inflammation subsided in animals examined several weeks following cessation of exposure. The 30-minute LC₅₀ values for RFNA and white fuming nitric acid (WFNA) were 310 and 334 ppm (~799 and 861 mg/m³), respectively. Deaths were due to pulmonary edema. Burns were noted on the skin of animals exposed to high concentrations of WFNA. Following ingestion, humans exhibited ulceration of all tissues and membranes with which the acid came into contact. Acute inhalation of nitric acid has been shown to result in respiratory distress and fatal pulmonary edema. Nitric acid is highly corrosive to skin and eyes of animals and humans due to its strong acidic nature. Acid aerosols are known to irritate the respiratory tract and may induce bronchoconstriction, and pulmonary edema at high vapor concentrations.

Repeated-dose toxicity studies were not available for nitric acid, but have been conducted with supporting compounds potassium nitrate; ammonium nitrate; and sodium nitrate. These data are applicable to nitric acid due to the ready dissociation of nitric acid and the nitrate salts to the nitrate ion (NO₃⁻) and the corresponding cations. In a combined repeated-dose/reproductive/developmental toxicity screening study, rats were administered potassium nitrate by oral gavage at 0, 250, 750 and 1,500 mg/kg bw/day for 28 days during the pre-mating period. No effect was observed on body weight, food consumption, functional observational battery, and motor activity parameters. Slight increases in levels of blood urea nitrogen (males and females) at 750 and 1,500 mg/kg bw/day and phosphates (males) at 1,500 mg/kg bw/day were not considered clinically relevant due to the absence of other indicators of renal dysfunction. The NOAEL was 1,500 mg/kg bw/day, the highest dose tested. Administration of sodium nitrate in the drinking water to rats for 14 months resulted in a LOAEL of 4,000 mg/L (ca. 200 mg/kg bw/day).

based on a decrease of plasma vitamin E and an increase in the incidence of pulmonary lesions. No effects were observed after inhalation exposure of rats and guinea pigs to ammonium nitrate for two to four weeks; the NOAEL was 1 mg/m³/day.

Nitric acid was not mutagenic in an *in vitro* bacterial system (Ames test) in the presence and absence of metabolic activation. Additional studies on nitric acid were not available. Potassium nitrate and ammonium nitrate (supporting chemicals) were not genotoxic *in vitro* in either bacterial or mammalian cell systems. Sodium nitrate (supporting chemical) was negative in an Ames test with and without metabolic activation and *in vitro* micronucleus test and chromosome aberration tests with mammalian human lymphocyte cells. Therefore, nitric acid (evaluated as NO₃⁻ in several of these tests) is not expected to be genotoxic. However, the H⁺ ion may react with the surfaces that it contacts.

In the combined repeated-dose/reproductive/developmental toxicity screening study described above, male rats were dosed by oral gavage with potassium nitrate at 0, 250, 750 or 1500 mg/kg bw/day for 28 days and females for 14 days prior to mating, during mating and gestation, and through day 4 of lactation. No treatment-related effects were seen on mating performance, fertility, gestation length, gestation index, litter size, offspring survival, sex ratio or offspring body weights. There were no gross pathological effects in offspring. The NOAEL for reproductive toxicity was 1,500 mg/kg bw/day, the highest dose tested. Sodium nitrate did not induce abnormalities of sperm heads in mice dosed by oral gavage at 600 or 1,200 mg/kg bw/day for three days, but following 14 days of treatment sex chromosomal univalency and abnormal sperm-head frequency were significantly higher in males. However, statistically significant reductions in fertility and litter size were not observed. Nitric acid is not expected to result in reproductive toxicity.

Environment

Nitric acid is produced as an aqueous solution with a concentration of 42 – 99%. The melting point of nitric acid is -41.6°C and the boiling point is 83°C at 1013 hPa. The vapor pressure is 84.1 hPa at 25°C. Nitric acid is considered miscible with water. The pKa of nitric acid is -1.4, and therefore, in water, nitric acid readily dissociates to its respective ions (H⁺; NO₃⁻) under environmental conditions. A log K_{ow} value for an inorganic compound such as nitric acid is not relevant.

Photodegradation and distribution modeling for nitric acid was not conducted. Nitric acid dissociates in water; therefore, a standard hydrolysis study is not relevant. Standard biodegradation tests are not applicable to inorganic substances. Bioaccumulation is not anticipated for inorganic compounds that are miscible with water such as nitric acid.

LC₅₀ value for nitric acid toxicity to fish was 72 mg/L (nominal) at pH of 3.25- 3.5, pH 3.7 and pH 4.0. LC₅₀ values for fish toxicity were greater than 100 mg/L (nominal) for the supporting substances. The observed toxicity was considered a result of pH effects (acidity), as opposed to any intrinsic toxicity. EC₅₀ values for daphnia toxicity were not available for nitric acid. For supporting substances sodium nitrate, potassium nitrate and ammonium nitrate, EC₅₀ values for daphnia toxicity range from 490 (nominal) – 3,581 mg/L (measured or nominal unknown). Data on acute toxicity to aquatic plants were not available for nitric acid. For the supporting substance ammonium nitrate, the 7-day EC₃ for algae was 83 mg/L (measured or nominal unknown). For the supporting substance potassium nitrate, data from testing with lower forms of algae (*Gyrosigma spencerii*, *Navicula spp.* and *Nitzschia spp.*) indicate EC₅₀ values >1,700 mg/L (measured).

Exposure

Nitric acid is predominantly produced in Europe (ca. 16,500 ktonnes or 36 billion pounds) and the USA (ca. 6,700 ktonnes or 15 billion pounds). Nitric acid is used in the manufacture of fertilizers, dye intermediates and explosives, metallurgy (e.g., steel pickling), photo-engraving, etching steel, ore flotation, in the synthesis of urethanes and rubber chemicals, and reprocessing of spent nuclear fuel.

Nitric acid is produced in closed reactor vessels (hard piped). Occupational exposure may occur during manufacturing (coupling/decoupling of pipelines). However, due to the corrosive nature of nitric acid, strict safety precautions are applicable. The dermal and inhalation routes will be the most important routes of exposure.

The U.S. Occupational Safety and Health Administration established a permissible exposure limit (averaged over 8 hours) of 2 ppm for nitric acid.

In consumer applications, nitric acid is used as an acidifier in some pharmaceuticals. It is a cauterizing agent (for warts) in veterinary applications. Consumer exposure is expected to be minimal.

In 2005, US manufacturers reported that 12.86 million pounds (ca 5833 tonnes) were released to air, surface water as well as landfills, underground injection, or other disposal options. Some of this total is contained and will result in minimal exposure but some releases may result in exposure.

NO_x are precursors to the formation of nitric acid, which is one component of acid rain, and thus nitric acid may be deposited on water, soil and vegetation.

RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (corrosivity to skin and eyes, acute toxicity to the respiratory tract). Based on data presented by the Sponsor country, risk management measures are being applied (occupational exposure limits). Consumer exposures are expected to be minimal. Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to aquatic organisms between 1 and 100 mg/L). However the hazard does not warrant further work as it is related to pH effects.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7757-83-7
	Sodium sulfite
Structural Formula	$\begin{array}{c} \text{O}^- \\ \diagup \quad \diagdown \\ \text{O}=\text{S} \\ \diagdown \quad \diagup \\ \text{O}^- \end{array} \quad 2 \text{Na}^+$

SUMMARY CONCLUSIONS OF THE SIAR**Analogue rationale**

In case of missing or insufficient data on sodium sulfite, also data from other S(IV) compounds have been included, as there is a pH dependent equilibrium with the different forms of S(IV) being bisulfite, sulfite, metabisulfite and sulfur dioxide in the aqueous milieu of biological systems. Sodium metabisulfite (CAS No. 7681-57-4) has already been assessed in the OECD HPV Chemicals Programme.

Human Health

Sodium sulfite is rapidly absorbed from the gastro-intestinal tract. Sulfate is the main metabolite formed by the action of sulfite oxidase in many tissues. Tissue accumulation of sulfite-derived S is highest in stomach, skin and hair, intestine and kidney. Excretion is rapid, mainly in the urine.

With oral LD₅₀ values $\geq 3,560$ mg/kg bw in rats and 820 – 920 mg/kg bw in mice, the acute toxicity of sodium sulfite is moderate to low. There are no acute standard inhalation tests and no LC₅₀ values available. Acute inhalation of sodium sulfite aerosols caused bronchoconstriction in guinea pigs (LOAELC 0.204 mg/m³). Acute dermal toxicity of sodium sulfite has not been investigated.

In studies according to OECD TG 404 and 405 sodium sulfite was not irritating to the skin or the eyes of experimental animals.

No dermal sensitization studies in animals are available. In humans some cases of sensitization from topical contact with sodium sulfite have been described. Only 1.4% of a population of 1762 eczema patients showed a positive reaction to sodium sulfite in patch tests. For S(IV) compounds, single cases of hypersensitivity have been reported for the respiratory tract and for the oral route. These reactions seem to be restricted to highly reactive persons, when considering the wide use of sodium sulfite as food preservative.

In dogs, exposed for 290 days to a well characterized aerosol of S(IV) particles, at a single concentration of 0.3 mg S(IV)/m³ (corresponding to 1.2 mg/m³ sodium sulfite), only minor changes were observed in pulmonary function parameters. Specific limited studies in the respiratory tract indicated 0.3 mg/m³ to be a LOAEC for impairment of bacterial defense, for hyperplastic and inflammatory changes in the nasal cavity, and for histological changes in the larynx, trachea and alveolar region.

In a 90-day feeding study, a NOAEL for male rats of 2% in diet corresponding to 1670 mg/kg bw/day was found. The LOAEL was 4% in diet based on decreased body weight gain and increased relative weights of testis and brain. In female rats, the highest tested dose of 4% in diet was the NOAEL corresponding to 3070 mg/kg bw/day.

There is no chronic toxicity study available with sodium sulfite. Waiving is possible based on chronic studies with other sulfites, especially a detailed study on 2-year feeding of sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$) to rats. An overall NOAEL of 0.5% in the diet was derived, which is equivalent to a dose of 144 mg/kg bw/day calculated as sodium sulfite. The LOAEL for local effects (forestomach and glandular stomach hyperplasia or inflammation) corresponded to 1.0% in diet being equivalent to a dose of 300 mg/kg bw/day calculated as sodium sulfite. The NOAEL for systemic effects corresponded to the highest dose of 2% in diet which would be equivalent to 625 mg/kg bw/day calculated as sodium sulfite.

In vitro, sodium sulfite gave no indication of mutagenic or clastogenic activity up to cytotoxic concentrations both in the absence and presence of metabolic activation systems when tested in Ames tests/*Salmonella typhimurium* reversion assays, in gene mutation tests with *Saccharomyces cerevisiae* and in mammalian V79 cells (without metabolic activation), in a DNA damage and repair assay with *Escherichia coli*, as well as in a chromosomal aberration test with CHL cells (without metabolic activation). There are no *in vivo* tests with application of pure sodium sulfite. Several genotoxicity studies *in vivo* with sulfites other than sodium sulfite were negative. The negative findings in whole animals are regarded as consistent with the high reactivity of sulfite e.g. with proteins and its rapid inactivation in mammals due to metabolism. However, in contrast to the consistent negative findings in earlier studies, recent investigations of a single working group demonstrated dose-dependent increases of micronuclei in bone marrow and DNA damage in tissues of mice after intraperitoneal injection of a mixture of Na_2SO_3 and NaHSO_3 . No parallel investigations were performed with the pure compounds as controls.

In conclusion, from the available data, there are no indications of a genotoxic potential of sodium sulfite per se.

There are no carcinogenicity studies available with administration of sodium sulfite.

As there are no indications of a carcinogenic action of sodium metabisulfite, when applied in long term studies in the diet or drinking water in rats or mice, there is no principal concern about a carcinogenic potential of sodium sulfite.

There are no reproductive toxicity studies with sodium sulfite investigating effects on male or female fertility. In a 3-month feeding study with male rats no relevant effects of sodium sulfite were seen in the testes. In a three-generation study with sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$), there was no suggestive evidence of reproductive toxicity or impairment of fertility in rats that received up to 2% in the diet. No effects on gonads were seen histologically. This NOAEL for reproductive toxicity would be equivalent to a dose of 625 mg/kg bw/day calculated as sodium sulfite, which is higher than the NOAEL for chronic toxicity of 0.5% in the diet (based on local irritation of the stomach), being equivalent to a dose of 144 mg/kg bw/day calculated as sodium sulfite.

No teratogenic effect of sodium sulfite was found in rats (feeding of sodium sulfite heptahydrate). Maternal toxicity was indicated by reduced body weight gain at 1650 mg/kg bw/day. The NOAEL for teratogenicity was 1650 mg/kg bw/day, the NOAEL for the maternal toxic dose was 1050 mg/kg bw/day (both as sodium sulfite).

Environment

Sodium sulfite is a white solid. The anhydrous substance is stable in dry air at ambient temperatures or at 100°C. In aqueous solutions, the substance is completely dissociated into sodium cations and the sulfite anion. Sodium sulfite is a salt of sulfurous acid (H_2SO_3). In aqueous solutions, sulfurous acid dissociates, the dissociation constants are $\text{pK}_{\text{a}1}$ of 1.8 and $\text{pK}_{\text{a}2}$ of 7.0 at 25°C. At neutral pH, a mixture of 50% sulfite (SO_3^{2-}) and 50% bisulfite (HSO_3^-) is present. At concentrations above 1M, bisulfite anions will dimerise with the elimination of water to form metabisulfite ($\text{S}_2\text{O}_5^{2-}$). At low concentrations, metabisulfite will hydrolyse to form bisulfite.

The water solubility of sodium sulfite was reported to be 313 g/L at 25°C and the relative density to be 2.633.

The octanol-water partitioning coefficient has limited relevance as the chemical is inorganic and dissociates in aqueous solution.

In surface waters, sulfite is oxidized to sulfate either catalytically by air oxygen or by microbial action. The half-life in deionized water was determined to be 77 hours. The presence of cations like iron, copper or manganese in the environment accelerates the oxidation rate significantly.

Experimental data on photodegradation of sodium sulfite are not available. Due to the molecular structure,

photodegradation can be excluded.

Because of its ionic structure, volatilization from the hydrosphere is unlikely. As well, sorption onto soil or sediment solids is not expected.

For the environmental hazard assessment, data from related sulfite salts are considered in addition. Numerous studies on the acute toxicity to fish, daphnids and algae are available. For the interpretation of the test results the instability of the test solutions has to be considered. Sulfite is rapidly oxidized to sulfate, the reaction is accompanied with consumption of dissolved oxygen. Therefore, the observed effects can be caused either by sulfite toxicity or by lack of oxygen. The available results indicate that algae represent the most sensitive trophic level, followed by daphnids and fish. The 96h-LC₅₀ for *Leuciscus idus* was determined to be between 170 and 370 mg/L (nominal concentrations). In a short-term test on *Daphnia magna*, a 48h-EC₅₀ of 118 mg/L (nominal concentrations) was obtained. Growth inhibition tests on 3 algal species (*Chlamydomonas reinhardtii*, *Chlorella vulgaris* and *Scenedesmus basiliensis*) exhibited identical effect values (96h-EC₅₀ = 63 – 126 mg/L, nominal concentrations).

Long-term tests were conducted on daphnids and algae. The 21d-NOEC for *Daphnia magna* was determined to be >13 mg/L (nominal concentrations). At a concentration of 12.6 mg/L, inhibitory effects between 0 and 33% were observed at 18 different algal species. However, it has to be taken into account, that for sulfites reliable experimental toxicity results on 25 different algal species as the most sensitive taxonomic group are available. In addition, the compound is a normal metabolite present in living organisms and it is oxidized in aquatic compartments.

Exposure

Sodium sulfite is primarily produced by treating a suspension of sodium hydroxide or sodium carbonate with sulfur dioxide. Some sodium sulfite is obtained from scrubbing of SO₂-containing off-gases. In 1987, 95,200 tons sodium sulfite were produced and 454 tons were imported in the USA. For the year 2002, the demand was estimated to be 107,000 tons. The envisaged production amount in the Japanese lead company was estimated to be approximately 10,000 t/year.

The major amounts of sodium sulfite are used in chemical industry, leather processing industry, photographic industry, polymers industry, pulp & paper industry, in the personal/domestic sector, and many other applications.

Sodium sulfite is expected to be released into waste waters during production and use. There are no quantitative data about release amounts available. In the environment sulfite is formed from sulfur dioxide being released into the atmosphere by natural and anthropogenic sources. Sulfur dioxide may reach soils or surface waters by dry and wet deposition.

Occupational exposure to sodium sulfite is possible in a variety of industries as described above, mainly to sodium sulfite solutions. Sodium sulfite dusts were measured at a production site. The highest values up to 40 mg/m³ were obtained for filling and cleaning operations. However, workers are recommended to wear protective gear such as a mask, rubber gloves and goggles.

Sulfite is present in the human body as a normal metabolite and intermediate of sulfur-containing amino acids, as a metabolite of sulfur dioxide inhaled via polluted air, and from ingestion of sulfiting agents used widely in foods and beverages. The daily intake varies widely depending on the diet. The US population has been estimated to consume an average of 10-15 mg/person of total sulfites. An acceptable daily intake (ADI) of 0.7 mg/kg body weight (total sulfites expressed as sulfur dioxide) was established by the Food and Agriculture Organisation of the United Nations and the World Health Organisation (FAO/WHO). Another source of exposure is from pharmaceutical preparations containing sodium sulfite as an antioxidant preservative and from its use as reducing agent in cosmetic formulations (up to 0.4%), mainly in hair dyes and colors (up to 3%).

**RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF
FURTHER WORK RECOMMENDED**

Human health: The chemical is considered to be a candidate for further work. The chemical possesses properties indicating a hazard for human health (respiratory tract reactivity and dermal sensitization). Member countries are invited to perform an exposure assessment for consumers and workers, and, if then indicated, a risk assessment.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for environment (acute toxicity to aquatic plants). However, the chemical has limited potential for bioaccumulation and rapidly degrades.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-21-0
Chemical Name	Peracetic acid
Structural Formula	$\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{COOH} \end{array}$

SUMMARY CONCLUSIONS OF THE SIAR

Peracetic acid (PAA) is commercialised as an equilibrium aqueous solution in which peracetic acid is in equilibrium with hydrogen peroxide, acetic acid and water. The concentration of peracetic acid, hydrogen peroxide and acetic acid can reach levels of about 40, 30 and 40 %, respectively, in certain equilibrium solutions. Nearly all toxicity studies, related with human health and environment, were done with equilibrium solutions. PAA is also commercialised as a distilled product containing primarily peracetic acid and water. Distilled PAA solutions are unstable under ambient conditions and re-equilibrate under formation of hydrogen peroxide and acetic acid. By cooling below 0 °C the hydrolysis reaction is slowed down. The amount of peracetic acid in these aqueous solutions ranges from about 0.15 to 40 %. All peracetic acid solutions are clear, colourless liquids with a pungent vinegar-like odour and the pH of these solutions is less than 1.5. Peracetic acid solutions have oxidising properties. Peracetic acid can be degraded to hydrogen peroxide and acetic acid. The hazards of hydrogen peroxide (CAS. 772-84-1) are described in the SIAP which was agreed at SIAM 9 (1999).

Human Health

An *in vitro* dermal penetration assay at 37 °C using 0.8 % PAA (non corrosive) indicated a low dermal uptake of peracetic acid through the intact skin of pigs. When the skin of rats was exposed to a corrosive concentration of ¹⁴C-labelled PAA a considerable uptake of ¹⁴C was found but it is unknown if the ¹⁴C was present as peracetic acid, acetic acid or CO₂. It is expected that corrosive concentrations of PAA would compromise the normal barrier function of the skin.

Two reliable *in vitro* studies, using different analytical methods, showed a rapid degradation of peracetic acid in rat blood. When rat blood was diluted 1000 times, the half-life of peracetic acid was < 5 minutes. In undiluted blood the half-life is expected to be several seconds or less. For this reason the distribution of peracetic acid is probably very limited and it is not expected to be systemically available after exposure to peracetic acid solutions. Degradation products have not been identified during the kinetic studies. However, based on the structure of the substance the following degradation products are expected: acetic acid, oxygen, hydrogen peroxide and water. Hydrogen peroxide is also presumed to be rapidly degraded into oxygen and water.

The results of acute toxicity tests are expressed on the component peracetic acid, which was calculated based on the composition of the product used for the acute tests. The available acute inhalation studies with aerosols and vapour revealed an 4h-LC₅₀ ranging from 76 to >241 mg/m³. The acute dermal toxicity of PAA solutions was tested in rats and rabbits. No sign of dermal toxicity was observed when rats were exposed to solutions of 0.15-15%, while LD₅₀ values of 56.1 and 228.8 mg PAA/kg bw were reported for rabbits for concentrations of 4.9 and 11.7 % PAA, respectively. The dermal toxicity depends on the degree of skin damage caused by the different PAA solutions, since the corrosive properties of PAA solutions may compromise the integrity of the skin. In oral toxicity studies LD₅₀ values ranged between 9.0 and 202.8 mg/kg bw based on the component peracetic acid. Sporadic contact with even dilute solutions with the oesophagus could lead to deaths due to corrosion of the tissue and could explain the variability in the LD₅₀.

The pathology and symptoms were similar across all studies, indicating irritation and corrosion of tissues in contact with the test material.

PAA solutions should be considered as corrosive (within 3 minutes) at concentrations of 10 % and higher when applied to the skin of rabbits. PAA was generally corrosive to rabbit skin at a concentration of 5 % if contact lasted 45 minutes or longer. Concentrations of less than 0.34 % PAA were only slight irritants or non-irritants, depending on the exposure duration of the skin. PAA was corrosive at concentrations of 0.34 % and higher when tested in the rabbit eye. Slight or no eye irritation was found at concentrations of 0.15 % or less PAA. Incidental human findings on skin and eye irritation are supporting the animal studies. Peracetic acid gave a positive response in Alarie assay in the mouse, with an RD50 value (concentration producing a 50 % decrease in the respiratory rate) of 12 and 17 mg/m³ (peracetic acid in vapour mixture from the formulation and peracetic acid only). Human data support the sensory irritating properties of peracetic acid.

No skin sensitisation was observed in three Bühler tests in guinea pigs with different formulations of PAA. The exposure concentration of peracetic acid ranged from 0.15 to 1.2 % during the tests. Additionally, long term experience with production and use of PAA has shown that PAA has no sensitisation potential.

To investigate the repeated dose toxicity, a GLP guideline study was done with rats, which were exposed by gavage for 13 weeks to 5 % PAA diluted to various concentrations (0.018 % to 0.55 % of the component peracetic acid). At 0.75 mg/kg/day transient or intermittent loud breathing was observed in two females but the effect was not considered adverse. Based on the results of this study the NOAEL was 0.75 mg/kg bw/day (component peracetic acid). The only observed effects were local effects that are concentration related. It is therefore reasonable to define a No Observed Adverse Effect Concentration rather than a classical NOAEL. Based on the component peracetic acid, the NOAEC for local effects was 0.055 %.

Gene mutation assays in bacteria tests, with and without metabolic activation, showed negative results. Two DNA repair tests in human foetal lung cells did not indicate a genotoxic potential of PAA. In the *in vitro* chromosome aberration test, positive findings were obtained only at cytotoxic concentrations. Under *in vivo* conditions, PAA (4.5 and 5.17% product) did not produce micronuclei in two mouse micronucleus tests after oral administration. In two *in vivo/ex vivo* assays of unscheduled DNA synthesis in rats after oral administration, PAA did not show significant genotoxicity potential. Overall these data do not raise concern with regard to the mutagenic and genotoxic potential of PAA. However, peracetic acid is not systemically available and this could explain the lack of *in vivo* mutagenicity, but site of contact effects cannot be excluded completely. No valid carcinogenicity study with PAA is available.

No valid data on fertility are available. However, in a well documented GLP and guideline study aqueous dilutions of 5 % PAA were administered daily by gavage to Sprague-Dawley rats for 13 weeks. No effects of peracetic acid on the reproductive organs of both sexes following macroscopic *post mortem* examinations and microscopic examinations (histopathology) were notable during the study. Because peracetic acid is rapidly degraded in blood, distribution to reproductive organs is not anticipated, and therefore it is unlikely to be a reproductive toxicant. In addition, the degradation product hydrogen peroxide did not indicate any effect in the reproductive organs during a 90-day drinking water study and furthermore, a rapid degradation was presumed resulting in a lack of systemic availability.

In a well documented GLP and guideline developmental toxicity study performed with 32-38 % PAA, pregnant Wistar rats were administered dose levels of 100, 300 or 700 mg peracetic acid/l (corresponding to 12.5, 30.4 and 48.1 mg peracetic acid/kg bw/day) via the drinking water from day 5 to 20 of gestation. No teratogenic effect was evident up to and including the high dose level of 700 mg peracetic acid/l (48.1 mg peracetic acid/kg bw/day). Dose and treatment-related maternal toxicity was observed, considering water and food consumption, above 100 mg/l (12.5 mg PAA/kg bw). At 700 mg peracetic acid/l (48.1 mg/kg bw) this resulted in severe reductions in drinking water and food consumption and in absolute body weight as well as by a drastic reduction in overall body weight gain and in body weight gain corrected for uterine weight. At the high dose level, fetal weight was statistically significantly reduced (5 %) but litter size at this dose level was about 13 % higher than in controls. However, it is doubtful if the reduction of

5% is biologically relevant. The overall NOAEL for foetal toxicity is therefore 300 mg/l (30.4 mg PAA/kg bw) based on a statistically significantly lower body weight and an increased incidence of poor and/or hypertrophic ossification (bone formation) in the presence of severe maternal effects (maternal NOAEL = 100 mg/l or 12.5 mg PAA/kg bw/day).

Environment

Peracetic acid is an organic substance which is completely miscible with water (water solubility of 1000 g/l at 20 °C) and which displays oxidising properties. Pure peracetic acid is not available because it is explosive. For this reason it is technically not possible to perform an experimental study according to the guidelines to determine the melting point, boiling point and vapour pressure of pure peracetic acid. Based on modelling, the melting point, boiling point and vapour pressure were estimated to be -42 °C, about 105 °C and 32 hPa (at 25 °C), respectively. The log Pow was reported to be -0.52 (measured value) and the Henry Law's constant is 0.22 Pa·m³/mol. The pKa of peracetic acid is 8.2 at 20 °C and therefore the substance is mainly present in the environment as peracetic acid at a neutral pH (pH = 7), while peracetate would mainly be present if the pH is significantly higher than 8.2.

Based on the high water solubility, low vapour pressure and low octanol-water partition coefficient, peracetic acid is expected to partition almost exclusively to the aquatic compartment (99.95 %). In air the half-life of peracetic acid is 22 minutes. The abiotic degradation of peracetic acid increases with temperature and pH. At a temperature of 25 °C and at pH of 4, 7 and 9, the degradation half-life values were 48, 48 and < 3.6 hours respectively. Peracetic acid was readily biodegradable during a biodegradation test when an inhibition of the micro-organisms (biocidal effect) was prevented. Peracetic acid will be degraded in a sewage treatment plant if the influent concentration is not extremely high (e.g. > 100 ppm). If effluents generated during the production or use of PAA are treated by a waste water treatment plant, no emission of peracetic acid to the aquatic environment is expected.

Several studies on acute toxicity to aquatic species are available for all trophic levels. The pH of the test solutions was not adapted during the studies because a decrease of the pH was not found. In most cases the endpoints of the aquatic toxicity tests were based on nominal concentrations. The 96-h LC₅₀ values for fish ranged between 0.9 and 3.3 mg/l in most freshwater species. The 48-h EC₅₀ for *D. magna* ranged between 0.5 and 1.0 mg/l. Based on the representative standard toxicity tests, the lowest 72-h NOEC of 0.084 mg/l was found for *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capricornutum*). The lowest EC₅₀ value of 0.18 mg/l was found during a 120-h growth inhibition test with *P. subcapitata*. To determine the toxicity for microorganisms, two respiration inhibition tests with activated sludge of predominantly domestic sewage treatment plants were conducted. The EC₅₀ after 3 hours was 5.1 and 38.6 mg peracetic acid/l (based on nominal concentrations), respectively. In general, the aquatic tests with fish, invertebrates and algae were reproducible if concentrations were expressed as peracetic acid irrespective of the concentrations of hydrogen peroxide and acetic acid. Thus, the peracetic acid concentration alone may explain the toxicity of PAA formulations.

Exposure

The global number of production sites is estimated to be 40-100 and the majority of the production sites are located in Europe.

The equilibrium peracetic acid consumption (as such) in 2004 was estimated to be:

- 40,000 – 80,000 tonnes in Europe
- less than 20,000 tonnes in the USA and
- less than 10,000 tonnes in the rest of the world.

The quantities of equilibrium peracetic acid, given above, are mainly used for disinfection. Neither use of peracetic acid for chemical synthesis nor *in situ* generation of peracetic acid is included.

Major uses of peracetic acid are in chemical synthesis, disinfection and bleaching. Low concentrations (1-15 %) are used as sanitisers, disinfectants and sterilants in agriculture, food, beverage and medical

industries. High-strength equilibrium ($> 15\%$) and distilled peracetic acid products are in general employed as oxidising agents in the manufacture of organic chemicals and pharmaceuticals. Distilled peracetic acid is also used as bleaching agent in TCF cellulose pulp production processes replacing chlorine dioxide. Peracetic acid seems to be used in certain European countries in consumer products, which are used for example for hard surface disinfection.

Peracetic acid is also generated *in situ* when products, containing an activator (e.g. tetra-acetyl ethylenediamine, TAED) and a persalt (sodium perborate or sodium percarbonate), are dissolved in water. These products could be laundry detergents but they could also be used for surface disinfection (e.g. hospitals, farms). World-wide consumption in chemical synthesis including captive use (internal use by a company) and *in situ* generation has been estimated at 45,000-50,000 tonnes peracetic acid (100 %) in 1998.

During use of peracetic acid the substance may be released to the aquatic environment. Also *in situ* formation may result in an exposure of the aquatic environment. However, if the effluents are treated by wastewater treatment plants no emission of peracetic acid to the aquatic environment is expected.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human health

The chemical is of low priority for further work. The chemical possesses properties indicating a hazard for human health (acute toxicity, corrosive to skin and eyes, respiratory tract irritation, repeated dose toxicity based on local effects); however, these hazards do not warrant further work as they are related to local effects. They should, nevertheless, be noted by chemical safety professionals and users.

Environment

The chemical is a candidate for further work. The substance has properties indicating a hazard for the environment (aquatic toxicity $< 1\text{ mg/l}$ for fish, aquatic invertebrate and/or algae based on peracetic acid). Member countries are invited to perform an exposure assessment and, if necessary, a risk assessment (mainly needed for sites without a biological waste water treatment plant).

Note: In the EU the active substance peracetic acid has been notified for the Biocidal Products Directive (98/8/EC). Therefore a comprehensive risk assessment is already ongoing for the biocidal applications of peracetic acid in the EU (submission of complete dossiers in 2007 and 2008). This includes not only a detailed exposure assessment but also a detailed evaluation of the need for further toxicity testing.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	919-31-3
Chemical Name	3-(Triethoxysilyl)propionitrile (CNE)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Supporting Chemicals Justification**

Ethanol (CAS No.64-17-5) and 3-(triethoxysilyl)-propanenitrile (CAS No. 182156-21-4) are used as supporting chemicals for 3-(triethoxysilyl)propionitrile (CNE) where data on the sponsored chemical are not available or to supplement certain endpoints. These two compounds are expected to be the immediate hydrolysis products of CNE. Ethanol data are used to address biodegradation, water solubility, partition coefficient and bioaccumulation. Ethanol assessment was agreed in the OECD HPV Chemicals Program at SIAM 19.

Human Health

There are no available data on the toxicokinetics, metabolism, or distribution of CNE. There are no reliable studies available for the acute inhalation of CNE. The dermal LD₅₀ of CNE in male rabbits is 5,753 mg/kg bw; erythema with slight necrosis was observed at application sites in an unspecified number of animals. At the high dose, slightly congested lungs, pale and pitted kidneys and mottled livers were seen at necropsy. The oral LD₅₀ of CNE in male rats is 5,600 mg/kg bw. Clinical signs included violent convulsions prior to death. Hemorrhagic lungs, mottled livers and kidneys and slightly congested adrenals were seen at necropsy. There are no data available for skin or eye irritation or skin sensitization.

In a combined oral repeated-dose/reproductive/developmental toxicity screening study conducted under OECD TG 422, CNE was administered via oral gavage to 10 male and 20 female (10 toxicity group and 10 reproductive group females) HanBrl:WIST rats at doses of 100, 500, and 1000 mg/kg-bw/day. A concurrent vehicle control group (corn oil) was also included. Males and toxicity group females were sacrificed after they had been treated for 28 days; reproductive group females were dosed 14 days before mating to day 3 of lactation up to a maximum of 44 days; reproductive group females and pups were sacrificed on day 4 postpartum. Increased organ weights (kidneys, spleen, heart and liver in males; kidneys and spleen in toxicity group females), slight reduction in red cell count (not statistically significant), hemoglobin concentration and hematocrit in males and toxicity group females and histopathological changes in kidneys (chronic tubular lesions of minimal to moderate severity with hyperplasia of the renal pelvis epithelium and renal pyelonephritis) were noted in males and toxicity group females dosed at 1000 mg/kg-bw/day. Administration of 500 mg/kg-bw/day resulted in increased organ weights (kidneys, heart and liver in males only) and histopathological changes in kidneys including chronic tubular lesions, hyperplasia of the renal pelvis epithelium and renal pyelonephritis (males and toxicity group females) and spleen including extramedullary hematopoiesis (males only). Based on these data, the NOAEL for systemic toxicity of CNE was considered to be 100

mg/kg-bw/day, with LOAEL of 500 mg/kg-bw/day.

CNE did not induce gene mutations in bacterial cells (OECD TG 471) and did not induce chromosomal aberrations *in vitro* in mammalian cells (OECD TG 473). Both studies were conducted in the presence and absence of metabolic activation. CNE is not expected to be genotoxic. No data are available on the carcinogenicity of CNE.

In the repeated-dose/reproductive/developmental toxicity screening test described above (OECD TG 422), systemic (parental) toxicity was seen at 500 mg/kg-bw/day and higher. Clinical signs of discomfort after test substance administration were seen such as pushing head through bedding material, stretched forelimbs and saltatory spasms. No effects were seen on reproductive organs of either sex in the toxicity groups and the reproductive group females. No effects were seen in the reproductive indices or development of fetuses. Therefore, the NOAEL for maternal, reproductive and developmental toxicity of CNE in the above combined repeated-dose/reproductive/developmental toxicity screening test is 1000 mg/kg-bw/day, the highest dose tested. Based on these results, CNE has not shown any potential for reproductive or developmental toxicity.

Environment

The EPISuite program developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure; therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported below; the estimated values reported here are assigned a reliability code of 4.

The measured melting point of CNE is -140.2 °C and the measured boiling point is 224 °C at 1013 hPa. The extrapolated vapor pressure value from measured data is 0.019 hPa at 20 °C. The estimated log K_{ow} of CNE is 0.315. The estimated Henry law's constant for CNE is 1.12×10^{-7} atm-m³/mole. CNE reacts with water with a measured hydrolysis half life of 6.5 hours at pH 7 and 20 °C; hydrolysis is more rapid in acid and alkaline solutions ($t_{1/2} < 0.5$ hrs at pH 4 and 9 and 20 °C). The estimated water solubility of CNE is 1,000,000 mg/L. The estimated water solubility and log K_{ow} values may not be applicable because the substance is hydrolytically unstable. The hydrolysis products are expected to be ethanol and 3-(trihydroxysilyl)-propanenitrile.

At high concentrations, 3-(trihydroxysilyl)-propanenitrile (and any subsequent hydrolysis products) will condense to form highly cross linked, high molecular weight polymers. Therefore, measured physicochemical properties for 3-(trihydroxysilyl)-propanenitrile are not available. In addition, current estimation models are not capable of calculating physicochemical properties for this type of chemical with any degree of accuracy. Thus, estimated values for 3-(trihydroxysilyl)-propanenitrile are unreliable and not used in this assessment.

Ethanol, the other hydrolysis product, has a measured water solubility and log K_{ow} of $> 10,000$ mg/l at 25 °C and -0.31 at 25 °C, respectively.

The half life of CNE for indirect photooxidation (reaction with OH radicals) is estimated to be 0.9 days. CNE may also hydrolyze when in contact with water vapor, which could result in a more rapid removal from air. The products resulting from the expected CNE hydrolysis in the atmosphere are estimated to further react with hydroxyl radicals. Level III Fugacity modeling, using equal releases to air, soil, and water (loading rates of 1000 kg/h to each medium), shows the following percent distribution of CNE: air = 0.89%, water = 6.69%, soil = 92.4%, and sediment $< 0.1\%$.

Hydrolysis is the dominant transformation process occurring with a half life of 6.5 hours as noted above. Ethanol and 3-(trihydroxysilyl)-propanenitrile are the expected hydrolysis products. Ethanol is readily biodegradable and 3-(trihydroxysilyl)-propanenitrile is not expected to be readily biodegradable. At high concentrations, 3-(trihydroxysilyl)-propanenitrile (and any subsequent hydrolysis products) will condense to form highly cross linked, high molecular weight polymers that are water insoluble and effectively non biodegradable.

Based on the hydrolysis half-life of 6.5 hours of CNE, for the duration of aquatic toxicity tests, the organisms were likely exposed to both CNE and the hydrolysis products, ethanol and 3-(trihydroxysilyl)-propanenitrile. A flow-through 96-h study (OECD TG 203) with CNE for rainbow trout (*Oncorhynchus mykiss*) resulted in $LC_{50} > 110$ mg/L. The 48-h EC_{50} for *Daphnia magna* of CNE was > 100 mg/L under flow-through conditions with measured concentrations (OECD TG 202). The 72-h E_rC_{50} and E_bC_{50} values for green algae (*Pseudokirchneriella subcapitata*) exposed to CNE were > 3.6 mg/L, the highest geometric mean measured concentration tested (nominal concentration of 120 mg/L) (OECD TG 201). The 72-h NOEC based on cell density, area under the growth curve (biomass) and growth rate was 1.8 mg/L.

Exposure

In the Sponsor country (the United States), production volume in 2005 was ca. 454 - 4536 tonnes. In Europe the production volumes were also ca. 454 - 4536 tonnes; there is no production or import in Japan. The percentage of global production from the US was ca.50% in 2005. This material is handled in closed systems (hard piped, as described below) and is not transported from the site of manufacture in the sponsor country and Europe. In production, CNE is used as a key intermediate in the manufacture of other chemicals (organofunctional silanes) that are used as industrial intermediates. The substance is reacted during use and loses its chemical identity. Final industrial products generally contain less than 0.1%, but may contain up to 0.5% CNE.

There are no intentional releases to the environment. Contact with water vapor in air may lead to a loss of the parent material due to hydrolysis.

CNE is produced in closed reactors and transferred by hard piping to storage tanks to exclude moisture until it is intentionally reacted. There is no intentional exposure to CNE during production. However, CNE may be sampled by chemical operators for analysis and both the chemical operator(s) and analytical technician(s) have the potential for dermal and inhalation exposure to CNE during the sampling.

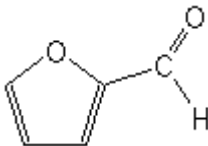
CNE is used as a chemical intermediate. It is not sold to industrial customers and is not shipped from the original point of manufacture. Therefore, consumer use can be excluded.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: This chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (repeated dose toxicity to kidneys and spleen). Based on data presented by the Sponsor country, relating to production in one country (which accounts for ca. 50% of global production) and relating to use pattern in one country, exposure to humans is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: This chemical is currently of low priority for further work based on its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-01-1
Chemical Name	Furfural
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

After oral exposure of rats to ^{14}C -furfural, at least 90% was absorbed in the gastro-intestinal tract. After inhalation exposure of humans, pulmonary retention was 78%. After dermal exposure of humans to liquid furfural, about $3\text{ }\mu\text{g}/\text{cm}^2/\text{min}$ were absorbed. Dermal absorption of humans exposed to furfural vapours is about 30% of the amount absorbed through inhalation.

Distribution of ^{14}C -furfural was studied in rats at 72 hrs after administration of single doses. The highest concentrations were found in liver and kidney and the lowest concentrations were found in the brain.

In rats and mice, the biotransformation of furfural occurs primarily via two routes. The major part is oxidised to furoic acid that is excreted free or conjugated with glycine as furoylglycine. The minor part condenses with acetic acid to form furanacrylic acid that is excreted after conjugation with glycine as furanacryluric acid. Metabolic profiles of these two species were very similar. After oral exposure the urinary metabolite profile was furoylglycine (approx. 80%), furoic acid (2%- 10%), furanacryluric acid 10-35%), furanacrylic acid (2%) and an unidentified very polar metabolite (1-2%). In humans, the main urinary metabolite after inhalation exposure is furoylglycine (120-130% of the amount of furfural retained by inhalation; the excess as compared to inhalation retention was explained by dermal absorption of the vapour). Furanacryluric acid (0.5 – 5%) and negligible amounts of furoic acid are also found. Observed differences in metabolite levels between humans and rodents are most likely due to differences in dose levels (in animals high dose levels may lead to glycine depletion) exposure routes and duration rather than being caused by intrinsic interspecies differences in metabolism.

In animals at 72 hrs post dosing, about 76-100% of the radioactivity was excreted in urine, 2-7% in faeces, 5-7% was exhaled and less than 1% was found in the carcass. Biological half-life of furfural after inhalation in humans is about 2-2.5 hours.

The oral LD_{50} values for rat ranged between 50 and 149 mg/kg bw whereas the oral LD_{50} values for mice and dogs ranged between 400-500 mg/kg and 650-950 mg/kg, respectively. The LD_{50} value for guinea pigs was 541 mg/kg bw. The inhalation LC_{50} for rats after 1-h, 4-h or 6-h exposure was $4075\text{ mg}/\text{m}^3$, $600\text{-}924\text{ mg}/\text{m}^3$, and $688\text{ mg}/\text{m}^3$ respectively, whereas the inhalation LC_{50} for mice was $490\text{ mg}/\text{m}^3$ after 6-h exposure. The dermal LD_{50} of $>310\text{ mg}/\text{kg}$ and $<1000\text{ mg}/\text{kg}$ were reported for rabbits and guinea pigs, respectively. A dermal dose of 620 mg/kg is reported to be lethal to rabbits. Sublethal effects were seen in the livers of rats after a single exposure by gavage of 50 mg/kg bw. The changes consisted of scattered eosinophilic globules and a significant increase in the number of mitotic hepatocytes. No zonal or massive necrosis was observed.

No standard skin and eye irritation studies were available. Intensive but reversible skin irritation was reported in guinea pigs after three daily 4-hour dermal applications of neat liquid furfural. With 5% furfural a very mild reaction was noted, whereas applications of 1% furfural did not produce any signs of irritation. When applied to intact shaved skin for 4 hours on 20 successive days, undiluted furfural resulted in hyperplasia, hyperkeratosis and exfoliation of the epidermis. Still in guinea pigs, similar but less severe effects were observed with 5 and 1% furfural. In a limited study report, undiluted furfural (45-1000 mg/kg bw) was applied to the shaved non-abraded skin of rabbits (occlusive conditions) for 48 hours. After another 48 hours, mild local irritation was observed in the 45-500 mg/kg bw exposure groups. No data were available on the extent (e.g., scores) and reversibility of this irritation. However, in the 1000 mg/kg bw group, all rabbits died within 12 hours, but no evidence of irritation was observed at the site of administration.

In humans, eye and respiratory tract irritation was attributed to furfural vapours which were detected at concentrations ranging from 20 to 63 mg/m³. Eye irritation was manifested by itching, burning, tearing and/or redness and respiratory irritation was manifested by frequent nasal irritation (stuffiness, dryness or soreness) and sometimes dryness of the mouth or throat.

Undiluted liquid furfural was instilled in the eyes of 15 male adult white rabbits. Slight oedema of the conjunctiva was observed after the application of 0.001-0.002 ml. After exposure to 0.04 ml, marked irritation, with eyelid spasm, for about 5 days was reported. The eyes appeared normal on day 7. Application of 0.09-1 ml furfural resulted in eyelid spasm for 7 days with gross corneal opacity. The eyes appeared normal at day 9. Furfural vapour is reported to be irritating to the eyes of rabbits, but no details (e.g., scores) are available.

In a study with two different strains, mice exposed to furfural showed a rapid decrease in respiratory rate with RD₅₀ values of 920 mg/m³ and 1128 mg/m³. In several repeated exposure studies respiratory tract irritation has been observed. Furfural-induced histopathological changes were observed in the nose in hamsters exposed to furfural vapours at concentrations up to 2165 mg/m³ for 6 hours/day, 5 days/week for a period of 13 weeks. The changes consisted of focal atrophy of the olfactory epithelium often accompanied by accumulation of sensory cells in the lamina propria as well as the occurrence of cyst-like structures lined by flat or cuboidal epithelium. The incidence and degree of these changes were clearly dose-related and for these local effects a NOAEL and a LOAEL of 77 and 448 mg/m³, respectively, were determined.

Rabbits were exposed up to 1000 g/m³ by inhalation, for 4 hours/day, 5 days/week, until death (<80 days). At 1000 g/m³/h, rabbits showed signs of irritation of the conjunctiva and the mucosa of the upper respiratory tract. At autopsy, the lungs appeared congested and oedematous. Rats (5 animals/sex/group) were exposed to furfural vapour for 28 days at concentrations up to 1280 mg/m³ for 6 hours/day. Histopathological changes were limited to the nasal passages, consisting of both respiratory epithelial lesions such as squamous metaplasia and atypical hyperplasia, and olfactory epithelial changes characterized by epithelial disarrangement. At the lowest concentrations of 20 and 40 mg/m³, effects were generally limited to the anterior part of the nose (metaplasia and hyperplasia of transitional respiratory epithelium). At higher exposure concentrations (≥80 mg/m³), treatment-related changes of the lining epithelium were also seen in more posterior areas of the nose. Incidence and severity were higher at higher concentrations.

Based on the information above, it is concluded that furfural is irritating to skin, eye and respiratory tract. Furfural is not a skin sensitiser based on Buehler and Maximisation tests, among which a test was conducted according to OECD TG 406.

In repeated dose toxicity studies in rats and mice using the oral route of exposure, NOAELs varied from < 11 – 200 mg/kg bw/day. In the study reporting a NOAEL of <11 mg/kg bw/day, male rats at all dose levels exhibited cytoplasmic vacuolization of hepatocytes in the centrilobular region that is considered treatment related based on the occurrence of mild centrilobular necrosis in male rats in an oral carcinogenicity study with gavage administration. In 16-day repeated dose gavage studies with rats and mice exposed up to 240 mg/kg bw

(rats) and 400 mg/kg bw (mice), increased mortality was observed in both species at the highest dose levels. Surviving animals did not show growth retardation or histopathological changes (tissues not specified), but at 120 mg/kg bw/d in rats a slight reduction in activity was observed. Based on this information for rats a NOAEL of 60 mg/kg bw was derived and for mice a NOAEL of 200 mg/kg bw was set. In a 13-week study with rats, furfural was applied via the diet in a microencapsulated form to prevent volatilisation. The doses used were 0, 26-28, 53-57, 82-86 and 160-170 mg/kg bw/day. Minor hepatocellular alterations were seen in males dosed with 82 and 160 mg/kg bw/day. A NOAEL of 53 mg/kg bw/d was set. The lowest NOAEC derived in inhalation studies was $< 20 \text{ mg/m}^3$ for local effects that included metaplasia and hyperplasia of transitional respiratory epithelium in the anterior part of the nose of the rat. The lowest NOAEC for systemic effects was 320 mg/m^3 . No usable dermal repeated dose studies are available.

Furfural has the potential to cause chromosomal aberrations and gene mutations *in vitro*. Furfural does not induce chromosome aberrations and SCEs in bone marrow cells of mice after i.p. treatment. There was limited evidence for chromosomal breaks from a less reliable *in vivo* Comet assay in mice. Furfural was negative in *in vivo* UDS tests with rat and mouse hepatocytes. Orally administered furfural was unable to induce gene mutations in the liver of λ lacZ transgenic mice. Overall, it is concluded based on a weight of evidence approach that furfural is not genotoxic.

It appears that furfural is carcinogenic in animals after oral administration. In 103-week oral gavage studies in rats and mice, furfural was carcinogenic in mice whereas less convincing evidence was found in rats. An increased incidence of hepatocellular adenomas was found in male and female mice at 175 mg/kg bw/d and at the same dose, male mice showed an increased incidence of hepatocellular carcinomas. A low incidence of uncommon cholangiocarcinomas and bile duct dysplasia with fibrosis were observed in male rats dosed with 60 mg/kg bw/d whereas no effects were seen in female rats. It should be noted that in both species, some target organ (liver) toxicity was observed at dose levels below those that induced tumours. No adequate inhalation and dermal exposure carcinogenic studies were available. Co-carcinogenic effects of furfural on the respiratory tract of hamsters were suggested based on a study where hamsters were treated with furfural alone or in combination with benzo(a)pyrene. Similarly, co-carcinogenic effects of furfural were also studied in oral and dermal studies when applied together with 2-acetylaminofluorene or tetradecanoylphorbol-acetate. Although the mode of action underlying the carcinogenic activity of furfural after oral exposure is still unclear, it is apparently not genotoxic. Rather, the tumours appear to be induced via a mechanism involving liver toxicity. The oral NOAEL was set at 53 mg/kg bw/d, which was one of the doses used in a repeated dose dietary study.

No fertility studies were available with furfural. However, no effects were found on the reproductive organs of both male and female F344/N rats and B6C3F1 mice in two-year gavage studies at dose levels up to 60 mg/kg in the rats and up to 175 mg/kg bw in mice. The animals were dosed 5d/wk. The following relevant tissues were examined: epididymis, penis, preputial gland, prostate, seminal vesicles, testes, coagulating gland, clitoral gland, ovaries, uterus, vagina, and tissues from all endocrine glands. In (sub)chronic inhalation exposure studies, hamsters were exposed to furfural at levels up to 2165 mg/m^3 , 6h/d, 5d/wk. The following relevant tissues were examined: testes, prostate and uterus. In these studies no treatment related effects were observed at any dose level on the tissues mentioned. In a developmental toxicity study in rats administered furfural by oral gavage at doses up to 150 mg/kg bw/d for days 6-15 of gestation (OECD TG 414), the NOAEL for developmental effects was $\geq 100 \text{ mg/kg bw/d}$. At the highest dose level, developmental toxicity was not observed, but due to high death rates among the dams, the sensitivity of the study was insufficient. The NOAEL for maternal toxicity was $< 50 \text{ mg/kg bw/day}$ based on exophthalmia during gestation day 6-18 at all dose levels. No treatment-related effects were found at scheduled necropsy in the females. Furfural is not considered to be a reproductive toxicant.

Environment

Furfural is a liquid with a melting point of -36.5 to -39°C and a boiling point of 162°C at 1013 hPa. The vapour pressure of furfural is 1.33-1.73 hPa at 18.5°C , its water solubility is 83 g/l at 20°C and its $\log K_{ow}$ is 0.41.

Furfural reacts rapidly with hydroxyl radicals in the atmosphere; this reaction has an estimated half-life of 0.44 days. Night time destruction of furfural by nitrate radicals may be important in urban areas. Direct photochemical degradation is expected to occur but no data exist for this process. Furfural is not expected to hydrolyse under

environmental conditions. In contrast, furfural is readily biodegradable under both aerobic (93.5% degradation after 28 days in a modified MITI test according to OECD TG 301C) and anaerobic conditions. Volatilisation of furfural from surface waters is not expected to be rapid because Henry law's constant for furfural has been calculated to range from 0.2 Pa.m³/mol to 0.375 Pa.m³/mol. Calculated K_{oc} values range from 1- 40 l/kg (a K_{oc} of 17.1 was calculated using a QSAR for non-hydrophobics). These values suggest that furfural is highly mobile in soil. Furfural may volatilize from soil to the atmosphere but this process is not expected to be rapid. Furfural in the atmosphere can be removed by wet deposition. Based on Level III distribution modelling using EPISUITE (assuming equal and continuous releases to air, water and soil), it is estimated that the majority of furfural released to the environment will partition mainly into soil (53.2%) and water (45.6%) with small amounts to air (1.1%) and sediment (<0.1%). With the SimpleTreat model the distribution of furfural in a Sewage Treatment Plant was simulated, showing that the substance will be degraded for 87% and the remaining part will go to the water compartment (13%). Because of high water solubility and low log K_{ow}, furfural is not expected to bioaccumulate. Calculated BCF for fish and worm are 1.41 l/kg and 0.95 l/kg, respectively.

All available ecotoxicity results were obtained using freshwater species. Short-term LC₅₀ values in fish range from 10.5 to 32 mg/l with *Poecilia reticulata* being the most sensitive species. It is noted that the LC₅₀ value of 10.5 mg/l (measured) for *P. reticulata* was derived from a 14-d prolonged toxicity test, while the other LC₅₀ values for fish (ranging from 16 to 32 mg/l; based on data for four different fish species) were derived from 48-h to 96-h acute toxicity tests. For the invertebrate *Daphnia magna* there are two acute LC₅₀ values, from different studies, being a 24-h LC₅₀ of 29 mg/l (nominal) and a 72-h LC₅₀ of 13 mg/l. Acute toxicity data for aquatic plants are not available. However, NOEC values of 2.7 and 31 mg/l (nominal) were obtained for blue and green algae, respectively, based on 8-day tests. A long-term NOEC of 0.33 mg/l, based on measured test concentrations, was obtained for fish in a 12-day early-life stage toxicity test using embryo and sac-fry stages of the zebrafish. A NOEC of 1.9 mg/l (measured) was obtained for *Daphnia magna* in a 21-day flow-through life-cycle toxicity test. An EC₅₀ value of 760 mg/l was obtained for activated sludge bacteria. NOEC values ranging from 0.59 to 16 mg/l were obtained for microorganisms.

Exposure

Furfural is produced industrially from pentosan polysaccharides that are natural substances in non-food residues and food crops. Furfural is produced in two European Union countries and imported by several EU countries from countries outside the EU. EU production and import for the year 2000 was assessed to be about 41,000 to 44,000 tonnes whereas export was estimated to be 1000 tonnes. The world production of furfural is estimated to be greater than 240,000 tonnes/year.

Furfural has numerous applications. The primary uses are as starting material for the production of derivatives (75% of total use) and use as extraction solvent in refineries (13.5% of total use). Other uses include manufacturing of refractories and pesticides, use as a chemical trace in gas-oil, as a solvent or reactive solvent, wetting agent, biocide, decolourizing agent for wood resin, flavour component in a range of food, fragrance in cosmetic products, reagent in analytical chemistry, in road construction and metal refining.

Furfural may be released to the environment during its manufacture, formulation or use in commercial products. In addition, humans are exposed to furfural because of its ubiquitous natural occurrence in various food sources such as fruits, vegetables, wine, bread and in several essential oils of plants. As an unintentional source, furfural is a major contaminant of the sulfite pulping processes used in the pulp and paper industry. It is also formed as a by-product in the treatment of hemicellulose feed stocks and in the refuse of chemical and fuel production. Furfural may also be released to the environment via the smoke from burning wood and tobacco.

Occupational exposure may occur during production of furfural and during its use in several industries. The routes of exposure for the worker are through inhalation and via dermal contact. Occupational Exposure Limits (OEL values) are available, but not harmonized.

The two most important sources of furfural exposure for the consumer are its use as fragrance material in cosmetic products and its use as flavouring substance in several food categories. Furfural concentrations in cosmetic products are reported up to a maximum of 0.1%. In the European Union, the average maximum use

level of furfural in food categories ranges from 4.2 to 63 mg/kg.

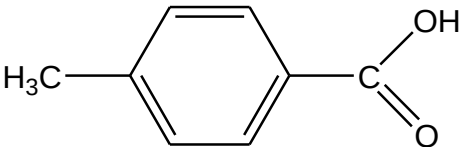
**RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED**

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (acute toxicity, skin, eye and respiratory tract irritation, limited evidence for carcinogenicity). Member countries are invited to perform an exposure assessment for workers, and if necessary, a risk assessment.

Note: A risk assessment performed in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union is available.

Environment: The chemical is currently of low priority for further work. The substance has properties indicating a hazard for the environment (acute toxicity to fish and invertebrates between 10 and 100 mg/l). However, the chemical is of low priority for further work because of its ready biodegradation and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	99-94-5
Chemical Name	<i>p</i> -Toluic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No data are available on the toxicokinetics, metabolism and distribution of *p*-toluic acid.

The oral LD₅₀ values were 2340 mg/kg bw for male and 2484 mg/kg bw for female ICR mice, and 3113 mg/kg bw for male and 2115 mg/kg bw for female Wistar rats. *p*-Toluic acid administered orally caused reversible disturbances (anesthetic action) of the central nervous system, including sedation, decrease in spontaneous locomotion, limb weakness, etc. in both species. Furthermore, *p*-toluic acid caused hemorrhage in the mucosa of the stomach and small intestine under oral administration in both species, suggesting that *p*-toluic acid has a local irritating effect.

No experimental data are available for skin and eye irritation in animals, but it has to be considered as skin and eye irritant according to its acidic properties.

There are no experimental animal data for sensitisation. In humans *p*-toluic acid is skin sensitizing. A cross-sensitivity between all three isomers, *p*-toluic acid, *m*-toluic acid and *o*-toluic acid, was found.

In a repeated dose oral toxicity study in Crj: CD(SD)rats [OECD TG 407], *p*-toluic acid was administered by gavage to male and female rats (5 or 10 animals/sex/group) for 28 days at 0, 100, 300 and 1000 mg/kg bw/day. No deaths were observed in any group. Although a transient salivation and urinary changes in male and female rats and increased food intake in female rats due to the increased water consumption were observed at 1000 mg/kg bw/day, these changes were considered to result from the local irritating effect of *p*-toluic acid and not due to its systemic toxicity. In females, a trend of decreased platelet count and blood protein together with an increase in AST were detected at the dose of 1000 mg/kg bw/day. Based on these findings, the NOAELs for repeated oral dose toxicity in male and female rats were considered to be 1000 and 300 mg/kg bw/day, respectively. In a reproductive and developmental toxicity screening test in Crj: CD(SD) rats [OECD TG 421], *p*-toluic acid was administered by gavage at 0, 100, 300 and 1000 mg/kg bw/day. A decreased body weight gain was found in females at 300 mg/kg bw/day and higher, but not in males at all doses. Histopathological examinations revealed an increased number of cauda epididymal lumen with a decreased number of spermatozoa and slightly increased cell debris in the epididymis at 1000 mg/kg bw/day. Based on these findings, the NOAELs for repeated dose toxicity is considered to be 100 mg/kg bw/day in maternal females and 300 mg/kg bw/day in males. The overall NOAEL for repeated dose toxicity is considered to be 100 mg/kg bw/day in females and 300 mg/kg bw/day in males.

No data are available for the repeated dose inhalation and dermal toxicity of *p*-toluic acid.

A bacterial reverse mutation assay [OECD TG 471] on *p*-toluic acid was negative both with and without metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells [OECD TG 473] was positive under continuous treatment without a decrease in the pH in the absence of metabolic activation. *p*-Toluic acid is considered to be clastogenic *in vitro*. However, the micronucleus assay [OECD TG 474] using CD-1 male mice was negative up to the limit dose of 2000 mg/kg. Although there are no ADME studies, it can be predicted, based on physical chemical considerations and toxicokinetic prediction, that the substance is likely to reach the

target tissue, the bone marrow. Based on these results, *p*-toluic acid is not anticipated to be genotoxic *in vivo*.

No data are available for the carcinogenicity of *p*-toluic acid.

In a reproductive and developmental toxicity screening test in Crj: CD(SD) rats [OECD TG 421], *p*-toluic acid was administered by gavage at 0, 100, 300 or 1000 mg/kg bw/day. A decreased body weight gain was found in females at 300 mg/kg bw/day and higher, but not in males at any dose. Histopathological examinations revealed an increased number of cauda epididymal lumen with a decreased number of spermatozoa and slightly increased cell debris in the epididymis at 1000 mg/kg bw/day and no abnormalities in the testis and ovary. No adverse effects were noted on the estrous cyclicity, precoital interval, copulation index, gestation index, gestation length, or numbers of corpora lutea. There were decreases in the fertility index at 1000 mg/kg bw/day and implantation index at more than 300 mg/kg bw/day. Decreased numbers of pups born at 300 mg/kg bw/day and higher, and of live pups on postnatal days 0 and 4 at 1000 mg/kg bw/day were observed. No changes were found in the sex ratio or body weight of pups. No structural abnormalities of pups were detected in any groups. *p*-Toluic acid causes adverse effects on fertility at doses of 300 mg/kg bw/day and above. These changes are not considered to have occurred as a consequence of maternal toxicity. Based on these findings, the NOAELs were 100 mg/kg bw/day for general toxicity in females, and 100 mg/kg bw/day for reproductive toxicity.

Environment

p-Toluic acid is white to yellow-brown crystal with a melting point of 179.3 °C, a boiling point of 273.9 °C and a vapour pressure of 8.11×10^{-3} Pa at 25 °C. The measured partition coefficient (Log K_{ow}) is 2.44 (neutral form), and water solubility is 349 mg/L at 20 °C. The dissociation constant (pKa) is 4.22 at 20 °C.

A hydrolysis test according to OECD TG 111 showed no hydrolysis at pH4, pH7 and pH9 at 50 °C for 5 days. As pKa is 4.22, *p*-toluic acid mainly exists in its dissociated form in water at environmentally relevant pH values. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 4.21 days. *p*-Toluic acid is readily biodegradable under aerobic conditions with BOD biodegradability of 95 % after 28 days (OECD TG 301C). Bioaccumulation potential is estimated to be low based on the Log K_{ow} of 2.44, which is supported by a calculated BCF value with BCFWIN of 3.16. A Henry law's constant of 1.2×10^{-2} Pa.m³/mole at 25 °C suggests that volatilization of *p*-toluic acid from the water phase is not expected to be high.

Level III fugacity model with equal and continuous distributions to air, water and soil compartments suggests that *p*-toluic acid will distribute mainly to the soil (69.8 %) and water (28.5 %) compartments with minor distribution to the air compartment (1.6 %) and negligible amount in the sediment compartment. This model calculation is conducted based on the assumption that the substance is present in its neutral form in the aqueous compartments. As *p*-toluic acid exists in its dissociated form in aqueous solution at environmentally relevant pH, the amount of *p*-Toluic acid partitioning to the water compartment may be underestimated in these calculations.

Eco-toxicity data of this chemical are available in aquatic species from three trophic levels. GLP tests using a freshwater fish (OECD TG 203, *Oryzias latipes*), daphnids (OECD TG 202, *Daphnia magna*) and green alga (OECD TG 201, *Pseudokirchneriella subcapitata*) have been conducted.

The following acute toxicity values have been determined for aquatic species:

Oryzias latipes; 96 h LC₅₀ = 64 mg/L (measured concentration)

Daphnia magna; 48 h LC₅₀ = 42 mg/L (measured concentration)

Pseudokirchneriella subcapitata; 72 h ErC₅₀ = 74 mg/L (growth rate method, measured concentration)

Pseudokirchneriella subcapitata; 72 h EbC₅₀ = 63 mg/L (area under growth curve method, measured concentration)

The chronic toxicities on daphnids (OECD TG 211, *Daphnia magna*) and on algae (OECD TG 201, *Pseudokirchneriella subcapitata*) are available. The following chronic toxicity values have been

determined for aquatic invertebrates and algae:

Daphnia magna; 21 d NOEC = 3.2 mg/L (measured concentration)

Pseudokirchneriella subcapitata; 72 h NOErC = 46mg/L (growth rate method, measured concentration)

Pseudokirchneriella subcapitata; 72 h NOEbC = 46 mg/L (area under growth curve method, measured concentration)

Exposure

p-Toluic acid is commercially produced with an annual production volume of 100 – 1000 tonnes in Japan. Worldwide production volume outside Japan is not available. *p*-Toluic acid is mainly produced by the oxidation of *p*-xylene. *p*-Toluic acid is used as an intermediate for photosensitive pigments, fluorescent dyes and colorants.

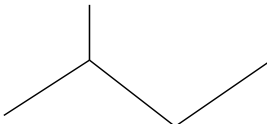
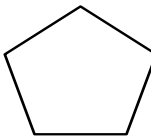
In the sponsor country, *p*-toluic acid is produced and processed in a closed system. Even if a small amount of *p*-toluic acid is released into the waste-water stream at production/processing sites, the waste water stream is treated in the waste-water treatment plant. Furthermore, as *p*-toluic acid is readily biodegradable, emission of *p*-toluic acid from the production and processing sites into the environment is anticipated to be very low in the sponsor country. No monitoring data from production and processing sites are available in the sponsor country. Workers are using personal protective equipments to minimize intake. *p*-Toluic acid is used only as an industrial intermediate in the production of photo pigments, dyes and colorants in the sponsor country. Therefore, consumer exposure is considered to be negligible. No other information on consumer exposure is available.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (sensitization and repeated dose and reproductive toxicity). Based on exposure data presented by the Sponsor country (closed system site limited intermediate with no transport globally), relating to production in one country (which accounts for an unknown fraction of the global production) and relating to the use pattern in the sponsor country, exposure to human is expected to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to aquatic organisms between 1 and 100 mg/L). However the chemical is readily biodegradable and has limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category:	C ₅ Aliphatic Hydrocarbon Solvents Category		
CAS Numbers and Chemical Names	Substance Name	CAS Number	
	n-Pentane	109-66-0	
	2-Methylbutane (Isopentane)	78-78-4	
	Cyclopentane	287-92-3	
CAS Numbers with Structural Formula	Structural Formula	CAS Number	
	CH₃-CH₂-CH₂-CH₂-CH₃ 	109-66-0	
	CH₃ CH₃-CH-CH₂-CH₃ 	78-78-4	
	CH₂ CH₂-CH₂ CH₂-CH₂ 	287-92-3	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analog Justification

The C₅ Aliphatic Hydrocarbon Solvents Category used n-pentane data which was adopted at SIAM 13. n-Pentane data are used as read across to other category members as needed.

The C₅ Aliphatic Hydrocarbon Solvents Category is composed of a straight chain (n-paraffins or n-alkanes), branched chain (isoparaffins), or cyclic (naphthenes) saturated hydrocarbons. For ecological effects, the category approach is reasonable because the substances in this category have similar physicochemical properties and are considered to be neutral organics. Log K_{ow} and ECOSAR estimated values indicate similar toxicity among the category members which has been supported by measured data. Additionally, the three category members act by a similar mode of action, e.g., nonpolar narcosis.

For mammalian toxicity, toxicokinetics studies support assessment of these substances as a category. Gas uptake studies have been conducted in rats for all three substances. n-Pentane and 2-methylbutane (isopentane) were evaluated in the same inhalation study showing 20% and 8.6% uptake at 2.95 – 14.75 mg/L (1000 - 5000 ppm), respectively. Cyclopentane uptake has also been evaluated in an inhalation study showing a 12% uptake at 2.95 mg/L (1000 ppm). Any unchanged n-, iso, or cyclo-pentane is rapidly eliminated via the exhaled air.

n-Pentane and isopentane are well absorbed, and widely distributed. Absorbed n-pentane and isopentane are similarly oxidized to the corresponding alcohol with subsequent conjugation primarily as a glucuronide. Excretion of the glucuronides is expected to be via the urine. There is no information on the toxicokinetics of cyclopentane; however, information from the structural analog, cyclohexane, indicates that it is oxidized to cyclohexanol. Conjugation and excretion of cyclohexanol is identical to n-pentane and isopentane. There is no evidence that cyclohexane is ring-opened and it is expected that the toxicokinetics of cyclopentane and cyclohexane are similar. Therefore, the information on the reproductive toxicity of cyclohexane is used in this assessment to fill the data gap for cyclopentane reproductive toxicity.

Commercial grade cyclopentane, consists of 80 – 85% cyclopentane; the remaining components are n-pentane (3 – 5%) and 2,2-dimethylbutane (10 – 15%). Data from pure and commercial grade cyclopentane

have been generated and reported in this dossier.

Human Health

Acute oral toxicity studies for n-pentane and cyclopentane show LD₅₀ values greater than 2000 mg/kg-bw and 5000 mg/kg-bw, respectively. However, based on the values of kinematic viscosity of n-pentane (3.58 x 10⁻⁷ m²/s), n-pentane is considered an aspiration hazard as it may cause lung damage if swallowed. Acute inhalation toxicity data in male and female rats for n-pentane, 2-methylbutane (isopentane) and cyclopentane show LC₅₀ values of greater than approximately 18 mg/L (6,106 ppm), 12.5 mg/L (4,094 ppm) and greater than 5.6 mg/L (1,960 ppm), respectively. At high air concentrations, all of these substances have the potential to cause anesthetic effects. Acute dermal toxicity data for n-pentane in rabbits show an LD₅₀ value of 3000 mg/kg bw. These chemicals are highly volatile and inhalation is the primary route of exposure.

The results of irritation studies indicate that the category members are slightly irritating to the skin and are minimally irritating to the eyes. n-Pentane, isopentane, and commercial grade cyclopentane (80 - 85%) are not respiratory irritants in mice. If these substances are in the compressed liquefied form and come into contact with the skin, they can cause freeze burns. Neither n-Pentane nor isopentane were found to be sensitizing to the skin of guinea pigs.

In a 90-day inhalation study in rats with n-pentane at exposure concentrations ranging from 5 - 20 mg/L (1694 - 6777 ppm), no effects were seen resulting in the determination of a NOAEC of 20 mg/L (6660 ppm). In a four week oral screening study designed to evaluate the nephrotoxicity of n-pentane, no histopathological changes were noted in the kidneys in rats exposed up to 2000 mg/kg bw/day. However, mortality was reported at 500 mg/kg bw/day (2/10) and at 2000 mg/kg bw/day (4/10). In a 16 week study in rats evaluating the neurobehavioral effects of n-pentane, none were observed after exposure to 8.85 mg/L (3000 ppm). In a 28-day inhalation study with cyclopentane, slight hematological changes (decreased erythrocyte count, decreased mean corpuscular hemoglobin and increased mean corpuscular volume) were observed only in male rats and were the only effect observed at the highest dose of 5.3 mg/L (1793 ppm). These effects were not present after the 2-week post-exposure recovery period. The NOAEC and LOAEC values for males were 1.12 mg/L (380 ppm) and 5.3 mg/L (1793 ppm), respectively and the NOAEC for females was 5.3 mg/L (1793 ppm), the highest dose tested. A subsequent 13-week repeat-dose inhalation study in rats at cyclopentane concentrations up to 30 mg/L (10,200 ppm), showed no effects on hematology or other clinical parameters including neurofunctional observations, clinical chemistry, and ophthalmology. Since the hematological changes were reversible in the first study and absent in the second study of 13-week duration, they were not considered relevant.

The studies that reported CNS effects were conducted prior to OECD guidelines and GLPs and were conducted at levels that exceed the minimum fire hazard concentrations (14,000 ppm and above). Studies conducted below these levels did not show CNS effects.

Cyclopentane and isopentane showed negative results in the standard Ames assays. In a mouse lymphoma gene mutation assay (OECD TG 476), cyclopentane showed an increase in mutation frequency in the absence of metabolic activation. Cyclopentane also showed a statistically significant increase in chromosome aberrations without activation in an *in vitro* test using human lymphocytes. However, via the inhalation route, cyclopentane did not induce chromosomal aberrations *in vivo* up to 10,000 ppm. Mixed results were seen for n-pentane in a chromosomal aberration assay in Chinese Hamster Ovary cells. However, an *in vivo* bone marrow micronucleus test for inhaled n-pentane, did not show any clastogenicity when tested up to 20 mg/L (6777 ppm). Weight-of evidence evaluation indicates that there is a minimal concern for genotoxicity.

No reproductive (one- or two-generation) toxicity studies were available for category members. In a 13-week subchronic inhalation toxicity study of n-pentane up to 20 mg/L (6777 ppm), the toxic effects on the reproductive organs in male and female rats were evaluated. At termination of the study, no statistical differences in the mean absolute weights for epididymis, seminal vesicles, prostate, testes or ovaries and uterus were noted between control and exposed animals of either sex. Furthermore, no microscopic changes were observed that were considered related to the exposure to n-pentane. In the two-generation reproductive toxicity study in rats, no effects were seen on reproductive parameters when cyclohexane (analog) was administered via inhalation up to 7000 ppm (24,080 mg/m³). Based on these results,, the category substances are not considered to be reproductive toxicants.

In a developmental toxicity study, orally administered n-pentane did not result in maternal and developmental toxicity at the highest dose tested, 1,000 mg/kg-bw/day, which was determined as the NOAEL. There were no statistically-significant differences in mean body weight, body weight change, uterine weight, corrected body weight, or uterine implantation data between treated and control dams. Additionally, there was no mortality observed, and no adverse clinical/post-mortem signs which were considered treatment-related. There was no evidence of growth retardation or increased fetal death in the treated group compared to controls. No statistically significant differences in total or individual fetal variations or malformations (external, visceral, or skeletal) were noted in the treated group compared to

controls. Based on these results,, the category substances are not considered to be developmental toxicants.

Studies that evaluate carcinogenicity were not available.

Environment

The members of the C₅ Aliphatic Hydrocarbon Solvents Category are liquids at room temperature. The melting point values range from -159.9 to -94.4°C (isopentane to cyclopentane). The boiling points range from 27.9 to 49.3°C. The vapor pressure values are 685, 918, and 424 hPa at 25°C for n-pentane, isopentane, and cyclopentane, respectively. Water solubility values range from 38.5 to 156 mg/L with a relative density range of 0.620 to 0.746 g/cm³. The log K_{ow} values for the category members are 3.39, 2.72, and 3.00 for n-pentane, isopentane, and cyclopentane, respectively.

Members of the C₅ Aliphatic Hydrocarbon Solvents Category have the potential to rapidly volatilize from surface waters, based on Henry's Law constants (HLC) that range from 19,064 to 138,564 Pa·m³/mole. In the air, category members have the potential to degrade through indirect photolytic processes mediated primarily by hydroxyl radicals (•OH) with calculated degradation half-lives ranging from 28 to 32 hours or 2.4 to 2.7 days, based on a 12-hr day and a •OH concentration of 1.5 x 10⁶ •OH/cm³.

Category members have no functional groups that are subject to hydrolysis or degrade in water at room temperature and neutral pH. These saturated hydrocarbons are stable in water under these conditions.

Two category members, n-pentane and isopentane, are readily biodegradable. In comparison, cyclopentane is not readily biodegradable, but was found to be inherently biodegradable.

A potential to bioaccumulate for category members is not likely, based on calculated BCF values that range from 25 to 81 (log BCF = 1.4 to 1.9). Results of Mackay Level I distribution modeling at steady state show that category members will partition to the air compartment (99.95 to 100%). Mackay Level III modeling indicates that category members partition primarily to the air (20.3 to 39.1%) and water (57.9 to 73.6%) compartments and slightly to soil (1.6 to 3.9%) and sediment (0.2 to 2.2%) compartments when an equal emission rate (1,000 kg/hr) to the air, water, and soil compartments is assumed.

A category member, n-pentane, demonstrated a measured fish 96-hour LC₅₀ of 4.26 mg/L. The three category members exhibited measured 48-hour EC₅₀ values for aquatic invertebrates between approximately 2 to 11 mg/L. The algal 72-hour EC₅₀ value was 7.5 mg/L for growth rate, which was measured for n-pentane. This study also provided a 72-hour EC₅₀ value of 10.7 mg/L for biomass. Calculated toxicity values for these endpoints for all category members range from approximately 2 to 13 mg/L, which is consistent with the measured data range of approximately 2 to 11 mg/L.

Use/Exposure

C₅ aliphatic hydrocarbon solvents are derived from petrochemical process streams refined out of natural gas and crude oil. In the U.S. in 2002, domestic production and importation totals for n-pentane and isopentane were reported at > billion pounds each and >1 to 10 million pounds (>454 to 4,535.92 metric tons) for cyclopentane, though it's unclear how much of that production was as a constituent or by-product in streams. There are several manufacturing facilities in the U.S. that produce neat n-pentane, isopentane, and cyclopentane with total production of approximately 50 to 100 million pounds (22,680 to 45,359 metric tons) for all three chemicals.

n-Pentane is used in consumer products such as spot lifters/cleaners (at concentrations <20.0%) and foaming shave gels (at concentrations of 1.0 to 5.0%) and in commercial products such as a blowing agent (at concentrations of 5.0%) for expanded polystyrene (foam) insulation. It may also be used as a solvent (in pure form) in laboratory, chemical analysis, and other settings where a highly volatile non-polar solvent is needed.

Isopentane is used in consumer products such as foaming shave gels (at concentrations of 1.0 to 5.0%) and in commercial products such as a blowing agent (at concentrations of 2.5%) for expanded polystyrene (foam) insulation. It may also be used as a solvent (in pure form) in laboratory and chemical analysis. It is also used as a chemical intermediate in the manufacture of chlorinated derivatives and the production of amyl-naphthalene and isoprene.

Cyclopentane is used as a solvent and a laboratory reagent. Commercially, cyclopentane has been used in the manufacture of insecticides and in the pharmaceutical industry for the manufacture of a variety of analgesics, sedatives, hypnotics, antitumor agents, central nervous system depressants, and prostaglandins.

Pentanes (n-, iso-, cyclo-) are also frequently constituents of gasoline streams. The sources for potential environmental exposure to C₅ aliphatics could include releases from chemical and petroleum manufacturing/processing facilities, releases from manufacturing facilities that use C₅ aliphatics, releases from consumer products that include C₅ aliphatics, and possibly biogenic and combustion sources (biomass, automobile emissions, fires, etc.). The International Hydrocarbon Solvent Consortium collected industrial

hygiene samples of n-pentane, isopentane, and cyclopentane at three manufacturing facilities from 1996 through 2001. The average concentration reported from this survey was approximately 5.3 mg/m^3 or about 2 ppm, with a range from 0 to 74 mg/m^3 (0 to 25 ppm). These results are well below the current ACGIH TLV of 600 ppm (8-hr TWA) and the U.S. Occupational Safety and Health Administration permissible exposure limit of 1,000 ppm. There is also a published review of occupational hydrocarbon solvent exposure studies over a period from the 1960s through 1997. Two papers with data on exposure to pentane in the solvent-use industries reported a total sample population of 203, with a mean 8-hr TWA exposure of 32 mg/m^3 (11 ppm) and a range of 0 to 567 mg/m^3 (0 to 200 ppm).

Non-occupational exposure to pentanes would most likely come from using consumer products such as foaming shave gels that contain n-pentane and isopentane. Non-occupational exposures have not been quantified but are likely to be low given the generally small amounts used in applications and the short duration of exposure.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

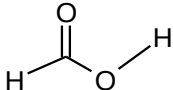
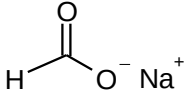
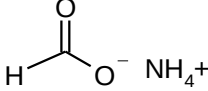
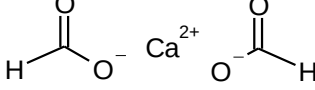
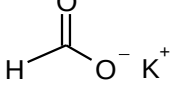
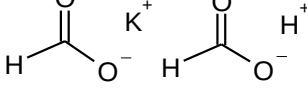
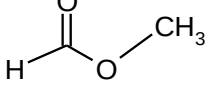
Human Health: The chemicals in this category are of low priority for further work. These chemicals possess properties indicating a hazard for human health (eye and skin irritation (defatting effects), possible lung damage if swallowed). These hazards do not warrant further work as they are related to reversible acute toxicity which may become evident only at high exposure levels.

Environment: The chemicals possess properties indicating a potential hazard for the environment (acute toxicity for fish, invertebrates, and algae between 1 and 100 mg/L).

n-Pentane (CAS No. 109-66-0) and 2-methylbutane (isopentane, CAS No. 78-78-4) are currently of low priority for further work for the environment because of their ready biodegradability and limited potential for bioaccumulation.

Cyclopentane (CAS No. 287-92-3) is not readily biodegradable. Therefore, this chemical is a candidate for further work. Member countries are invited to perform an exposure assessment and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

Chemical category	Formic acid and Formates
Category Members: CAS Registry Numbers and Chemical Names	64-18-6 Formic acid (FoA) 141-53-7 Sodium formate (NaFo) 540-69-2 Ammonium formate (AFo) 544-17-2 Calcium diformate (CaFo) 590-29-4 Potassium formate (KFo) 20642-05-1 Potassium hydrogen diformate (KHFo) 107-31-3 Methyl formate (MeFo)
Category Members: Structural Formulas	64-18-6  141-53-7  540-69-2  544-17-2  590-29-4  20642-05-1  107-31-3 
SUMMARY CONCLUSIONS OF THE SIAR CATEGORY/SUPPORTING CHEMICAL JUSTIFICATION The sponsored Formates Category consists of FoA, five of its salts, and MeFo. The salts dissociate immediately in aqueous and biological surroundings to the formate ion. With a pKa of 3.7, FoA will also exist almost entirely as the formate ion at pH 7. It is therefore expected that the toxicological profiles of the acids and salts will be similar. Ammonium has already been assessed in the OECD HPV Chemicals Programme as ammonium chloride (CAS. 1212-502-9) and the hazard assessment is published:	

[http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=78FA6AC9-ADF3-4A43-894E-7D632A5BFFC3].

MeFo is included in the category for human health because it is enzymatically hydrolyzed to formate. However, it is also biotransformed to methanol and therefore must be treated somewhat differently from the other category members.

For aquatic toxicity endpoints, the category is appropriate for formic acid and its salts because salts dissociate in water to formic acid and counter ions. However, MeFo is handled separately from the other category members for ecological effects because it is an ester and does not dissociate in water with a hydrolysis half life of 67 hours (2.9 days) at pH 7 and 20 °C. Therefore, MeFo is not used to read across to other category members.

Subcategory I: Formic acid and its dissociative salts

FoA is a volatile, strong acid (pH<2) and its acute toxicity and irritation to skin, eyes and respiratory tract is caused by local toxicity. The dissociative salts are less irritating. The category member cations (sodium-, potassium-, potassiumhydrogen-, calcium- and ammonium) are present in the environment and body fluids. They are not likely to influence the toxicity of the formate ion; therefore, reading across is possible among this subcategory.

Neither FoA nor the KH-salt were skin sensitizers; so reading across to the other salts is possible as also none of the cations are known to be skin sensitizers.

Studies on repeated exposure (subchronic to chronic toxicity effects, developmental toxicity and effects on fertility) were predominantly performed on dissociative salts to elucidate the toxicity of the formate ion. Tests with formic acid would obscure this effect due to the caustic nature of the acid. However, evaluation for worker safety requires inhalation toxicity testing of the acid for which data were available. Read across of cations is possible as none of them are known to cause toxic effects after repeated oral exposure or with respect to developmental toxicity or fertility. While data on KHFO were generated in the course of an animal feed additive registration, testing of NaFo was performed to address fertility via the oral route.

In vitro mutagenicity testing requires testing of chemicals at physiological pH values which is routinely done by neutralization in culture mediums containing the dissociative salts as nutritional parameters for the respective bacterial or mammalian cells. As none of the cations is known to be mutagenic, read across between the salts and the acid seems possible. This is also applicable to *in vivo* studies.

Subcategory II: Methylformate

As the methylformate ester does not hydrolyze rapidly in aqueous medium, it is not fully comparable to the dissociative salts. However, as it is effectively, rapidly cleaved by esterases in body fluids and even in nasal tissue as evident in a rat inhalation study with similar local toxicity of the acid and the ester, a subcategory was determined.

Data were available on acute toxicity, irritation (skin, eye and respiratory tract), mutagenicity (Ames Test) and repeated inhalation exposure of MeFo. Data for effects on fertility, developmental toxicity and mutagenicity (mammalian cell systems) from the cleavage products of methylformate, formate and methanol, were bridged. Methanol was evaluated in the OECD SIDS program (SIAM 19).

The availability of valid toxicity permitting read across is summarized as follows.

Endpoint	FoA	Salts ^s	MeFo
Acute toxicity	✓	✓	✓
Skin irritation	✓	✓	✓

Eye irritation	✓	✓	✓
Sensitization	✓	✓	⊗
Repeated toxicity	✓	✓	✓
Development	○	✓	○
Fertility	○	✓	⊗
Genotoxicity			
Bacteria	✓	✓	✓
Mammalian	○	✓	⊗

§ = data for at least one salt available

✓ = valid data available ○ = read across from formates ⊗ = read across from methanol / formates

Local effects: With respect to human health, **local effects** have been observed following contact with FoA based on its acidity. KHFO exhibited eye and respiratory irritation, which is expected because it liberates FoA in aqueous solution; the proportion of FoA would be 35% on a weight basis. MeFo is hydrolyzed by esterases after inhalation (with a half life of 6 seconds at the site of exposure) and causes damage to the upper respiratory tract similar to formic acid.

Systemic effects: Systemic mammalian effects are expected to rely on the formate ion, which is common to FoA and its salts and is one of the breakdown products of MeFo. Therefore, data for the acid and salts are used in this assessment to read across to other category members. The toxicity of the counter ions of the salts is well understood. Sodium, calcium, and potassium occur in body fluids, and the toxicity of simple ammonium salts has been reviewed at previous SIAMs (Ammonium chloride at SIAM 17, and Ammonium sulfate at SIAM 19). As noted above, **the mammalian toxicity of MeFo** is also related to methanol, which is formed in equimolar amounts with formate. Therefore, as support for MeFo, methanol (CAS No. 67-56-1) data (approved at SIAM 19) are included for repeated-dose, chromosomal aberrations, and reproductive/developmental toxicity endpoints.

HUMAN HEALTH

Toxicokinetics, Metabolism, and Distribution: Formate is the common metabolite of all category chemicals. Formate is formed from precursors in the intermediary metabolism and is used as an important constituent of the C₁ intermediary metabolism which is required for the biosynthesis of amino acids and nucleic acid bases (purines and pyrimidines). Formate may also be formed from ingested methanol via formaldehyde and further oxidation to formate. Pharmacokinetic models have been established from methanol inhalation studies which allow calculating the time course of all metabolites including formate in good correlation with animal studies. Peak plasma formate levels were reached within 1 hour (rabbits) and 4-5 hours (pigs) after oral administration of KHFO. The elimination from blood follows first order kinetics and the blood levels rapidly return to background levels in all species, i.e. formate does not persist or accumulate. However, there are significant species differences in the elimination rates and the elimination half-lives (from plasma): rat (12 minutes) < guinea pig (22 minutes) < rabbit (32 minutes) < humans (45 minutes) < cat (67 minutes) < dog (77 minutes) < pig (87 minutes). This reflects the species differences in the hepatic concentrations of folates and folate-dependent enzymes which affect the formate degradation to CO₂. Only minor quantities are excreted unchanged via urine in all species.

All category members may be absorbed via the oral route. FoA and MeFo may generate vapors that can be taken up by inhalation.

Subcategory I: Formic acid and its dissociative salts

Acute Toxicity

The acute **inhalation** 4-h LC₅₀ value for **FoA** vapor in rats was 7.4 mg/L in a study conducted comparable to OECD TG 403. Clinical signs in all treated groups included closed eyelids, discharge and corrosion of the nose and eye, salivation, corneal opacity, loss of pain reflex, dyspnea, noisy breathing, apathy, hunched posture, unsteady gait, and decreased body weight. Dead animals had dilated and hyperemic hearts and inflated lungs.

An LC₅₀ of > 5.16 mg/L was determined for **KHFO** in a study conducted according to OECD TG 403. Clinical signs included strongly decreased breathing rates in all rats throughout exposure, piloerection, moderate sluggishness in all animals, rales, and blepharospasms. Lower body weight gain and changes in lungs (bleeding/discoloration) and intestines were seen.

An LC₅₀ of > 0.67 mg/L for **NaFo** in a study similar to OECD TG 403 was associated with decreased activity and eye closing, lacrimation and nasal discharge, and a slight and transient reduction in body weight gain.

FoA was not tested for **dermal toxicity** due to its caustic nature (pH < 2). An LD₅₀ of > 2000 mg/kg bw was obtained following 24-hour dermal exposure of rats to **NaFo** under semi-occlusive conditions (OECD TG 402). No mortality, clinical signs of toxicity, skin reactions or effects on body weight were noted. No changes in any organs were noted during necropsy.

The acute **oral** LD₅₀ of **FoA** in the rat was 730 mg/kg bw (OECD TG 401). Severe clinical signs were noted approximately 30 minutes after dosing and included hunched posture, dyspnea, bloody nose and blood in urine. Gross pathology revealed hyperemia of the stomach and mottled livers and kidneys. An LD₅₀ of > 2000 mg/kg bw in rats was determined for **AFo** in an OECD TG 423 study. No deaths occurred. Piloerection and hunched posture were seen immediately following dosing without pathological changes at termination. An LD₅₀ of 3050 mg/kg bw was determined for **CaFo** in a study that was similar to OECD TG 401; clinical signs included sedation, increased diuresis, and reduced general state. An LD₅₀ > 2000 mg/kg bw in rats was determined for **KHFO** in an OECD TG 401 study; clinical signs included lethargy, piloerection and tachypnea.

Studies using rats were not available for **NaFo** or **KFo**, but mouse LD₅₀s were 11200 mg/kg bw and 5500 mg/kg bw, respectively.

Overall, category members exhibit low acute toxicity via inhalation, dermal and oral routes.

Irritation/Sensitisation

No animal studies were available for **skin irritation** for **FoA**. However, in agreement with the low pH (<2), it is known that **FoA** is corrosive to the skin and gastro-intestinal tract in humans. **CaFo** (OECD TG 404) and **KHFO** (OECD TG 404) were not irritating to the skin.

FoA is assumed to be corrosive to the **eyes** due to its inherent properties as a strong acid and does not require testing. **NaFo** caused transient irritation of the rabbit's eye conjunctivae in a study that was conducted according to US EPA OTS guidelines. **CaFo** caused irritation to the rabbit's eye which was reversible within 13 days (OECD TG 405). **KHFO** was corrosive to the eyes both as a solid and as a 50 % aqueous solution (OECD TG 405).

FoA showed signs consistent with respiratory tract irritation in acute inhalation toxicity studies (OECD TG 403). **KHFO** caused sensory irritation in the respiratory tract in mice when tested according to Alarie's method.

FoA and **KHFO** were not sensitizing to skin when tested in the Buehler and the Guinea pig maximization tests, respectively, both according to OECD TG 406.

Conclusion: FoA is corrosive to human skin and assumed to be corrosive to eyes (based on strong acidic properties) while the salts of formic acid are neither corrosive nor irritating to skin. NaFo and CaFo showed transient eye irritation while KHFO was corrosive to rabbit eyes. FoA and KHFO showed respiratory tract irritation. The category members FoA and KHFO are not dermal sensitizers.

Repeated-Dose Toxicity

The studies in rodents that are described below must be interpreted with caution because rodents have high tetrahydrofolate and 10-formyl tetrafolate dehydrogenase levels, which allows them to rapidly metabolize formate to CO₂. Humans have much lower levels of this coenzyme and enzyme and therefore, might be more sensitive to formate.

FoA was evaluated in 13-week inhalation studies in rats and mice, and **KHFO** was tested in 13-week and 104-week rat and 80-week mouse dietary studies.

In an OECD TG 413 test, rats were exposed to **FoA** vapor at 0, 0.015, 0.030, 0.062, 0.122, or 0.244 mg/L (0, 8, 16, 32, 64, or 128 ppm) via whole-body inhalation 6 hours/day, 5 days/week for 13 weeks. Increased absolute or relative liver weights and decreased lung weights were seen without histopathological correlation. Irritation of the upper respiratory tract was seen at 128 ppm (0.244 mg/L) along with degeneration of the olfactory epithelium and squamous metaplasia of the respiratory epithelium. The NOAEC and LOAEC were 0.122 mg/(L*d) (i.e. 64 ppm) and 0.244 mg/(L*d) (i.e. 128 ppm) based on respiratory effects.

A 13-week study (OECD TG 413) in B6C3F1 mice with **FoA** using the same protocol and concentration as those used in the rat study, resulted in decreased body weights and increased liver weights in males at all doses. Mild degeneration of the olfactory epithelium was seen at the two highest concentrations. Based on the changes in olfactory epithelium, the NOAEC and LOAEC were determined to be 0.062 mg/(L*d) (32 ppm) and 0.122 mg/(L*d) (64 ppm), respectively.

KHFO was administered to rats in a 13-week oral feed study (OECD TG 408) at 0, 600, 1200, and 3000 mg/kg bw/d, followed by a 4-week recovery period. In males, body weight gain was decreased in a dose-dependent manner. Increased red blood cells, white blood cells, and platelets were seen in males at the highest dose, and additionally several changes in clinical chemistry were observed. Most treatment-related hematological and clinical chemical changes subsided within the recovery period. Adrenal weights were decreased and liver weights increased in both sexes. Thickening of stomach walls was increased in a dose-dependent manner in both sexes. Squamous cell hyperplasia of the forestomach correlated with thickening of stomach walls in all treated groups. Only high-dose animals still showed low incidences of mild hyperplasia at the end of the recovery period. Based on the changes in the stomach, no NOAEL could be established and the LOAEL was 600 mg/kg bw/d.

In a 104-week dietary study comparable to OECD TG 453, **KHFO** was administered to rats, at 0, 50, 400, and 2000 mg/kg bw/d. Body weight was consistently lower at the highest dose, accompanied by slight decreases in food consumption. Urea was increased in high-dose males. Macroscopically, increased incidences of raised foci and thickened walls in the stomachs were seen at 400 mg/kg bw*d and above. Microscopic changes were observed in the stomach, duodenum, salivary glands, and kidney. In the stomach, these changes included basal and squamous cell hyperplasia of the limiting ridge at 400 and 2000 mg/kg bw/d. At 2000 mg/kg bw/d, mild inflammation and foveolar epithelial hyperplasia were seen in the stomach, Brunner's gland hypertrophy was seen in the duodenum, and acinar cell hypertrophy was seen in the salivary gland. Based on the stomach lesions, the NOAEL was 50 mg/kg bw/d, with a LOAEL of 400 mg/kg bw/d.

In a combined oral feed 80-week toxicity and carcinogenicity study in mice, comparable to OECD TG 453, **KHFO** was administered in the diet at 0, 50, 400, and 2,000 mg/kg bw/d. Body weight gain was markedly lower (approx 15%) in the males at the highest dose. At 2000 mg/kg bw/d, mucosal hyperplasia was seen in the stomachs, which was characterized by a minor increase of thickness and folding of the squamous epithelium of the limiting ridge in males, but not in females. Based on these stomach lesions, the NOAEL was 400 mg/kg bw/d and the LOAEL was 2000 mg/kg bw/d.

Conclusion: Inhalation data for FoA and oral (dietary) toxicity data for KHFO are used as read across in this assessment for the other category members. The NOAECs for inhalation studies

with FoA range from 0.062 mg/L/day (mice) to 0.122 mg/L/day (rats) with respiratory tract irritation as the main effect. The three dietary studies of KHFO showed a range for NOAELs of 50 (rat) to 400 (mice) mg/kg-bw/day and a LOAEL range from 400 (rat) to 2000 (mice) mg/kg-bw/day with main effects on body weights and stomach.

Genotoxicity – Gene Mutations

Ames tests (OECD TG 471) performed on FoA (and NaFo, as this is formed whenever FoA is tested in buffers containing Na), CaFo and KHFO, with and without metabolic activation did not induce gene mutations. FoA was also negative in the HGPRT forward mutation test (OECD TG 476) using Chinese hamster ovary (CHO) cells at concentrations up to 500 µg/mL. In an *in vivo* sex-linked recessive lethal test in *Drosophila melanogaster* (similar to OECD TG 477), 0.1% FoA vapor resulted in mutations that were statistically significant. FoA in feed increased mutation frequency (but without statistical significance), and NaFo (in feed neutralized FoA with NaOH) did not induce gene mutations. KHFO was negative for gene mutations in an *in vitro* assay using mouse lymphoma L5178 cells (OECD TG 476) at test concentrations up to and including 1200 µg/mL.

Genotoxicity – Chromosomal Aberrations

In an *in vitro* chromosomal aberration test (OECD TG 473) using Chinese hamster ovary (CHO) cells, FoA induced chromosomal aberrations at concentrations of 10-14 mM (associated with pHs of 6.0 to 6.8) but not at lower concentrations associated with higher pH values. Also, when tested using a buffer, FoA did not induce chromosome aberrations unless the buffer capacity was exceeded (e.g., at FoA concentrations of 25-27.5 mM and pH values of 5.7-6.7).

KHFO was negative for chromosomal aberrations when tested in an *in vitro* assay using human peripheral blood lymphocytes (OECD TG 473) and did not increase percent of micronuclei in an *in vivo* rat bone marrow micronucleus test performed according to an European Economic Community (EEC) Directive (similar to OECD TG 474) when tested at up to 50 mg/kg bw.

Genotoxicity – DNA Effects

FoA did not induce sister chromatid exchange (SCE) in Chinese hamster V79 cells (OECD TG 476) or in human lymphocytes at concentrations lower than 10 mM. However, SCEs were induced by FoA at 10 mM in human lymphocytes.

FoA and its salts were not gene mutagens in bacterial or mammalian cells *in vitro*. There is evidence that FoA may be a chromosome mutagen in mammalian cells *in vitro*, but, due to issues of pH and high dosage levels, the evidence is equivocal. There are data on KHFO that indicate that FoA and its salts were not mutagenic *in vivo* in mammals.

Conclusion: Genetic toxicity data (gene mutation and chromosomal aberrations) for FoA, NaFo and KHFO were negative based on weight of evidence evaluation and can be extrapolated to the other category members.

Carcinogenicity

In oral feed studies comparable to OECD TG 453, KHFO did not show potential for carcinogenicity in mice in an 80-week study or in rats in a 104-week test using doses up to 2,000 mg/kg bw/d. It is unlikely that the other category members would have the potential to exhibit carcinogenicity.

Conclusion: KHFO did not show potential for carcinogenicity in two long-term rodent feed studies. This can be extrapolated to FoA and the other salts.

Reproductive Toxicity

Reproductive organs were examined in rats and mice exposed to FoA at 0, 8, 16, 32, 64, and 128 ppm (0, 0.015, 0.030, 0.061, 0.122, and 0.244 mg/(L*d) in the 13-week studies described above (OECD TG 413). In rats, there were no effects on testicular or epididymal weights, sperm density and sperm motility, or estrous cycles. In mice, sperm motility values were lower at all concentrations, but no dose-response relationship was seen and the values were within the range of historical controls. There were no effects in female mice. The NOAEC was therefore 0.244 mg/L,

the highest concentration used.

Conclusion: No reproductive toxicity data were available on the category members but evaluation of reproductive organs from the repeated-dose toxicity studies in rats and mice showed no effects on reproductive organs. This data can be extrapolated to the other category members.

Developmental Toxicity

In a developmental study, female rats (25/dose, OECD TG 414) were given **NaFo** via oral gavage at 0, 59, 236, and 945 mg/kg bw/d during gestation days 6 to 19. Maternal toxicity was not seen and there were no effects on the developing fetuses. No malformations or skeletal variations were seen. The NOAEL for maternal and developmental toxicity was 945 mg/kg bw/d, the highest dose tested.

In a developmental study (OECD TG 414), rabbits were administered NaFo at 0, 100, 300, and 1000 mg/kg bw/d via oral gavage during gestation days 6 to 28. The following parameters were increased without statistical significance and were in the range of the historical control data (2003-2006) of the same rabbit strain and laboratory: The post-implantation losses of 13.0 and 13.9% at 300 and 1000 mg/kg bw/d, respectively compared with 7.3% in controls (range of historical control: 5.8 – 50%); the total external, skeletal, and soft tissue malformations were 6.7% at 1000 mg/kg bw/d compared with 3.8% in controls (range of historical control 1.1 – 8.7 %). The incidence of total variations (external, skeletal, and soft tissue) was 66.1 to 67.2% in treatment groups compared with 58.0% in controls (range of historical control 55.9 – 85.1%). The NOAEL for maternal toxicity and prenatal developmental toxicity was determined to be 1000 mg/kg bw/d, the highest dose tested.

The effect of **KHFO** on breeding sows was examined in 27 female pigs exposed to 0, 1.2, and 3.6% KHFO in feed (approximately 0, 140, and 430 mg/kg bw/d; group sizes of 7 – 8 pigs) at day 28 before the first mating and extended through two breeding periods until weaning of the second breed. Total exposure period was > 300 days. The study design was not comparable to an OECD method. The NOAEL for maternal toxicity and reproductive effects was 430 mg/kg bw/d, the highest dose tested.

In a non-guideline reproductive/developmental study, 42 female pigs were mated and administered 0, 1.2, 3, or 6 % KHFO in feed (equivalent to 0, 157, 384, or 753 mg/kg bw/d during gestation. The sows received the test diets for more than 150 days, from acquisition through gestation and lactation until weaning. No maternal, reproductive, or developmental toxicity was seen and the NOAEL was determined to be 753 mg/kg bw/d (the highest dose tested).

Supporting information is available from several non-guideline studies. No toxicity for reproduction and development was seen in two multi-generation studies using Wistar rats receiving **CaFo** at 0.2% in drinking water (approx. 150-200 mg/kg bw/d) in one study and 0.4% (approx. 300-400 mg/kg bw/d) in a second study, although details from these studies were limited.

Conclusion: Developmental toxicity studies for NaFo in rats and rabbits showed no effects on the developing fetuses with NOAEL values of 945 and 1000 mg/kg-bw/day, respectively. These data can be extrapolated to the other category members.

Subcategory II: Methyl Formate

Acute Toxicity

A 4-hr **inhalation** LC₅₀ of 35 mg/L was obtained for MeFo in an OECD TG 403 study with rats. At the lowest dose (25 mg/L), animals exhibited gasping. Additional signs at higher concentrations included poor coordination, prostration, lacrimation, salivation, lung congestion with some scattered hemorrhages and fluid. In other acute inhalation studies using MeFo, animals exhibited forced breathing and heart dilatation and myodegeneration. Mortality was 100% within minutes when rats were exposed to saturated atmospheres of either FoA or MeFo.

In two separate studies for MeFo, **oral** LD₅₀ values in rats were 1382 and 1500 mg/kg bw (similar to OECD TG 401). Animals showed signs of sluggish, heavy breathing/gasping, hemorrhages in the lungs, and discolored/mottled livers, spleens, kidneys, stomachs and intestines. Other signs included

difficulty breathing, apathy, unsteady gait, and corrosion of intestines or gastritis in the stomach.

The acute dermal LD₅₀ of **MeFo** in rabbits was > 15,680 mg/kg bw with no clinical signs reported (study similar to OECD TG 402).

Conclusion: Acute toxicity of MeFo is low via inhalation and oral routes.

Irritation/Sensitisation

MeFo was slightly irritating under 24-hour occlusive skin contact (similar to OECD TG 404 except for prolonged occlusive skin contact). **MeFo** was irritating to the eyes of rabbits (method according to US Federal Register guidelines). Sensitization data on **MeFo** were not located. **MeFo** showed signs consistent with respiratory tract irritation in acute inhalation toxicity studies (OECD TG 403).

Conclusion: Acute toxicity of MeFo was low via inhalation and moderate via oral route. Methyl formate was slightly irritating to rabbit skin and irritating to rabbit eyes. MeFo showed signs of respiratory tract irritation in an acute inhalation toxicity study. Sensitization data on MeFo were not located.

Repeated-Dose Toxicity

Methyl Formate

Repeated dose toxicity data on MeFo were restricted to an inhalation study where MeFo was administered as a vapor to Wistar rats at concentrations of 0, 100, 500, or 1500 ppm (0, 0.252, 1.237, or 3.693 mg/(L*d)) for 2 weeks, 6 h/day, 5 days/week (OECD TG 412). Terminal body weights were markedly decreased in both sexes at the highest concentration. Changes in several organ weights were observed (liver, lung, kidneys, and spleen) at the highest concentration. In addition, histopathological changes in the nasal epithelium, squamoid metaplasia, and infiltration of inflammatory cells into the respiratory tract were observed at the middle and highest concentration in a dose-related manner. Based on respiratory tract changes and effects on body weight and organ weights, the NOAEC and LOAEC for local and systemic effects were 0.252 mg/(L*d) and 1.237 mg/(L*d), respectively.

Methanol (Supporting chemical)

Data were available for the supporting chemical methanol from 20-day and 29-month inhalation studies in monkeys, 12-month studies in rats and mice and a 13-week gavage test in rats. No dermal studies were available. It should be noted that NOAEC/NOAEL values from rodent studies must be interpreted with caution because of the rapid metabolism of formate to CO₂ in rodents compared to humans.

In a whole body inhalation study in monkeys exposed to 0, 0.013, 0.13, and 1.3 mg/L methanol was given for 21 hours/day, 7 days/week for 7, 19, and 29 months. Several general clinical signs as well as degenerative effects in the brain (at 0.13 and 1.3 mg/(L*d)), slight peripheral nerve damage (at 0.13 and 1.3 mg/(L*d)), very slight degeneration of the optic nerve (concentrations not noted), increased fat granules and slight fibrosis in the liver (all concentrations), and Sudan positive granules in the kidney (at 0.13 and 1.3 mg/(L*d)) were observed. Also, a slight myocardial disorder (at 0.13 and 1.3 mg/(L*d)), localized effects in the trachea and possible slight fibrosis in the lungs (concentrations not noted) were observed. Although the statistical significance of the effects cannot be verified from the study report, the number of effects and systems affected indicate a relationship with methanol.

In another whole body inhalation study in monkeys exposed up to 20 days for 21 hours/day, coma and lethality were observed at concentrations > 9.1 mg methanol/(L*d). At 6.5 mg/(L*d), necrosis of the basal ganglia plus cerebral edema were observed in the brain and fibrosis was seen in the liver. Partly vacuolated hyaline degeneration in the kidney was also seen at this concentration. At 3.9 mg/(L*d), hyperplasia and fibrosis around myelin sheaths of the basal ganglia, increases in astroglia cells and mild fatty liver were observed. The optic nerve showed atrophy at 3.9 mg/(L*d) and above, along with reduction in myelin fibers.

In a whole body inhalation study in mice exposed for 12 months to concentrations of 0, 0.013, 0.13, and 1.3 mg methanol/(L*d) 20 hours/day, slight changes in clinical signs, body and organ weights, and some changes in histopathology were observed. In rats exposed in the same manner, slight changes in body weight and organ weights were observed at the highest concentration. The NOEC was 0.13 mg/(L*d). In rats, gavage doses of 100, 500, and 2,500 mg/kg bw/d for 90 days resulted in increased liver enzymes and reduced brain weights at the highest dose resulting in determining a NOAEL of 500 mg methanol/kg bw/d.

Conclusion: The NOAEC for inhalation studies with MeFo was 0.252 mg/L/day (rat) with a LOAEC of 1.237 mg/L/day based on respiratory tract irritation as the main effect.

Genotoxicity – Gene Mutations

Methyl Formate

MeFo did not induce gene mutations in an Ames test (OECD TG 471), with and without metabolic activation.

Methanol (Supporting chemical)

Data on methanol (supporting substance) were used for the chromosomal aberrations endpoint. Of four *in vitro* micronucleus and cytogenetic assays and ten *in vivo* micronucleus and cytogenicity assays, all were negative for chromosomal aberrations except one cytogenetic assay, which was positive for aneuploidy, sister chromatid exchange, and micronuclei. Thus, most studies indicate that methanol does not have the potential to induce chromosomal aberrations.

Conclusion: MeFo did not induce gene mutations in bacteria. Weight of evidence evaluation indicates that methanol (supporting substance) does not have the potential to induce chromosomal aberrations. MeFo is therefore unlikely to be genotoxic.

Carcinogenicity

Methyl Formate

No data.

Methanol (Supporting chemical)

There was no evidence of a carcinogenic potential when methanol was tested in two valid long-term whole body inhalation studies in rats (24 months) and mice (18 months) at exposure concentrations up to 1.3 mg/L, 19 or 20 hours per day.

Conclusion: MeFo is unlikely to have a potential for carcinogenicity, based on the negative results obtained for methanol.

Reproductive Toxicity

Methyl Formate

No data.

Methanol (Supporting chemical)

Reproductive and developmental toxicity studies were available for **methanol** (supporting substance for methyl formate) in monkeys, rats, and mice. Methanol was evaluated in the OECD SIDS program (SIAM 19).

In monkeys, parents were exposed via inhalation prior to and during breeding as well as during pregnancy to concentrations of 0, 0.26, 0.78, and 2.34 mg/(L*d). A late wasting syndrome was observed at the highest dose in 2/7 female offspring, with signs of severe malnutrition and gastroenteritis. Mild neurobehavioral effects in offspring and some vaginal bleeding in mothers were seen at all concentrations; an association with the test substance was difficult to establish.

Several inhalation studies in rats resulted in a variety of effects in offspring due to prenatal and/or postnatal dosing. In a 2-generation whole body inhalation reproductive study in which rats were exposed for 19-20 hours/day, decreased brain weights in the first and second generation offspring (F1, F2) resulted in a NOAEC of 0.13 mg/(L*d).

In a study of reproductive effects in mice, there were no treatment-related effects after oral dosing up to 1000 mg/kg bw/d for five weeks.

Developmental Toxicity

Methyl Formate

No data.

Methanol (Supporting chemical)

In a developmental study rats were exposed by whole body inhalation on gestation days 1 to 19 at the two lowest concentrations of 6.63 mg/L and 13.3 mg/L and on days 7 to 15 at the highest concentration of 26.6 mg/L for 7 hours/day. Malformations and fetal weight changes resulted in a NOAEC of 6.5 mg/(L*d). In a second whole-body rat inhalation developmental study (gestation days 7 to 17 for 23 hours/day), malformations, increased fetal resorptions, and fewer live fetuses were observed, resulting in a NOAEC of 1.3 mg/(L*d).

A developmental whole body inhalation study in mice exposed on gestation days 6 to 15 for 7 hrs/day resulted in increased exencephaly and cleft palate, fully resorbed fetuses, decreased numbers of live pups, and decreased body weights, with a NOAEC of 1.3 mg/(L*d). Oral studies in mice resulted in malformations at 4000 mg/kg bw/d (the LOAEL) and higher; no NOAELs could be established from these studies.

Blood methanol concentrations associated with serious teratogenic effects and reproductive toxicity observed in the rodent studies were in the range of 1000 – 2000 mg methanol/L blood, which is associated with formate accumulation in humans, and can result in metabolic acidosis and clinical signs. Also humans have exhibited transient central nervous system (CNS) effects at blood methanol levels above 200 mg/L and impairment of vision at levels above 500 mg/L. Fatalities have occurred in untreated patients with initial methanol concentrations in the range of 1500-2000 mg/L.

Conclusion: In the absence of data on MeFo, read across of the data on the salts and methanol was used. Via the oral route, the NOAEL of NaFo was 945 mg/kg bw/day in rat and rabbit developmental toxicity studies, and the LOAEL for methanol was 4000 mg/kg bw/day in oral studies using mice.

The inhalation NOAEC for methanol was 1.3 mg/(L*d) in studies using rats and mice. A conservative NOAEC for MeFo can be estimated to be 2.44 mg/(L*d) if one assumes that all the methyl formate is hydrolysed to methanol (one mole of MeFo gives one mole of formate and one mole of methanol), and that the toxicity of MeFo is dominated by methanol.

NTP concluded that rodent data on reproductive and developmental toxicity of methanol are relevant for humans despite the known differences in methanol metabolism between rodents and humans. Rodents are adequate models for human exposure to methanol at levels where formate does not accumulate. However, blood methanol concentrations associated with serious teratogenic effects and reproductive toxicity are in the range associated with formate accumulation, which is likely to result in metabolic acidosis, and visual and clinical effects in humans. Other effects (e.g., subtle, not yet definitive neurological effects observed in primates) may be exhibited at lower inhalation doses and lower methanol blood levels.

ENVIRONMENT

Subcategory I: Formic acid and its dissociative salts

At room temperature FoA is a colorless liquid. The salts NaFo, AFo, CaFo, KFo, and KHFo are white or colorless solids. The melting point of the pure FoA is 4 °C. The salts have melting points

ranging from 108.4 °C (KHfO) to > 300 °C (CaFo). The boiling point for pure FoA is 100.2 °C. The corresponding boiling points of the salts range from > 130 °C to > 350 °C with indication for decomposition. The relative densities of the category members at ambient temperature vary between 1.22 (FoA, 20 °C, liquid) and 2.015 (CaFo, solid). The category members are all miscible in water with solubility ranging from 144 g/L (CaFo) to 972 g/L (NaFo). The pure FoA is semi-volatile with a vapor pressure of 42.7 hPa at 20 °C. The Henry's Law Constant (HLC) for pure FoA is 0.014 Pa·m³/mol at 20 °C. The salts have low to negligible vapor pressures and HLC values, which will be enhanced in aqueous solution due to dissociation to formate and the counter ions. The low log K_{ow} values of < 0 and the calculated BCF values of 3.2 show low potential for bioaccumulation for all category members. The dissociation constant (pKa) of pure FoA was experimentally determined to be 3.70 at 20 °C. Compared to the pure substance, formic acid in aqueous solution shows some different physico-chemical properties. For an 85% solution, the melting point is -50.8 °C, the boiling point is 107.3 °C at 1013 hPa and the vapor pressure at 20 °C is 24.2 hPa.

In the atmosphere, **FoA** will be photodegraded by reactions with OH radicals with a half-life of 36 days. **FoA** will not undergo hydrolysis at pH 4, 7, or 9. The same refers to the salts, where the formate anion and the corresponding cations are hydrolytically stable.

The category members can generally be regarded as **readily biodegradable** as demonstrated in ready biodegradability tests. In two Modified OECD Screening Tests following OECD TG 301E, **FoA** was degraded to 99 and 98 % related to DOC after 11 and 14 days, respectively. More than 75 % of **CaFo** (BOD/ThOD) was degraded after 20 days in a Closed Bottle Test following OECD TG 301D, and 70.5 % of **AFo** (BOD/ThOD) was degraded after 28 days in a Manometric Respirometry Test performed according to OECD TG 301F. Following OECD TG 301D, the biodegradation rate of **KFo** was 82 and 92 % (BOD/ThOD), respectively, each after 28 days.

According to Mackay Level I, the category members are likely to distribute nearly completely into water. Only small amounts of **FoA** (6.5 %) would also distribute to air. Using Mackay Level III, emissions of FoA to air (33 %), water (33 %), and soil (33 %) would lead to equal distributions of ca. 45 % each into water and soil. The next largest amount would be found in air (8 %).

For most category members reliable studies on acute toxicity to fish, *Daphnia* and algae growth inhibition were available.

Tests using **FoA** show EC/LC₅₀ values between 1 and 100 mg/L. These results appear to be due to acidity as demonstrated in the test with *Leuciscus idus*, where a neutralized test solution of 100 mg/L produced no mortality. For the **salts** experimental acute EC/LC₅₀ values were > 100 mg/L.

In a chronic toxicity test following OECD TG 211, *Daphnia magna* was given **FoA** under neutralized conditions; the 21-d NOEC for effects on reproduction was 100 mg/L.

Subcategory II: Methyl Formate

MeFo is a colorless liquid at room temperature. The melting point is at -99.8 °C. The boiling point for pure MeFo is 31.5 °C and the relative density at 20 °C is 0.97. MeFo is volatile with a vapor pressure of 781 hPa (25 °C). It has a HLC of 22.6 Pa·m³/mol at 25 °C. The log K_{ow} value was measured to be 0.03 and the BCF was correspondingly calculated to be 3.2.

In the atmosphere, **MeFo** will be photodegraded by reactions with OH radicals with a half-life of 67 days. **MeFo** was shown to have a hydrolysis half-life of 67 hours at pH 7.0 from an experimentally-derived alkaline hydrolysis rate. **MeFo** was found to be **readily** biodegradable with 93 % degradation after 28 days (TIC/ThIC) in the CO₂-Headspace Test following OECD TG 310.

According to Mackay Level I and due to its volatility, **MeFo** would distribute nearly completely to air (98.1 %). Using Mackay Level III, emissions of MeFo to air (33 %), water (33 %), and soil (33 %) would lead to equal distributions of ca. 45 % each into air and water. The next largest amount would be found in soil (10 %).

For aquatic toxicity, **MeFo** was tested in 96-hour static study with the golden orfe (*Leuciscus idus*), the 96-h LC₅₀ was calculated to be approximately 115 mg/L. The 48-h EC₅₀ for *Daphnia magna* was > 500 mg/L, based on nominal concentrations. Green algae, *Desmodesmus subspicatus*, were exposed to MeFo over 96 hours to nominal concentration, the 72-h EbC₅₀ and ErC₅₀ were 351 and

1063 mg/L, respectively. **MeFo** showed the experimental acute toxicity of EC/LC₅₀ values > 100 mg/L.

EXPOSURE

Subcategory I: Formic acid and its dissociative salts

The annual world production capacity of **FoA** in 2006 was estimated at 450,000 – 600,000 metric tons. Most of the producers are located in the Asia/Pacific region (more than 10 different production sites). Additional sites are in Western Europe (3 sites) and North/South America (1 site).

The total global capacities of the **formates** were estimated at 100,000 – 150,000 (NaFo), 10,000 – 25,000 (each AFo and KHfO), 25,000 – 50,000 (KFo) and 50,000 – 100,000 (CaFo) metric tons. The capacities for CaFo can be subdivided into > 85 % for Europe, approximately 10 % for Asia/Pacific, and < 5 % for North/South America. Most of the big producers are located in Europe (more than 7 different production sites).

Several of the category members are used to manufacture other category members or are byproducts of a manufacturing process. **FoA** is mainly produced by hydrolysis of MeFo but can also be produced using NaFo. **NaFo** and **CaFo** are byproducts in the synthesis of polyols such as pentaerythritol and can be produced directly from the corresponding hydroxide and carbon monoxide. **AFo** can be prepared from FoA and ammonia and can be produced using CaFo. **KHFo** is produced from FoA and KFo.

FoA is used as acidulant and decalcifying agent, for pH-adjustment in cosmetic formulations as well as in dye baths for dyeing of natural and synthetic fibers. Other applications of FoA are as an additive for cleaning agents, in the synthesis of the sweetener aspartame, and in the desulphurization of flue gas. In the EU, FoA has been notified for the Biocidal Products Directive (98/8/EC) and complete dossiers have been submitted in 2007/2008 for registration. A total of 422 preparations containing FoA were registered in 2003 in the Nordic countries Denmark, Finland, Norway, and Sweden. The main amount of FoA (by weight) was used in the categories “food/feedstuff flavourings and nutrients,” “surface treatment,” “pH-regulation agents,” and “non-agricultural pesticides and preservatives.” The largest number of FoA-containing preparations was in the categories “cleaning/washing agents” (> 100 listings) and “adhesives, binding agents” (> 40 listings).

NaFo is used to produce FoA. Also, an important process for manufacturing sodium dithionite starts with NaFo. Oxalic acid production employs NaFo as an intermediate. NaFo is also used in chrome tanning and as a mordant in the dyeing and printing of fabrics by the textile industry. The reducing power of NaFo is used in electroplating baths and photographic fixing baths. In chemistry applications, it is employed as precipitant for noble metals, for buffering of strong mineral acids to higher pH and as reducing, complexing, and analytical agents. In medication, it is applied as a caustic, astringent agent, and in foodstuffs as additive for preservation. Other usages for NaFo are as runway deicer, drilling and completion fluids, and enzyme stabilizer in liquid detergents. NaFo is also used as a processing chemical in the manufacturing sector and in the oil/gas exploration industry. In 2003, 239 preparations containing NaFo were registered in the Nordic countries adding up to a total annual volume of about 23,417 metric tons of NaFo.

AFo solutions are used as a low corrosion silage aid. In chemistry applications, AFo is employed for separation of base from noble metals, for production of amines, and as a buffer. A total of 15 preparations containing AFo were registered in the Nordic countries adding up to a total annual volume of about 74 metric tons of AFo.

Major uses of **CaFo** are as concrete admixture, animal feed additive and as chemical intermediate. CaFo is further used in tanning (leather industry) and as preservative for silage and food. It is applied as a binder for fine ore briquets, in drilling fluids and lubricants, for flue gas scrubbing and as concrete settings accelerators. CaFo is also used for the production of FoA. In 2003, 150 preparations containing CaFo were registered in the Nordic countries and were mostly categorized as

“adhesives/binding agents”, “construction materials”, “fillers”, and “process regulators”.

Main usages of **KFo** are as drilling and completion fluids and runway deicer. Moreover, **KFo** is applied as a secondary coolant for indirect cooling systems, in fire extinguishing applications, in wood preservation applications and as insulation material. **KFo** is further applied in fungicides and bactericides for agriculture, in chemical synthesis, e.g. to prepare potassium oxalate, as a catalyst/process regulator and as a polyurethane component. In 2003, 24 preparations containing **KFo** were registered in the Nordic countries adding up to a total annual volume of about 1,361 metric tons of **KFo**.

KHFo is used in feed mixtures for pigs as a growth promoter. **KHFo** is also applied as an intermediate in chemical synthesis, in food/foodstuff additives, and in pharmaceuticals.

Subcategory II: Methyl Formate

The annual world production capacity in 2005 for **MeFo** was estimated at 500,000 – 700,000 metric tons. The major producers are located in the European Union (2 different productions sites). Additional sites are located in the Asia/Pacific region (5-8 sites) and USA (1 site). **MeFo** is produced by base-catalyzed carbonylation of methanol, but can also be produced by oxy-dehydrogenation of methanol or by heating methanol with **NaFo** and hydrochloric acid with subsequent distillation.

Most of the **MeFo** produced is used as an intermediate in the production of **FoA** and formamide. It can also be used as a starting material in the production of high purity carbon monoxide. Dimethylformamide is produced by reacting **MeFo** with dimethylamine. A new use has been found for **MeFo** in the production of foundry molds. **MeFo** is also employed as a solvent for fats, oils, fatty acids, cellulose ester and acrylic resins. It has crop protecting applications as fumigant and larvicide for tobacco and food crops. Use as high-boiling refrigerant for house appliances is also reported. In 1999 - 2001, four **MeFo**-containing preparations were registered in Denmark.

Environmental exposure

Subcategory I: Formic acid and its dissociative salts

The occurrence of **formates** in the environment is ubiquitous. In food, **FoA** occurs naturally in animals, plants and foods such as fruits (20 – 40 mg/kg), honey (20 – 2000 mg/kg), wine (1 – 340 mg/kg), roasted coffee (30 – 40 mg/kg), evaporated milk (30 – 40 mg/kg), and cheese (20 – 200 mg/kg). **FoA** is also added intentionally to some foods as a flavor adjunct.

In the atmosphere, photochemical reactions, i.e. ozone-olefin reaction, isoprene oxidation, gas-phase reaction of formaldehyde with $\text{HO}_2\bullet$, and aqueous phase oxidation of formaldehyde, are important indirect sources of **FoA** formation. In mid-latitude continental regions, possible sources of **FoA** are direct emission from vegetation and biomass burning. In tropical continental sites, direct emission from vehicles, ants, soil, vegetation, and biomass-burning are important sources for **FoA**.

Newer findings in tropical forest studies suggest that the exchange of **FoA** and acetic acid between vegetation and the atmosphere is due to a bidirectional exchange behavior of the plants. The tropical forest is a sink rather than a source for organic acids. High atmospheric concentrations of organic acids in Brazil during the dry season have been attributed to biomass burning. During the wet season (low biomass burning activity), indirect emission by the vegetation, i.e. photochemical oxidation of primarily emitted biogenic hydrocarbons, was assumed to dominantly contribute to the atmospheric burden of the organic acids. **FoA** is scavenged by wet and dry deposition with wet deposition being more effective than dry deposition.

The possible sources at marine locations are photochemical reactions, biogenic emissions, and long-range transport.

Concentrations of **FoA**, as detected in the atmosphere, range from below the detection limit to about

35 $\mu\text{g}/\text{m}^3$ depending on season and location (urban/suburban, rural/remote, lower/upper troposphere, etc.). FoA concentrations in residential houses in suburban and urban areas ranged from $> 16 \mu\text{g}/\text{m}^3$ up to ca. 35 $\mu\text{g}/\text{m}^3$. Mean total concentrations of FoA motor exhaust emissions were determined to be 29 - 106 $\mu\text{g}/\text{m}^3$ (gasoline) and 225 $\mu\text{g}/\text{m}^3$ (diesel). When typical biomass fuels like wood and bushes with or without leaves are burned, FoA can reach smoke concentrations of up to 1 mg/m^3 . Emitted amounts of FoA from painted steel ranged from 0.4 to 30 mg/m^3 .

According to the data reported to the German Emission Register 2004, during production and processing 11,660 kg of FoA were emitted to air at a production and processing site in Germany in 2004. One company in Finland and the Netherlands reported that during production and processing, AFo and KFo were not emitted to air or water.

Because of their high solubility, formic and acetic acids are the most abundant acids in rainwater and are significant in the acidification of rainwater. Concentrations of FoA in rainwater around the world range from 55.2 to 340.4 $\mu\text{g}/\text{L}$ at marine sites, from below the detection limit to 1048.8 $\mu\text{g}/\text{L}$ at remote sites, from 354.2 to 1035 $\mu\text{g}/\text{L}$ at semi-urban sites, and from 36.8 to 492.2 $\mu\text{g}/\text{L}$ at urban sites. Clouds are considered important for FoA, providing either a source or sink for it. Average concentrations of FoA in fog, dew and cloud water were reported to be 0.2 – 2.3 mg/L (max. 29 mg/L). Surface water concentrations between 12 and 115 $\mu\text{g}/\text{L}$ were determined. FoA concentration in the 0 – 1 cm layer of sediments ranged from 23 to 437 mg/kg wet weight. Depending on the industry, FoA concentrations of up to 584 mg/L were reported from effluents before waste water treatment (produced water from oil production platforms).

Subcategory II: Methyl Formate

MeFo production and use as a solvent and organic synthesis intermediate may result in its release to the environment through various waste streams. MeFo use as a fumigant and larvicide will result in its direct release to the environment. MeFo was detected in the volatiles of chicken, beef, and pork flavor. MeFo was identified as a volatile constituent in brewed, roasted, and dried coffee. It has also been detected as an aroma substance in apples. MeFo was qualitatively identified in the volatile emissions of leaves litter from poplar trees, in drinking water samples, and in vapor-phase ambient air samples.

MeFo was also detected in cigarette smoke and gasoline engine exhaust. It is present in wastewater from urea-formaldehyde resin manufacturing plants. MeFo is released in vent effluents during the commercial production of methanol. It can be released in waste streams from its commercial manufacture and use in the production of formamide. MeFo has also been detected in exhaust gases from the combustion of various hydrocarbon fuels (< 0.1 to 0.7 ppm).

According to the data reported to the German Emission Register 2004, during production and processing 3,150 kg of MeFo were emitted to air at a production and processing site in Germany in 2004.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals of the formic acid and dissociative salts subcategory are currently of low priority for further work. The chemicals possess properties indicating a hazard for human health (moderate inhalation toxicity of FoA; local effects including corrosion of skin (FoA) and eye (FoA, KHfO), eye irritation (NaFo, CaFo), respiratory tract irritation (FoA, KHfO), and stomach irritation following repeated high doses (KHfO)). Exposure in occupational settings is controlled. Countries may wish to investigate any exposure scenarios that have not been presented by the Sponsor country.

MeFo is a candidate for further work based on ongoing work related to methanol. MeFo and

methanol (its metabolic product) possesses properties indicating a hazard for human health (MeFo: moderate inhalation toxicity, eye and respiratory tract irritation; methanol: neurological effects, CNS depression, ocular effects, and reproductive/developmental toxicity). In the US, further work is being performed on methanol regarding the use and refinement of pharmacokinetic models for extrapolating animal data to humans.

Environment: The chemicals of this category are currently of low priority for further work due to their low hazard profiles. Formic acid has properties indicating a hazard for the environment (acute toxicity to aquatic organisms between 1 and 100 mg/l) due to pH effects. This chemical, however, is also of low priority for further work for the environment because of its rapid biodegradation and limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	335-67-1	3825-26-1
Chemical Name	Perfluorooctanoic Acid (PFOA)	Ammonium Perfluorooctanoate (APFO)
Structural formula	$ \begin{array}{c} \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \\ \quad \quad \quad \quad \quad \quad \\ \text{F} - \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{COOH} \\ \quad \quad \quad \quad \quad \quad \\ \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \end{array} $	$ \begin{array}{c} \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \\ \quad \quad \quad \quad \quad \quad \\ \text{F} - \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{COOH} \cdot \text{NH}_3 \\ \quad \quad \quad \quad \quad \quad \\ \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \end{array} $

SUMMARY CONCLUSIONS OF THE SIAR**Chemical Identity**

For the purposes of this document, the anion of PFO (perfluorooctanoate) is frequently referenced as PFOA or APFO. APFO and PFOA are sometimes used interchangeably. Perfluorooctanoic Acid (PFOA) is a fully fluorinated carboxylic acid. APFO is the ammonium salt of PFOA.

Human Health

APFO is the ammonium salt of PFOA and the two substances are metabolically equivalent. PFOA is a strong acid and it is expected to dissociate in biological media.

Several epidemiology and medical surveillance studies have been conducted on workers employed at various APFO manufacturing sites in the U.S. Most of the studies were cross-sectional and focused primarily on males. A retrospective cohort mortality study demonstrated a statistically significant association between prostate cancer mortality and employment duration in the chemical facility of a plant that manufactures PFOA. However, in an update to this study in which more specific exposure measures were used, a significant association for prostate cancer was not observed. Other mortality studies lacked adequate exposure data which could be linked to health outcomes. A study which examined hormone levels in workers reported an increase in estradiol levels in workers with the highest PFOA serum levels; however, these results may have been confounded by body mass index. Cholesterol and triglyceride levels in workers were positively associated with PFOA exposures, which is inconsistent with the hypolipidemic effects observed in rat studies. A statistically significant positive association was reported for PFOA and T3 levels in workers but not for any other thyroid hormones.

Little information is available concerning the pharmacokinetics of PFOA and its salts in humans. Preliminary results of a 5-year half-life study in 26 retired workers indicate that the mean serum elimination half-life of PFOA in these workers was 3.8 years (1378 days, 95% CI, 1131-1624 days) and the range was 1.5-9.1 years.

The pharmacokinetics of PFOA in non-human primates has been studied both in classical intravenous elimination studies using three male and three female cynomolgus monkeys and in a six-month, repeat-oral-dose toxicology study in male cynomolgus monkeys with recovery. These studies confirmed urinary elimination as the primary excretion mode. From the intravenous study, in which males and females were given a 10 mg/kg dose, mean elimination half-lives were 20.9 days for males and 32.6 days for females. In the six-month study, monkeys were dosed with 3, 10, or 30/20 mg/kg-d ammonium PFOA. Steady-state serum concentration was reached within four to six weeks, with steady state levels lower than those that would be predicted based on the elimination rates and not in linear proportion to dose. Males in the six-month toxicology study had elimination half-life rates approximating 20 days.

Studies in adult rats have shown that the ammonium salt of PFOA (APFO) is absorbed following oral and inhalation exposure; less absorption occurs following dermal exposure. Serum pharmacokinetic parameters and the distribution of PFOA has been examined in the tissues of adult rats following administration by gavage and by intravenous (i.v.) and intraperitoneal (i.p.) injection. PFOA distributes primarily to the liver, serum, and kidney, and to a lesser extent, other tissues of the body. It does not partition to the lipid fraction or adipose tissue. The distribution of PFOA is predominantly extracellular. PFOA is not metabolized and there is evidence of enterohepatic circulation of the compound. The urine is the major route of excretion of PFOA in the female

rat, while the urine and feces are both main routes of excretion in male rats.

There are gender differences in the elimination of PFOA in adult rats following administration by gavage and by i.v. and i.p. injection. In female rats, following oral administration, estimates of the serum half-life were dependent on dose and ranged from approximately 2.8-16 hours, while in male rats estimates of the serum half-life following oral administration were independent of dose and ranged from approximately 138-202 hours. In female rats, elimination of PFOA appears to be biphasic with a fast phase and a slow phase. The rapid excretion of PFOA by female rats is believed to be due to active renal tubular secretion (organic anion transporters); this renal tubular secretion is believed to be hormonally controlled. Hormonal changes during pregnancy do not appear to cause a change in the rate of elimination in rats.

Several recent studies have been conducted to examine the kinetics of PFOA in the developing rat. These studies have shown that PFOA readily crosses the placenta and is present in the breast milk of rats. The gender difference in elimination is developmentally regulated; between 4-5 weeks of age, elimination assumes the adult pattern and the gender difference becomes readily apparent. Distribution studies in the postweaning rat have shown that PFOA is distributed primarily to the serum, liver, and kidney.

In acute toxicity studies in animals using APFO, the oral LD₅₀ values for CD rats were >500 mg/kg for males and 250-500 mg/kg for females, and <1000 mg/kg for male and female Wistar rats. There was no mortality following inhalation exposure of 18.6 mg/l APFO for one hour in rats. The dermal LD₅₀ in rabbits was determined to be greater than 2000 mg/kg. APFO is a primary ocular irritant in rabbits, while the data regarding potential skin irritancy are conflicting.

APFO did not induce mutation in either *S. typhimurium* or *E. coli* when tested either with or without mammalian activation. APFO did not induce gene mutation when tested with or without metabolic activation in the K-1 line of Chinese hamster ovary (CHO) cells in culture. APFO did not induce chromosomal aberrations in human lymphocytes when tested with and without metabolic activation up to cytotoxic concentrations. APFO was tested twice for its ability to induce chromosomal aberrations in CHO cells. In the first assay, APFO induced both chromosomal aberrations and polyploidy in both the presence and absence of metabolic activation. In the second assay, no significant increases in chromosomal aberrations were observed without metabolic activation. However, when tested with metabolic activation, APFO induced significant increases in chromosomal aberrations and in polyploidy. APFO was negative in a cell transformation assay in mouse embryo fibroblasts and in the mouse micronucleus assay.

Repeat-dose studies have been conducted in non-human primates. In a 13-week study with Rhesus monkeys, exposure to doses of 30 mg/kg-day or higher resulted in death. Clinical signs of toxicity were noted at doses as low as 3 mg/kg-day. Unlike rodent studies, analyses of the serum and liver levels did not reveal a gender difference in monkeys, but the sample size was very small. In a 6-month study of male cynomolgus monkeys, there was a steep dose response curve for mortality. Increases in liver weight were noted at doses as low as 3 mg/kg-day, but there was no evidence of peroxisome proliferator-activated receptor alpha activity (PPAR α). The LOAEL for the study was 3 mg/kg-day, and a NOAEL was not identified.

Repeat-dose studies in rats and mice demonstrated that the liver is the primary target organ. Due to gender differences in elimination, adult male rats exhibit effects at lower administered doses than adult female rats. Dietary exposure to APFO for 90 days resulted in significant increases in liver weight and hepatocellular hypertrophy in female rats at 1000 ppm (76.5 mg/kg-day) and in male rats at doses as low as 100 ppm (5 mg/kg-day). Chronic dietary exposure of rats to 300 ppm (males, 14.2 mg/kg-day; females, 16.1 mg/kg-day) APFO for 2 years resulted in increased liver weight, hepatocellular hypertrophy, hematological effects, and testicular masses in males; and reductions in body weight and hematological effects in females.

The carcinogenic potential of PFOA has been investigated in two dietary carcinogenicity studies in rats. Under the conditions of these studies, there is some evidence that PFOA is carcinogenic, inducing liver tumors, Leydig cell tumors (LCT), and pancreatic acinar cell tumors (PACT) in male rats. The evidence for mammary fibroadenomas in the female rats is equivocal since the incidences were comparable to some historical background incidences. There is sufficient evidence to indicate that PFOA is a PPAR α -agonist and that the liver carcinogenicity (and toxicity) of PFOA is mediated by PPAR α in the liver.

PFOA appears to be immunotoxic in mice. Feeding mice a diet containing 0.02% PFOA resulted in adverse effects to both the thymus and spleen. In addition, this feeding regimen resulted in suppression of the specific humoral immune response to horse red blood cells, and suppression of splenic lymphocyte proliferation. The suppressed mice recovered their ability to generate a humoral immune response when they were fed a diet devoid of PFOA. Studies using transgenic mice showed that the PPAR α was involved in causing the adverse effects to the immune system.

In an oral prenatal developmental toxicity study in rats, the LOAEL and NOAEL for maternal toxicity were 150 mg/kg-day and 5 mg/kg-day, respectively. There was no evidence of developmental toxicity after exposure to

doses as high as 150 mg/kg-day. In a rat inhalation developmental toxicity study, the NOAEL and LOAEL for maternal toxicity were 1 and 10 mg/m³, respectively. The NOAEL and LOAEL for developmental toxicity were 10 and 25 mg/m³, respectively. In a rabbit oral prenatal developmental toxicity study there was a significant increase in skeletal variations after exposure to 5 mg/kg-day APFO, and the NOAEL was 1.5 mg/kg-day. There was no evidence of maternal toxicity at 50 mg/kg-day, the highest dose tested. In a mouse oral developmental toxicity study, there was evidence of maternal toxicity and developmental toxicity and the authors calculated benchmark doses for a variety of endpoints. Decreased weight gain and increased liver weight was observed in adult females; the BMD5 and BMDL5 estimates for decreases in maternal weight gain were 6.76 and 3.58 mg/kg, respectively, and the BMD5 and BMDL5 estimates for increases in maternal liver weight were 0.20 mg/kg and 0.17 mg/kg, respectively. The BMD5 and BMDL5 estimates for the incidence of full-litter resorptions and neonatal mortality (determined by survival to weaning) observed at the 5 mg/kg/day dose group were 2.84 and 1.09 mg/kg, respectively. Significant alterations in postnatal growth and development were observed at 1 and 3 mg/kg/day, with BMD5 and BMDL5 estimates of 1.07 and 0.86 mg/kg, respectively, for decreased pup weight at weaning; and 2.64 and 2.10 mg/kg, respectively, for delays in eye opening. The BMD5 and BMDL5 estimates for reduced phalangeal ossification were <1 mg/kg. BMD5 and BMDL5 estimates for reduced fetal weight at term were estimated to be 10.3 and 4.3 mg/kg, respectively.

A variety of endpoints were evaluated throughout different lifestages in a two-generation reproductive toxicity study in rats exposed to 0, 1, 3, 10, or 30 mg/kg/day APFO. In that study, a reduction in F1 pup mean body weight on a litter basis was observed during lactation (sexes combined) in the 30 mg/kg-day group. F1 male pups in the 10 and 30 mg/kg-day groups exhibited a significant reduction in body weight gain during days 8-50 postweaning, and body weights were significantly reduced in the 10 mg/kg-day group beginning on postweaning day 36, and in the 30 mg/kg-day group beginning on postweaning day 8. F1 female pups in the 30 mg/kg-day group exhibited a significant reduction in body weight gain on days 1-15 postweaning, and in body weights beginning on day 8 postweaning. Reproductive indices were not affected in the F1 animals. There was a significant increase in mortality mainly during the first few days after weaning, and a significant delay in the timing of sexual maturation for F1 male and female pups in the 30 mg/kg-day group. No effects were observed in the F2 pups. However, it should be noted that the F2 pups were sacrificed at weaning, and thus it was not possible to ascertain the potential post-weaning effects that were noted in the F1 generation. Adult systemic toxicity consisted of reductions in body weight in both the F0 and F1 animals.

Environment

Both PFOA and APFO are solid at environmental relevant temperatures. The melting point for PFOA is 54.3°C and the boiling point is 190°C at 1013 hPa. APFO starts to decompose above 105°C. At 20°C, the water solubility of PFOA is 9.5 g/l and of APFO >500 g/l. When dissolved in water, the strong acid PFOA (pKa 2.5) dissociates.

Pure PFOA at room temperature has moderate vapor pressure (2.3 Pa). The vapor pressure of APFO is much lower with 0.008 Pa. APFO or PFOA dissolved in water dissociate to ions. Although the dissociated fraction is not subject to volatilization, depending on the pH, pure PFOA might volatilize from water to a certain degree.

Due to emissions for more than 50 years, PFOA is distributed worldwide in the marine environment, and hence may be transported to remote areas via the aqueous phase and the atmospheric phase. However, the significance of these sources are not currently known. Both atmospheric and aquatic transport mechanisms are actively being investigated.

Possible substances subject to atmospheric long-range transport are PFOA precursors rather than PFOA itself. Potential precursors are fluorotelomer alcohols, -olefins and perfluoroalkyl sulfonyl derivatives. These substances are degraded by OH radicals via gas-phase reactions to result partially in PFOA. The relative environmental significance of these sources is not known at this time.

Due to the stability of the C-F bond, PFOA is persistent in the environment. No degradation could be observed in the studies on abiotic or biological degradability in water. Also the examinations on photolytic and photochemical degradation in air indicate high stability under environmentally relevant conditions. The half-life of the reaction with OH-radicals in the atmosphere is 130 days.

According to the low adsorption potential and the water-solubility, PFOA is mobile in soil.

The available ecotoxicological studies using APFO indicate a low acute toxicity for aquatic organisms. In the short term tests using fish, invertebrates, and algae, effective concentrations were as follows:

<i>Oncorhynchus mykiss</i>	LC ₅₀ (96 h)	= 707 mg/l	(nominal)
<i>Daphnia magna</i>	EC ₅₀ (48 h)	= 480 mg/l	(measured)
<i>Pseudokirchneriella subcapitata</i>	EC ₅₀ growth rate/biomass (72 h)	> 400 mg/l	(nominal)

The NOEC values determined in the chronic tests using fish and daphniae, were 40 mg/l (*O. mykiss*, NOEC, 85 d, measured) and 20 mg/l (*D. magna*, NOEC, 21 d, measured). In a 10 day study using *Chironomus tentans* no effects were observed up to a nominal concentration of 100 mg/l. In addition to that, the following information about effects on community level (indoor and outdoor microcosm studies) is available:

Zooplankton community	35 d-LOEC _{species richness}	= 10 mg/l	(nominal)
<i>Myriophyllum spicatum</i>	35 d-EC ₁₀	= 5.7 mg/l	(measured)
<i>Myriophyllum</i> spp.	35 d-NOEC	= 23.9 mg/l	(measured)

In several tests on effects using activated sludge, no inhibition of microbial activity was measured up to a nominal concentration of 1000 mg/l.

Concerning the effects on terrestrial organisms, in a test using *Caenorhabditis elegans* without analytical verification, an EC₅₀ (48 h) of 973 mg/l (nominal) was calculated. In a chronic study using the same species, a reduction of abundance and egg production was observed at the 4th generation at a concentration of 4.1×10^{-3} mg/l (nominal). The NOEC for this endpoints was 4.1×10^{-4} mg/l.

In tests with the rainbow trout *Oncorhynchus mykiss* a bioconcentration factor (BCF) of 0.038 and bioaccumulation factors (BAF) for organs of 27 (blood), 8.0 (liver) and 4.0 (carcass) were obtained. These laboratory studies indicate a low bioaccumulation potential in fish. Some monitoring data suggest a low biomagnification potential in aquatic food webs, while in some marine and Canadian Arctic mammalian food web studies a potential for biomagnification has been suggested. Further elucidation of the mechanisms leading to uptake and accumulation in biota is required.

Exposure

APFO is used as a processing aid in the production of fluoropolymers. In 2002, its world-wide production was about 200-300 metric tons. Entry into the environment occurs during production and use of PFOA / APFO. Other sources for releases to the environment are residual contents of PFOA in fluoropolymer and fluoroelastomer products, PFOA as a byproduct in end products and fire-fighting foams containing perfluorocarboxylates, PFOA contaminations in perfluorooctyl sulfonyl (PFOS) based products, and PFOA contamination in fluorotelomer products. An indirect source for PFOA in the environment is the degradation (biotic and abiotic) of some fluorotelomer-based products.

The global distribution of PFOA was demonstrated by several monitoring studies. Elevated PFOA concentrations were measured near industrialized and urbanized regions. PFOA could be detected in air in concentrations in the range of pg/m³, ng/g dw in soil, in sediment, suspended matter, and sewage sludge.

PFOA concentrations up to 67,000 ng/l and 3,200,000 ng/l were analysed in sewage effluent and landfill effluent. Sporadically, PFOA was determined in ground water samples (up to 3,400,000 ng/l). In fresh water samples (rivers, lakes, rain water) PFOA was regularly measured. The maximum concentration determined was 11,300 ng/l. Elevated concentrations of PFOA were also detected in coastal waters near industrialized and urbanized areas; the maximum concentration was 15,300 ng/l.

In freshwater and salt water fish PFOA was detected occasionally. The maximum concentration (91 ng/g ww) was found in common shiner (liver samples) after a spill of fire retardant foam. The highest PFOA concentration in birds was determined in liver samples of cormorants (450 ng/g ww). However, it should be noted that for this colony of cormorants the highest value (450 µg.kg⁻¹ ww) appeared to be an outlier as the concentration was 4.5 times greater than the standard deviation of the mean. The occurrence of PFOA even in remote areas, was demonstrated by analysis of polar bear liver samples (highest concentration: 55.8 ng/g ww). Liver samples of other mammals (e.g. seals, whales, walrus, dolphin) contained PFOA; concentrations up to 62 ng/g ww.

In addition to the environmental measurements, PFOA was regularly analysed in human blood samples. While the pathways of human exposure to PFOA and its salts are unknown, there are limited data on PFOA blood serum levels in both occupationally- and non-occupationally-exposed populations. It has been detected in samples of human blood (plasma, serum and whole blood), liver, seminal plasma, and breast milk from several countries throughout the world, including the US, Canada, Columbia, Poland, Belgium, India, Korea, Sri Lanka, Japan, Sweden and Germany. Preliminary US reports indicate that individuals living near a facility that uses PFOA have much higher PFOA serum concentrations than the levels previously reported for US populations.

The routine finding of PFOA in human blood initiated research on the sources of human exposure. Fluoropolymers and fluoroelastomers are typically manufactured through telomerization. As APFO is an essential processing aid in this process, trace amounts of PFOA may be generated as an unintended by-product.

Fluorotelomer-based products have numerous uses in many industrial and consumer products, including soil-,

stain-, grease-, and water-resistant coatings on textiles and carpet, personal care products, and nonstick coatings on cookware, and uses in the automotive, mechanical, aerospace, chemical, electrical, medical, and building and construction industries. Consumer exposure to PFOA due to impurities in the finished products can not be excluded. However, based on analysis of consumer articles and using a simple compartmental model estimation, an explanation for the PFOA concentrations found in humans can not be given.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The chemical is a candidate for further work. The chemicals possess properties indicating a hazard for human health (eye irritation; subchronic toxicity; potential carcinogenicity; developmental toxicity). In the US, data collected in the National Health and Nutrition Examination Survey (NHANES) will provide data on exposure profiles of individuals across the U.S. Epidemiologic studies have not shown conclusively an association of PFOA exposure and health outcomes but most of the studies were cross-sectional; further work is needed to understand any potential associations. Further work on the species differences in toxicokinetics and mode of action to enhance our ability to predict risk in humans is currently underway. Member countries are invited to perform an exposure assessment and then if indicated, a risk assessment.

Environment:

The chemical is a candidate for further work. PFOA is persistent in the environment. The primary environmental sink is the aqueous phase. PFOA tends to be dissipated into organisms and is eliminated from the body very slowly. Laboratory studies and monitoring data in some aquatic food webs indicate a low bioaccumulation potential in fish, but other data suggest a potential for biomagnification, e.g. in marine mammals and Canadian Arctic food webs. Hence, for substances like PFOA, bioconcentration values in fish may not be the most relevant endpoint to consider. For PFOA, biomagnification may occur in air-breathing species (e.g., terrestrial mammals, birds and marine mammals). Further elucidation of the mechanisms leading to uptake and accumulation in biota is required.

The main industrial sources of environmental emissions appear to have been identified. Further research is needed to quantify the sources leading to the ubiquitous environmental distribution and human exposure. In conclusion, member countries are invited to perform an exposure assessment (consideration should be given to precursors to PFOA) and, if indicated, a risk assessment. Member countries are invited to consider risk management measures, e.g. environmental emission reductions.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	10039-54-0
Chemical Name	Bis(hydroxylammonium)sulphate
Structural Formula	$ \begin{array}{c} \text{O} \\ \parallel \\ \text{O}=\text{S}-\text{O}^- \\ \\ \text{O}^- \end{array} \begin{array}{c} \text{HO}-\text{NH}_3^+ \\ \text{H}_3\text{N}^+-\text{OH} \end{array} $

SUMMARY CONCLUSIONS OF THE SIAR**Analogue rationale**

Depending on the pH, bis(hydroxylammonium)sulphate is dissociated into SO_4^{2-} and NH_3^+-OH . Therefore in case of few or missing data read across from hydroxylamine (CAS-No. 7803-49-8) or its hydrochloride (CAS-No. 5470-11-1) has been performed eg. mutagenicity and sensitisation.

Physical-chemical properties

Bis(hydroxylammonium)sulphate (BHAS) is a white crystalline powder (relative density 1.883 at 20°C) which decomposes above 120 °C. The vapour pressure was not determined because of the salt character. The measured partition coefficient (log Kow) is -3.6 (at pH 3.2), and the water solubility is 587,000 mg/L at 20 °C.

Human Health

For bis(hydroxylammonium)sulphate (BHAS) no *in vivo* data are available on absorption, distribution or excretion, and only few *in vitro* studies exist. Hydroxylamine is formed as an intermediate during cellular metabolism. Hydroxylamine reductase is detected in the mitochondria of livers from mice, rats and pigs. Its activity appears to be age-dependent. An *in vivo* rat study described partial metabolic oxidation of hydroxylamine to nitrate. Absorption via oral and inhalation uptake is expected to be high, because of experimental data. Based on physical-chemical data of BHAS, animal data on systemic effects and occupational dermal exposure scenario under non-occlusive conditions, dermal uptake is assumed to be low.

Human data on the acute toxicity of BHAS are not available. In tests with rats, cats and rabbits BHAS caused methaemoglobin formation by the oral and the dermal routes. Respective data after inhalation are not available. Oral LD₅₀ values are 545-652 mg/kg bw for rats and appr. 200 mg/kg bw for female cats; dermal LD₅₀ values are over 500 mg/kg bw for rats and between 100 mg/kg bw and 500 mg/kg bw for rabbits. In two inhalation studies in rats saturated vapours of BHAS did not cause any toxic effects. After dermal exposure toxicity is significantly higher under occlusive compared to semi-occlusive conditions. A dose of 1 mg/kg bw can be considered as NOAEL for occlusive application of the substance in the rabbit. A dermal NOAEL of 500 mg/kg bw can be derived for semi-occlusive exposure.

Information from non-standard animal data demonstrate moderate to severe irritating and even corrosive properties of BHAS depending on the time of exposure. Brief exposures of 15 minutes to an 80% BHAS solution caused some irritation, and a longer exposure of 20 hours caused more severe reactions. Limited information in humans indicates that concentrations of 1% and above caused skin irritation. Limited information from experimental animals indicates that BHAS is an eye irritant.

Skin sensitising properties of BHAS and hydroxylamine were demonstrated in animal experiments and in humans. Limited information from experimental animals indicates that BHAS is not a respiratory sensitiser.

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In a subchronic oral toxicity study similar to OECD TG 408 (no recovery period), groups of 10 male and 10 female rats received BHAS (purity $\geq 99\%$) in the drinking water at concentrations of 0, 10, 50, or 250 ppm for 90 consecutive days. The doses administered corresponded to a mean daily BHAS intake of about 0, 0.9, 4 or 21 mg/kg bw/d. Repeated administration of 50 and 250 ppm BHAS (equivalent to about 4 and 21 mg/kg bw/d respectively) to rats via the drinking water for 3 months led to toxicity in male and female rats at both dose levels. In the males and females of the 50 and 250 ppm groups the administration of BHAS led to hemolytic anemia (dose-related) with methaemoglobinemia and to organ weight increases in the spleen and liver together with the specific histopathological findings in the liver and spleen seen as increased hemosiderin deposits in both sexes. The NOAEL for all adverse effects of this rat study was 10 ppm (equivalent to about 0.9 mg/kg bw/d) for both sexes.

In a combined chronic toxicity/carcinogenicity study according to OECD TG 453, BHAS (purity commercial grade) was administered to groups of 50 male and 50 female rats in the drinking water at concentrations of 0, 5, 20 and 80 ppm for 24 months (main groups). In order to define the hematotoxic potential of the test substance, groups of 10 animals per sex and dose were treated for 12 months (satellite groups). In these satellite animals, assays of blood parameters were performed every three months. The doses administered corresponded to a mean daily BHAS intake in the main groups of about 0, 0.2, 1.0, and 3.7 mg/kg bw/d in males and 0, 0.4, 1.6, and 6.2 mg/kg bw/d in females; and in the satellite groups of about 0, 0.3, 1.1, and 4.5 mg/kg bw/d in males and 0, 0.4, 1.6, and 6.2 mg/kg bw/d in females. In conclusion, the prolonged oral administration of 80 ppm BHAS via the drinking water to male and female rats caused hemolytic anemia, characterized by significant reduced counts of erythrocytes, haemoglobin concentrations and hematocrit values, increases in MCV, MCH, and furthermore, increased number of Heinz bodies, Howell-Jolly bodies, and reticulocytes in the peripheral blood. These adverse effects were associated with increases of spleen weights, increased red blood cell regeneration by the bone marrow and increased extramedullary hematopoiesis in the spleen and the liver. At 20 ppm (equivalent to about 1.0 mg/kg bw/d in males and 1.6 mg/kg bw/d in females), hemosiderin storage in the spleen, sign of hemolysis, were significantly increased when compared with controls in male rats after 12 months of treatment and in female rats after 24 months of treatment, respectively. No hematotoxic effects were detected in animals given 5 ppm. Therefore, the NOAEL for systemic effects was 5 ppm, corresponded to a mean daily BHAS intake of about 0.2/0.3 mg/kg bw/d in males and 0.4 mg/kg bw/d in females.

BHAS was negative in a bacterial test in *Salmonella typhimurium*. In mice, a bone marrow micronucleus test (OECD TG 474) and a screening for dominant lethal mutations were negative. Hydroxylamine and its hydrochloride were mainly negative in bacterial genotoxicity tests; hydroxylamine hydrochloride was weakly positive in mouse lymphoma assays. However, clearly negative results were obtained concerning UDS in rat hepatocytes and chromosomal aberrations in rodent bone marrow cells. Further data were of relatively low reliability or significance. Overall, BHAS has no genotoxic potential.

There are no data in experimental animals available for the inhalation and dermal route of exposure and there are no human data on carcinogenicity. In a standard combined chronic toxicity/carcinogenicity toxicity study according to OECD TG 453 (24 month drinking water study, details see description under repeated dose toxicity). BHAS treatment was associated with an increased incidence of hemangiosarcomas in males treated at ≥ 5 ppm, equivalent to about ≥ 0.2 mg/kg bw/d and hemangioma development in females treated at 80 ppm, equivalent to about 6.2 mg/kg bw/d, both in the spleen. Angiomatous hyperplasia in the spleen considered as a precursor lesion of angiomatous tumours (hemangioma, hemangiosarcoma) was observed in animals of both sexes at 80 ppm. The LOAEL was 5 ppm. Although the database for mice is insufficient, the data available did indicate that BHAS may induce spleen tumours as it does in the rat. It was considered that BHAS has no genotoxic potential, and the carcinogenicity observed in experimental animals is mediated via a non-genotoxic mechanisms involving especially erythrotoxicity.

Guideline-compliant generation studies, respectively fertility studies for BHAS are presently not available. Regarding a subchronic oral repeated dose toxicity study with rats no indications for an impairment of male and female reproductive organs could be revealed up to and including the highest tested dose level of about 21 mg/kg bw/d (NOAEL). Data from oral repeated dose toxicity studies in mice and rats showed that in female animals BHAS induced impaired ovarian functional state and morphology and in addition impaired development and morphology of mammary gland tissues. In an oral repeated dose toxicity study with rats a LOAEL of about 67 mg/kg bw/d was determined based on retardation of the development of the mammary gland.

In a guideline compliant prenatal toxicity study (OECD TG 414) in rats groups of 22-24 pregnant rats had been

treated with BHAS at dosages of 1,3,10, and 20 mg/kg bw/d from day 6 to day 15 post coitum. A NOAEL (oral) for embryo-/fetotoxicity of 20 mg/kg bw/d (highest dose) was derived due to the absence of any relevant treatment effects. No human data are available.

Environment

BHAS is a crystalline powder. In the aqueous environment, the salt dissociates completely and rapidly to $[\text{NH}_3\text{OH}]^+$ and $[\text{SO}_4]^{2-}$. Depending on the pH, the hydroxyl-ammonium ion is rapidly converted to hydroxylamine which could be degraded further by abiotic and biotic processes. In the pH range 6 to 9 representative of most aquatic ecosystems, the free hydroxylamine base is very reactive and is expected to decompose further by abiotic processes and nitrification. The expected ultimate degradation products are ammonia, nitrogen and water.

Due to the structure of the substance, degradation by photolytic mechanisms can be excluded.

Normally, distribution of a substance in the environment can be estimated using a Mackay-type model. Since BHAS is an inorganic substance dissociating in water, it is not reliable to estimate the distribution using a Mackay-type model.

The substance does not exhibit any measurable vapour pressure. Taking into account the inorganic character of BHAS and its high solubility in water, a complete distribution to the aqueous compartment can be expected. In the aqueous phase, the substance is expected to dissociate, and hence not volatile. According to these findings, volatilisation from the aqueous phase can be excluded.

Due to the specific properties of the substance it can be expected that the adsorption to organic matter is negligible.

Although the QSARs for adsorption estimation are not valid for inorganic substances, an approximate estimation was carried out using a QSAR for Nonhydrophobics and the measured partition coefficient octanol/water. Using this correlation, a Koc of 0.141 L.kg^{-1} was estimated indicating a very low adsorption to organic matter.

The Log K_{OW} determined experimentally for bis(hydroxylammonium)sulphate is -3.6 indicating no potential for bioaccumulation. No accumulation in organisms and the food chain is expected.

The following acute toxicity test results have been determined for aquatic species (with nominal concentrations):

e.g., Fish <i>Pimephales promelas</i>	96-h LC_{50} = 7.2 mg/L (not reliable)
Invertebrate <i>Daphnia magna</i>	48-h EC_{50} = 1.6 mg/L
Algae <i>Scenedesmus subspicatus</i>	72-h ErC_{50} = 0.8 mg/L (growth rate method)

The following chronic toxicity test results have been determined:

<i>Daphnia magna</i>	21-d, semi-static,	NOEC = 0.31 mg/L (length); $\text{NOEC} \geq 0.62 \text{ mg/L}$ (reproduction weight) [mean of the measured concentrations]

The inhibition of oxygen consumption of activated sludge was investigated according to OECD 209. After 3h at a test concentration $\leq 5 \text{ mg/L}$ the test substance did not inhibit respiration (EC_{20} , corresponds to NOEC), at 50.4 mg/L 56% inhibition was observed (EC_{50}).

Exposure

BHAS is commercially produced at three sites with an annual production volume of approximately 490,000 tonnes in the EU 15. Worldwide production volume is not available. BHAS is mainly produced by catalytic hydrogenation of nitric oxide.

BHAS is used as intermediate for the production of cyclohexanone oxime or caprolactam (large-scale chemical industry). In addition, bis(hydroxylammonium)sulphate is used in many branches of the chemical industry.

BHAS is an intermediate for the production of pharmaceuticals, e.g. antibiotics and tranquilizers, Intermediate for the production of active ingredient for plant protection products, like insecticides and herbicides, and of sweeteners for the food industry.

In the Photographic industry BHAS is used as a stabilizer for developers, additive in emulsions for colour films (containing 1 – 30 % BHAS).

BHAS is also used in the Rubber industry (accelerator for the vulcanizing of synthetic rubber, antioxidant for natural rubber), for soaps (auxiliary for refining fats for soap production), plastics (regulator and inhibitor in various polymerisations) metallurgy (additive for surface treatment of steel), nuclear industry (auxiliary for separation of uranium and plutonium) and textile industry (auxiliary for specific dyeing processes; fixative for textile dyes).

Monitoring data for effluents are available from two of the production sites in the EU.

Occupational exposure by inhalation or dermal contact is possible but controlled.

Exposure of consumers is assumed to be negligible.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (acute toxicity, skin sensitisation, repeated dose toxicity and carcinogenicity). Based on data presented by the sponsor country, exposure is controlled and anticipated low. Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

Environment

The chemical is a candidate for further work. The substance has properties indicating a hazard for the environment (aquatic toxicity < 1 mg/l for algae). Member countries are invited to perform an exposure assessment and, if necessary, a risk assessment.

Note: A risk assessment performed in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union is available.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	10361-37-2
Chemical Name	Barium chloride
Structural Formula	$\text{Ba}^{2+} 2\text{Cl}^{-}$

SUMMARY CONCLUSIONS OF THE SIAR**Physical and chemical properties**

Barium chloride is a white hygroscopic orthorhombic crystal with a melting point of 962 °C, a boiling point of 1560 °C and a vapour pressure of essentially zero. The calculated octanol-water partition coefficient ($\log K_{ow}$) is not applicable and the water solubility is 375 g/L at 25 °C.

Human Health

Radiolabelled barium chloride ($^{131}\text{BaCl}_2$) was administered via intubation in rats. When ^{131}Ba concentrations in the eyes, heart, liver, kidney, and muscle was determined 24 hours after dosing, the ^{131}Ba concentration in those tissues, appeared 2-8 times higher than the ^{131}Ba concentration in blood. This demonstrates that $^{131}\text{BaCl}_2$ is not only absorbed, but concentrated above the blood levels at least in some tissue compartments. The absorption, distribution and excretion of $^{133}\text{BaCl}_2$, administered orally or intra-peritoneal, were studied in weanling male rats. ^{133}Ba was rapidly absorbed from the gastrointestinal tract with the peak concentration in the blood and soft tissues occurring 30 min after administration. Total uptake of ^{133}Ba increased with increasing dosage. Absorbed ^{133}Ba was mainly distributed in the combined gastrointestinal tract and contents. The barium chloride was excreted in both urine and feces, but with majority of the excretion occurring via the fecal route. Barium chloride is rapidly taken up by the soft tissues, more slowly taken up by the skeleton, and excreted primarily in the feces.

Male and female rats were gavaged with barium chloride in deionized water over a dosage range of 60 to 960 mg/kg (10 animals per sex per dose). The acute oral LD_{50} values were 408 mg/kg bw for male and 419 mg/kg bw for female rat. Hemorrhagic areas in the stomach and inflammation of the intestines were seen at necropsy. The dermal LD_{50} values were >2,000 mg/kg bw for male and female rat [OECD TG 402]. The LD_{50} studies suggest a moderate acute oral toxicity and a low acute dermal toxicity. No studies were available on acute inhalation toxicity.

There were no reliable skin/eye irritation studies nor skin sensitization studies available.

Barium chloride was administered via the drinking water to rats, equivalent to 0, 1.7, 8.1 or 38.1 mg/kg bw/day for males and 0, 2.1, 9.7 or 45.7 mg/kg bw/day for females for 4, 8 and 13 weeks, respectively. Any changes noted were not considered to be toxicologically or biologically relevant as they were within normal variation or did not occur in a dose related manner. The NOAEL of the repeated-dose oral toxicity study was considered to be 250 ppm (38.1-45.7 mg/kg bw/day).

Barium chloride dihydrate was given to rats and mice in drinking water for 13 weeks at concentrations of 0, 125, 500, 1,000, 2,000 or 4,000 ppm. The NOAEL was 2,000 ppm (corresponding to the average daily dose of 110 and 115 mg Ba/kg bw/day to male and female rats, respectively, and 205 and 200 mg Ba/kg bw/day to male and female mice, respectively) based on mortality, renal toxicity, decreases of mean body weight gains and of water consumption.

In *in vitro* bacterial reverse mutation tests, barium chloride and barium chloride dihydrate were negative both with and without metabolic activation in multiple strains of *Salmonella typhimurium*. In an *in vitro* chromosomal aberration test, barium chloride dihydrate did not exhibit clastogenic effects with and without S9 mix. In contrast, barium chloride dihydrate, at concentrations of 250 µg/mL and above, induced gene mutation at the TK+/- locus of L5178Y mouse lymphoma cells in the presence of S9; without S9, no increase in the number of mutant colonies was observed. In cytogenetic tests with cultured Chinese hamster ovary cells,

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barium chloride dihydrate did not induce sister chromatid exchanges or chromosomal aberrations, with or without S9. No cell cycle delay was observed at any of the concentrations tested. Based on the results, barium chloride is considered to be non genotoxic *in vitro*. No *in vivo* genotoxicity studies were available.

There was no evidence of carcinogenic activity when barium chloride dihydrate was given at 0, 500, 1,250 or 2,500 ppm in the drinking water to rats or mice (50 sex/species/dose level) for 2 years. The highest concentrations were equivalent to 60-75 mg barium/kg bw/day in rats and 160-200 mg barium/kg bw/day in mice.

Barium chloride dihydrate was administered to rats and mice (males for 60 days; females for 30 days) via the drinking water prior to mating. No treatment-related decreases in pregnancy rate or gestation length were observed in rats. A small reduction in pup birth weight was shown at 4,000 ppm at 1 day but not at 5 days of age. No alterations in epididymal sperm counts, sperm motility, sperm morphology, testis or epididymal weight or vaginal cytology were observed in rats and mice exposed to 4,000 ppm and 2,000 ppm, respectively. The NOAEL for fertility and developmental toxicity was determined to be 4,000 ppm for rats (equivalent to 201.5 mg/kg bw/day for males and 179.5 mg/kg bw/day for females) and 2,000 ppm for mice (the average dose was 206 mg Ba/kg bw/day for males and 199.8 mg Ba/kg bw/day for females), the highest concentration tested. Note that these doses are expressed as barium, not barium dichloride (or barium dichloride dihydrate). Thus, based on drinking water studies with barium dichloride dihydrate, barium is considered to have low potential for developmental and reproductive toxicity.

Environment

Environmental biodegradation and environmental fate analysis based on log K_{ow} and log K_{oc} is not applicable for inorganic salts such as barium chloride. Photodegradation and biodegradation are not relevant transformation processes for barium chloride but, upon emission to water, it will dissolve and release the divalent cation in solution. Under natural conditions, barium will form compounds in the +2 oxidation state. Soil adsorption of barium was studied in a sandy soil and a sandy loam soil. Sludge solutions appeared to increase the mobility of elements in soil. Barium adsorption in algae increased proportionally with decreasing barium concentration in the medium. The current state of the science does not allow for the unambiguous interpretation of the significance of various measures of bioaccumulation (e.g., BCF, BAF) for metal-containing inorganic substances.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Fundulus heteroclitus</i>]	96-h $LC_{50} > 1,000$ mg Ba/L (measured)
Invertebrate [<i>Daphnia magna</i>]	48-h $LC_{50} = 14.5$ mg Ba/L (measured)
Plant [<i>Lemna minor</i>]	96-h $EC_{50} = 26$ mg/L and 61 mg Ba/L (measured)

The following chronic toxicity test results have been determined:

Invertebrate [<i>Daphnia magna</i>]	21 days, $EC_{50} = 8.9$ mg Ba/L (measured)
	$EC_{16} = 5.8$ mg Ba/L (measured)

Exposure

Barium chloride was commercially imported with an annual import volume of 1,933 tonnes in the Republic of Korea in 2006. The Republic of Korea's annual production of barium chloride was not reported in 2006. Barium chloride is mainly used as an intermediate in production processes. Barium chloride is used for manufacturing of pigments, colouring agents, paints, inks, additives, heat transferring agents, and stabilisers in the sponsor country.

No monitoring data for effluents, surface water, or in occupational settings are available from the production and processing sites in the Republic of Korea. Occupational and consumer exposures are considered to be negligible. The general population is exposed to barium primarily through ingestion of drinking water and consumption of food. Concentrations of barium in raw surface waters and drinking water supplies have been found in concentrations ranging from 7 to 15,000 $\mu\text{g/L}$. Concentration of barium in seawater is on average 6 $\mu\text{g/L}$. Ambient barium concentrations in air ranged from 0.0015 to 0.95 $\mu\text{g/m}^3$ in the USA.

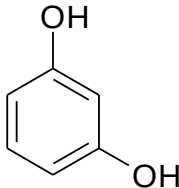
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**RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED****Human Health**

This chemical is of low priority for further work. The chemical possesses properties indicating a hazard for human health (moderate acute oral toxicity). Based on exposure data presented by the Sponsor country exposure to human is expected to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment

Barium chloride is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to aquatic organisms between 1 and 100 mg/L). However, chronic toxicity to aquatic organisms is typically > 1 mg/L.

SIDS INITIAL ASSESSMENT PROFILE	
CAS Nos.	108-46-3
Chemical Names	Resorcinol (1,3-Benzenediol)
Structural Formula	
SUMMARY CONCLUSIONS OF THE SIAR Physical-chemical properties The melting point of resorcinol ranges between 109-111°C and the boiling point ranges between 276.3 - 277 °C at 1013 hPa. The vapor pressure is 0.00065 hPa at 25°C. The water solubility of resorcinol is 717 g/L and the log Kow is 0.8 at 25°C. Human Health Toxicokinetic studies in rats and rabbits suggest that orally-administered resorcinol is rapidly absorbed, metabolized and excreted in the urine primarily as a monoglucuronide conjugate. Minor metabolites included a monosulphate conjugate, a mixed sulfate-glucuronide conjugate, and a diglucuronide conjugate. Rats given repeated oral doses of resorcinol appeared to increase the rate of metabolism. Dermal absorption of resorcinol is slow in humans but shows the same urinary excretion pathway and metabolites as those in orally treated rats and rabbits. Following OECD TG 401, the acute oral LD₅₀ of resorcinol in rats is 510 mg/kg bw. Clinical signs of toxicity included ptosis, respiratory effects, lethargy, abnormal gait, tremors, convulsions and salivation. An additional acute oral toxicity study in rats resulted in an LD₅₀ of 980 mg/kg bw. Hyperemia and distention of stomach and intestines were observed in the animals that died. In rats exposed by inhalation to an aerosol of resorcinol, the 1-hr and 8-hr LC₀ values were ≥ 7800 mg/m³ and 2800 mg/m³, respectively. No lesions attributable to inhalation of the aerosol were seen at gross necropsy. The rabbit 24 hour dermal LD₅₀ was 3360 and 2830 mg/kg bw, for flaked and industrial grade resorcinol, respectively. Both grades produced necrosis of the skin; clinical signs included salivation, tremors, and convulsions prior to death. The overt CNS effects were considered to be associated with bolus dosing. In an OECD TG 404 study, resorcinol was not a skin irritant when applied to the skin of rabbits. In a study conducted similar to OECD test guideline 405, resorcinol was not considered an eye irritant in rabbits when applied at a concentration of 2.5% in water. In additional studies, resorcinol was found to be slightly to severely irritating to the skin and severely irritating to eyes when administered in a dissolved and semi-solid state. In an OECD TG 406 study, resorcinol was a moderate skin sensitizer in guinea pigs. In two separate studies following OECD TG 429, resorcinol was determined to be a weak skin sensitizer in mice. Resorcinol has elicited allergic skin reactions in patch tests carried out on dermatitis patients. An OECD TG 408 study was performed with male and female rats receiving 0, 40, 80 or 250 mg/kg	

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bw/day via oral gavage 5 days/week for 90 days. At 250 mg/kg bw/day, intermittent convulsive movements and excessive salivation were observed along with loud breathing in two males, one during week 6 and the other between weeks 11 and 13. However, the functional observational battery did not reveal any treatment related neurological effects. Female animals receiving 250 mg/kg/day from week 4 to 8 showed reduced body weight gains. The NOAEL for both sexes was 80 mg/kg/day.

A series of studies was conducted by NTP in rats and mice at 17 days, 13 and 104 weeks. The lowest NOAEL reported in rats was in the 17 day study oral bolus (gavage) study and was 27.5 mg/kg bw (females) based on overt CNS effects at doses of 55 mg/kg bw and higher. The lowest LOAEL in rats was identified in the 104 week study with a LOAEL = 112 mg/kg bw (males) based on overt CNS effects at all doses, body weight changes (decreased) and increased mortality at the highest dose of 225 mg/kg bw. In the 13-week study increased absolute and relative liver weights were seen in females and males at 65 and 130 mg/kg bw, respectively. In addition, absolute and relative adrenal gland weights were significantly increased in all surviving male dosed groups.

In the NTP studies, the lowest NOAEL reported in mice was in the 17-day study at 75 mg/kg bw/day based on overt CNS effects in males at 150 mg/kg bw/day. The lowest LOAEL in mice was identified in the 104 week study at 112 mg/kg bw/day based on overt CNS effects (in both sexes) at 112 and 225 mg/kg bw/day. As with the rats, acute CNS effects were observed in mice. An NTP review panel concluded that the overt CNS effects seen in the NTP studies were an acute response to treatment. The dosing method (bolus) was probably a key factor, since no CNS effects were seen when similar or higher doses were given via the drinking water. Decreased adrenal gland weights were reported for male mice in the 13 wk gavage study only while increased adrenal gland weights were reported in male rats. The significance of the adrenal and liver weight changes remains unclear as neither effect were reproduced in the 104 week and subsequent studies.

Acute CNS effects, adrenal weight changes and liver weight changes reported in the 17-day and 13-week studies in rats and mice were not observed in a subsequent reproduction drinking water study (OECD TG 416) conducted in rats at concentrations up to 3000 mg/L. Mean cumulative body weights were decreased in the 3000 mg/L group in both sexes and generations. The NOAEL was considered to be 3000 mg/L for parental systemic and offspring toxicity (ca. 233 mg/kg/day (males), 304 mg/kg/day (females (during premating and gestation)), 660 mg/kg/day (females (during lactation))). This study also included a detailed evaluation of the thyroid endpoints. No significant effects on the thyroid were observed in rats given up to 233 mg/kg bw/day (males) or 304 mg/kg bw/day (females).

Given the weight of evidence from the above repeated dose studies, the lowest value associated with a reproducible effect (reduced body weight) was 250 mg/kg/day resulting in a NOAEL = 80 mg/kg/day.

Resorcinol generally showed no evidence of activity in Ames bacterial mutation assays. In mammalian cells in culture, it induced chromosome aberrations (breaks and micronuclei), but no SCE effects. In an *in vitro* Unscheduled DNA Synthesis Assay in rat hepatocytes, resorcinol was negative. In an OECD TG 476 (*in vitro* thymidine kinase locus) study, resorcinol was positive without activation in the L5178Y mouse lymphoma cells; however, this result was probably due to chromosome aberrations (induction of small colony mutants), not mutagenicity. In an OECD TG 487 (*in vitro* Micronucleus assay) study, resorcinol was positive with and without activation in female human lymphocytes. In an *in vitro* hamster embryo cell morphological transformation assay following OECD guidelines, resorcinol was negative. Resorcinol was negative for inducing micronuclei in six *in vivo* micronucleus assays in which one study was conducted following OECD TG 474. In one of two NTP *in vivo* micronucleus assays, resorcinol was positive for inducing micronuclei. In a transgenic mouse model, resorcinol was negative for activating RasH2. In studies to evaluate the effectiveness of the transgenic mouse model, resorcinol was negative in p53+/- while positive in Tg.AC. Based on the weight of evidence, resorcinol appears to induce chromosome aberrations *in vitro* but not *in vivo*.

No evidence of carcinogenic activity was seen in studies conducted according to US EPA/FDA guidelines where rats and mice were given resorcinol by gavage on 5 days/week for 2 years.

In an OECD TG 416 study, rats (30/sex/group) were exposed to resorcinol via drinking water for at least 70 days prior to mating. Resorcinol concentrations were 0, 120, 360, 1000 or 3000 mg/L water for both the F0 and F1 generations. On a body weight basis (average F0 and F1 animals), the

concentrations corresponded to resorcinol intakes of approximately: 0, 11, 31, 86 or 233 mg/kg bw/day for males over the entire generational span; 0, 16, 48, 126 or 304 mg/kg bw/day for females during pre-mating and gestation; and 0, 28, 85, 225 or 660 mg/kg bw/day for females during lactation, respectively. Reproductive performance and spermatogenic endpoints were unaffected by resorcinol. No treatment-related effects were observed on F1 and F2 pup survival, macroscopic findings or effects on organ weights. Mean cumulative body weights were decreased in the 3000 mg/L groups in both sexes and associated with decreased water consumption.

The NOAEL for male reproductive toxicity was determined to be 3000 mg resorcinol/L (ca. 233 mg/kg bw/day). The maternal NOAEL was 3000 mg/L (304 mg/kg bw/day during premating and gestation and 660 mg/kg/day during lactation). The NOAEL for reproductive toxicity (fertility and development) was 3000 mg/L which corresponds to 245 mg/kg bw (males) and 295 mg/kg bw (females) in the F1 generation.

In an OECD TG 414 study, female rats (24/group) were exposed to resorcinol via oral bolus dosing (gavage) from days 6 – 19 of gestation at 0, 40, 80 or 250 mg/kg bw/day. The maternal and developmental NOAELs were 80 (based on statistically significant decreased body weight gains) and 250 mg/kg bw/day (highest dose tested), respectively. Teratogenicity was not observed. Ten to thirteen female rats were administered resorcinol by gavage at doses of 0, 125, 250 or 500 mg/kg bw/day during days 6 – 15 of gestation. No significant differences were observed in fetal parameters (anomalies, and weights) or on resorptions. Teratogenicity was not observed. The maternal and developmental NOAEL was 500 mg/kg bw day (highest dose tested).

Based on the above studies, resorcinol was not a developmental toxicant and did not cause reproductive effects in the rat when administered by gavage or in drinking water.

Some early laboratory animal studies via dermal and oral routes along with human case reports (at high dermal exposures to damaged skin) have suggested that resorcinol may have an effect on the mammalian thyroid. However, no thyroid effects were seen in numerous other studies, including occupational investigations of exposed worker populations. A well-conducted study (OECD TG 416 with detailed evaluation of thyroid endpoints) found no significant effects on the thyroid of rats given up to 233 mg/kg bw/day (males) or 304 mg/kg bw/day (females) in the drinking water through two generations.

Environment

Resorcinol is not expected to disassociate at environmentally relevant pHs (pKa = 9.81.) Resorcinol is not expected to undergo direct photolysis. The overall OH rate constant for resorcinol is $200 \text{ E-}12 \text{ cm}^3/\text{molecule-sec}$ with an estimated half-life of 0.053 days (38.16 minutes) with a hydroxyl radical concentration of $1.5 \times 10^6 \text{ OH-radicals/cm}^3$. Based on its chemical structure resorcinol has no functional groups susceptible to hydrolysis under environmentally relevant pH and temperature conditions. Therefore, hydrolysis is not expected to occur. Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 1000 kg/h for each medium, shows the following percent distribution: Air = 0.002%; Soil = 63.8%; Water = 36.1%; Sediment = 0.07%. Resorcinol was biodegradable under aerobic and anaerobic conditions. Several aerobic biodegradation studies are available following inherent and ready biodegradation protocols. In a MITI test following OECD Test guideline 301C, resorcinol was determined to be readily biodegradable with elimination rates being 66.7% after 14 days. Following OECD Test guideline 302B, 97% degradation was observed after 4 days. Under anaerobic conditions, resorcinol was considered to have 95% utilization after 110 days acclimation.

The bioaccumulation potential is estimated to be low based on the log Kow of 0.8, which is supported by a BCF of 3.16 estimated with BCFWIN.

Using EPISUITE, volatilization from a model river and lake are anticipated to be 709.3 and 7738 years, respectively.

The 96-hour LC₅₀s of resorcinol in fathead minnows (*Pimephales promelas*) ranged from 26.8 mg/L (mean measured) to 100 mg/L (nominal) under flow through conditions and from 40 – 60 mg/L under static conditions. In a chronic fish study following OECD early life stage guideline the 7 day EC₅₀ (weight) in Zebra fish (*Danio rerio*) was =54.8 mg/L (nominal) and the LC₅₀ (embryo lethality) was

=262 mg/L (nominal). Under static conditions the 48 hour EC₅₀ for the water flea (*Daphnia magna*) was 1.28 mg/L (nominal). Analytical monitoring was not conducted in the study so the measured EC₅₀ may be lower than the nominal EC₅₀. Additional studies are available: however they were typically shorter or longer in duration than current guidelines. In an OECD TG 201 study in *Pseudokirchneriella subcapitata*, the 72 hr E_bC₅₀ (for biomass) was > 97 mg/L (mean measured, highest dose tested) and the NOEC for biomass was = 47 mg/L (mean measured). The corresponding mean measured 72 hr E_rC₅₀ values and NOEC for growth rate were > 97 mg/L and = 97 mg/L, respectively. In a chronic fish study following OECD early life stage guideline in *Salmo gairdneri*, the 60 day LOEC (weight) = 32 mg/L and the EC₅₀ for lethality and malformations was =260 mg/L while the LC₅₀ (total embryotoxicity) was =320 mg/L. In an OECD *Daphnia magna* reproduction test (TG 211) no effects were observed up to the highest concentration tested. Limited data were available in micro-organisms; the 96 hr IC₅₀ of 1600 mg/L (methane-producing micro-organisms) and a 24 hr EC₅₀ of 7.8 mg/L (*Nitrosomonas*) was reported. In *Eisenia foetida* (earthworms), resorcinol showed no effect on growth rate or body weight; the LC₁₀₀ was = 40000 mg/kg soil dw and the LOEC was = 10000 mg/kg soil dw.

Exposure

Total global production of resorcinol was 48 thousand tonnes (106 million pounds) in 2004. In the Sponsor Country, production volume in 2004 was 24.7 thousand tonnes. Japan is the largest producer of resorcinol globally while the United States is the largest consumer.

Resorcinol is produced commercially worldwide in a few specialized plants. All of these plants use benzene (CAS No. 71-43-2) as the main feedstock and two production routes are used commercially on a large scale. Resorcinol is produced either via sulfonation of benzene under conditions promoting di-substitution in meta position followed by fusion with anhydrous caustic ("classical" route via 1,3-benzenedisulfonic acid) or via hydroperoxidation of 1,3-diisopropylbenzene (CAS No. 99-62-7).

The purity of the material is dependent on the manufacturing method. Technical grade resorcinol is available with a minimum purity of 99.3% (which accounts for over 98% of the total global production) and contains one or more of the following impurities depending upon method of manufacture: <0.2%, catechol, phenol, o-cresol, m-/p-cresol, and 3-mercaptophenol, hydroquinone, acetone and acetylphenol (maximum 0.1% each unless otherwise stated).

In production, this material is handled in closed systems. In order to minimize exposure(s) and gain efficiencies, necessary engineering controls and measures are in place during production and processing. Once produced, resorcinol is transferred into bags (e.g 25 kg) or flexible containers (e.g. 500 kg). When appropriate, personal protective equipment is worn during various procedures at the manufacturing facilities.

The ACGIH and MAK recommended time weighted average (TWA) value for resorcinol is 10 ppm (45 mg/m³). NIOSH also recommends a short term exposure limit (STEL) of 20 ppm (90 mg/m³).

Resorcinol is used as a key intermediate in the manufacture of other chemicals. In the United States and Western Europe, resorcinol is used primarily in the production of specialty adhesives and/or as an adhesion promoter for tires and wood products. In Japan, resorcinol's use in hair dyes is addressed by the Standards of Approval for the Manufacture and/or Import of Hair Dyes (Notification no. 533 of the Pharmaceuticals Affairs Bureau) which allows for a maximum concentration of 0.1% in use. In the United States (US), resorcinol's use in cosmetics and other medicinal products is restricted to a maximum concentration of 2% as set forth by the Cosmetics Ingredient Review and US Food and Drug Administration. In the European Union (EU), resorcinol's use in hair dyes is controlled under the Cosmetics Directive 76/768/EEC which allows for a maximum concentration of 5%. In oxidative hair dyes, resorcinol is regulated to a maximum of 5% (in the EU) or below (in US and Japan) but in practice many manufacturers limit the level of free resorcinol in oxidative hair dyes to 1.25%. Resorcinol is limited to 0.5% in shampoos and hair lotions. It is used in pharmaceutical preparations for the topical treatment of skin conditions such as acne, seborrheic dermatitis, eczema, psoriasis, corns and warts. Resorcinol in anti-acne preparations is usually used up to a maximum of 2%. In extreme cases, up to 50% resorcinol is reported in the literature as being used by medical professionals with the intended purpose to wound and disrupt the epidermis. Application times are documented as ranging from 30 seconds to 10 minutes. The prescribing professional must determine

the significance of the benefits when using resorcinol in this manner as it is not consistent with the existing regulations within Japan, the EU and the US.

Resorcinol may be released indirectly during use and disposal of resorcinol containing consumer and professional products. The concentration of resorcinol in food and drinking water is not known.

**RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED**

Human Health

The chemical is currently a low priority for further work. The chemical possesses properties indicating a hazard for human health (sensitization). Based on data presented by the Sponsor country, adequate risk management measures are being applied. Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment

The chemical is a low priority for further work. The chemical possess properties indicating a hazard for the environment (acute toxicity between 1 and 100 mg/L; no effects were observed up to the highest concentration tested in the 21 day chronic aquatic invertebrate study.) The chemical is readily biodegradable and has limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	109-60-4
Chemical Name	n-Propyl Acetate
Structural Formula	CH ₃ -CH ₂ -CH ₂ -COO-CH ₃

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

Data from the analogue substances n-propyl alcohol, ethyl acetate and n-butyl acetate have been included in the assessment of n-propyl acetate for repeated-dose, genetic toxicity and reproductive/developmental toxicity endpoints.

Data for n-propyl alcohol (CAS No. 71-23-8) can be used for the systemic toxicity endpoints of n-propyl acetate because inhalation exposure of rats to n-propyl acetate results in hydrolysis of the acetate to n-propyl alcohol, with blood levels of the alcohol that peak after 15 minutes exposure; concentrations of the alcohol in blood were between 2.6 to 7.7 times higher than n-propyl acetate throughout the 90-minute exposure period. Endpoints of n-propyl acetate toxicity that are associated with direct contact-mediated effects (e.g. eye, skin, and respiratory tract irritation) cannot be extrapolated from n-propyl alcohol data due to the difference in physical-chemical properties of the two materials.

Data for two analogue compounds, ethyl acetate (CAS No. 141-78-6) and n-butyl acetate (CAS No. 123-86-4), are also provided to address the above endpoints based on similar chemical structures. Ethyl acetate and n-butyl acetate exhibit similarities in mammalian toxicity. Effect levels are lower for ethyl acetate than for n-butyl acetate, and it is expected that n-propyl acetate would have effect levels between those of ethyl acetate and n-butyl acetate. Ethyl acetate and n-butyl acetate have previously been assessed in the OECD HPV programme.

Physical-Chemical Properties

n-Propyl acetate is a clear, colourless liquid with a melting point of -93 °C, boiling point of 101.5 °C, vapour pressure of 33.3 hPa at 20 °C, and water solubility of 20,000 mg/L at 20 °C. n-Propyl acetate has a density of 0.882 mg/m³ at 25°C, a measured Henry's law constant of 2.2×10^{-4} atm-m³/mol (22.3 Pa-m³/mol) at 25 °C, and a measured log K_{ow} of 1.24. It is a flammable liquid with a flash point of 13°C (closed cup) and a flammable range of 1.7 to 8 volume percent. n-Propyl acetate has an odour threshold of 0.21 mg/m³ or 0.88 ppm. It has a sweet, fruity odour and a bittersweet taste.

Human Health

As noted above, an *in vivo* respiratory bioavailability study in rats showed that n-propyl acetate hydrolyses to n-propyl alcohol. Blood levels of the alcohol exceeded the acetate levels by 2.6 to 7.7 times at each time point tested between 0 and 90 minutes. No data are available on kinetics and routes of excretion of n-propyl acetate *in vivo*.

In a 4-h acute inhalation study in female rats (6/concentration) exposed to n-propyl acetate vapour, the LC₅₀ was greater than 4000 ppm. All rats died at 16,000 ppm; rats were unconscious and 4 of 6 died (mortality 67%) at 8000 ppm; and animals were inactive but conscious with no deaths at 4000 ppm. Necropsy of animals dying during exposure revealed pulmonary haemorrhage and necropsy of surviving animals after the 14-day observation period revealed evidence of earlier lung damage. The dermal LD₅₀ in male rabbits after 24 hours of exposure was > 17,756 mg/kg bw. Erythema and necrosis of the skin were observed at the site of application. The acute oral LD₅₀ value for n-propyl acetate was 8700 mg/kg bw for male rats. Signs of toxicity included sluggish behaviour and laboured breathing prior to death. Necropsy of animals that died revealed congestion of abdominal organs and surface "burns" of the viscera in contact with the stomach.

n-Propyl acetate was mildly irritating to skin under non-occluded conditions. However, prolonged skin exposure

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under occlusive covering can cause necrosis. n-Propyl acetate induced diffuse corneal injury that healed quickly when instilled into rabbit eyes. No reliable studies are available for respiratory irritation for n-propyl acetate. There are no sensitisation studies for n-propyl acetate.

There were no repeated-dose data available for n-propyl acetate. However, data were available for the analogue substances, n-propyl alcohol, ethyl acetate and n-butyl acetate. In a repeated-dose inhalation toxicity study, rats (10/sex/concentration) were exposed to **n-propyl alcohol** vapour at 0, 100, or 500 or 1000 ppm (0, 0.246, 1.23 or 2.46 mg/L) for 6 h/day for 9 days. Rats exposed to 1000 ppm exhibited evidence of nasal and ocular irritation. Based on nasal and ocular irritation observed in one animal at 500 ppm, the NOAEC for this study was 100 ppm (0.246 mg/L). As noted earlier, the point of contact effects of n-propyl alcohol may not be predictive of effects for n-propyl acetate. In another repeated-dose inhalation study, rats (10/sex/ concentration) were exposed to **ethyl acetate** vapour at 0, 350, 750 or 1500 ppm (0, 1.28, 2.75, or 5.49, mg/L) for 6 h/day, 5 days/week for 13 weeks. Rats exposed to 750 and 1500 ppm exhibited decreased food consumption, decreased body weight gains, and decreased alerting response to an auditory stimulus that was transient and confined to the exposure period. Decreased numbers of circulating erythrocytes were seen in males at 1500 ppm. Lower serum triglycerides were also observed in both sexes at 1500 ppm and in males at 750 ppm. Serum albumin and total protein levels were mildly decreased in females at 1500 ppm. Necrosis of the olfactory epithelium was observed in some rats (8/20) exposed to 350 ppm and all rats exposed to 750 and 1500 ppm. The LOAEC for this study was 350 ppm (1.28 mg/L), the lowest dose tested. In another inhalation study, rats (10/sex/concentration) were exposed to **n-butyl acetate** vapour at 0, 500, 1500 or 3000 ppm (0, 2.35, 7.05 or 14.1 mg/L) for 6 h/day, 5 days/week for 13 weeks. Nasal discharge of porphyrin was observed in all **n-butyl acetate** groups after exposure. Decreased food consumption was seen at all concentrations. Decreased body weight gains and increased salivation were observed at 3000 ppm. Reductions in mean body weights and minimal reductions in activity during exposure were seen at both 1500 and 3000 ppm. Organ weight changes independent of body weight included lower spleen and higher lung weights in males at 3000 ppm, and higher testes weights in males and higher adrenal weights in females at 1500 ppm and in both sexes at 3000 ppm. Necrosis of the olfactory epithelium was observed in some rats (10/20) exposed to 1500 ppm and all rats exposed to 3000 ppm. Signs of stomach irritation were observed in females at 3000 ppm. The NOAEC based on multiple effects was determined to be 500 ppm (2.35 mg/L).

Neurotoxicity studies have also been conducted for the analogue substances, **ethyl acetate** and **n-butyl acetate**. Rats (minimum 12/sex/concentration) were exposed to 0, 350, 750, or 1500 ppm (0, 1.28, 2.75, or 5.49 mg/L) **ethyl acetate** vapour for 6 h/day, 5 days/week for 100 days. Decreases in body weight, body weight gain and feed consumption and feed efficiency were seen at 750 and 1500 ppm. A diminished response to an alerting stimulus was noted during exposure at 750 and 1500 ppm, and females exposed to 1500 ppm exhibited a decrease in motor activity. The NOAEC for subchronic neurotoxicity for **ethyl acetate**, based on decreased motor activity observed in females at 1500 ppm, is 750 ppm (2.75 mg/L). Rats were exposed to 0, 500, 1500 or 3000 ppm (0, 2.35, 7.05, or 14.1 mg/L) **n-butyl acetate** vapour for 6 h/day, 5 days/week for 13 weeks. Body weights and/or body weight gains were reduced at 1500 and 3000 ppm. There was no evidence of neurotoxicity based on functional observational battery testing and schedule-controlled operant behaviour endpoints or neuropathological examinations. The NOAEC for subchronic neurotoxicity for n-butyl acetate was determined to be 3000 ppm (14.1 mg/L). For both ethyl acetate and n-butyl acetate, the results of the neurotoxicity tests support the conclusion that these chemicals show minimal neurological effects.

In a bacterial reverse mutation assay, n-propyl acetate was negative both in the presence and absence of metabolic activation. n-Propyl acetate was also negative when tested in a mitotic aneuploidy assay in yeast. n-Propyl alcohol was negative when tested in a yeast forward gene mutation assay in the presence and absence of metabolic activation. n-Propyl alcohol was also negative in two *in vitro* SCE assays conducted in Chinese hamster ovary or lung (V79) cells, and in an *in vitro* micronucleus test conducted in V79 cells. **Ethyl acetate** did not induce chromosomal aberrations in three *in vivo* micronucleus assays (one in mice, two in Chinese hamsters). Although weakly positive for chromosomal aberrations in Chinese hamster lung cells at the highest dose tested *in vitro*, **ethyl acetate** was negative in other *in vitro* tests using Chinese hamster ovary cells both with and without metabolic activation. **n-Butyl acetate** was negative for chromosomal aberrations in an *in vitro* test using Chinese hamster lung cells. The available data on n-propyl acetate and related compounds suggest that it is unlikely to induce genotoxic effects *in vivo*.

No carcinogenicity data are available for n-propyl acetate. There are no valid studies available for n-propyl alcohol or the structural analogues of n-propyl acetate (n-butyl acetate, ethyl acetate).

There are no reproductive or developmental toxicity studies available for n-propyl acetate. Studies are available for the supporting chemicals n-propyl alcohol and n-butyl acetate. Rats (18/sex/concentration) were exposed to 0,

3500 or 7000 ppm (0, 8.61 or 17.2 mg/L) **n-propyl alcohol** vapour for 7 h/day, 7 days/week for 62 days prior to being mated with unexposed rats of the opposite sex. Females exposed to 7000 ppm displayed decreased food consumption and reduced body weight gains. There was no effect on female fertility, reproduction or neonatal survival. Among offspring from rats maternally exposed to 7000 ppm n-propyl alcohol, there was an increase in the incidence of pups with crooked tails. Among males, there was a marked reduction in fertility in the 7000 ppm group, which was reversed after a 13-week recovery interval. The NOAEC for female fertility was 7000 ppm or 17.2 mg/L, and the NOAEC for male fertility was 3500 ppm or 8.61 mg/L. Among offspring from rats paternally or maternally exposed to 7000 ppm n-propyl alcohol, there were no significant differences relative to controls on any of the neurodevelopmental tests (MA, SCOB, FOB, neurochemistry). Groups of rats (10/sex/group) were exposed to **n-butyl acetate** at concentrations of 0, 500, 1500 or 3000 ppm (0, 2.35, 7.05 or 14.1 mg/L) for 6 h/day, 5 days/week for 13 weeks. Among males, there was no difference in testicular spermatid head counts and epididymal spermatozoa counts relative to controls. Mating and reproductive performance were not affected in female rats exposed to 1500 ppm (7.05 mg/L) **n-butyl acetate** for 7 h/day, 5 days/week for 3 weeks prior to mating.

In a developmental toxicity study, pregnant female rats were exposed to **n-propyl alcohol** vapour at 0, 3500, 7000 or 10,000 ppm (0, 8.61, 17.2 or 24.6 mg/L) for 7 h/day during gestation days 1 to 19. Decreased maternal food consumption, decreased maternal body weight gain and increased incidence of malformations, including pups with crooked tails, were observed at 10,000 ppm (24.6 mg/L); increased pre-and post-implantation loss was also reported. Decreased maternal food intake and body weight gain and increased incidence of pups with rudimentary cervical ribs were observed at 7000 ppm. In groups exposed to 7000 and 3500 ppm n-propyl alcohol, there was no effect on litter size, gestation length, birth weight, pup weight or pup survival. The NOAEC for maternal and developmental toxicity for **n-propyl alcohol** in rats in this study was 3500 ppm (8.61 mg/L). In a behavioural teratogenicity study, female rats were exposed to 3500 or 7000 ppm (8.61 or 17.2 mg/L) **n-propyl alcohol** vapour from gestation days 1 to 20. Increased incidence of crooked tails were observed in offspring of dams exposed to 7000 ppm (17.2 mg/L); however, behavioural testing of offspring revealed no differences from controls after maternal exposure to n-propyl alcohol. The NOAEC for behavioural effects for this study was 7000 ppm (17.2 mg/L) n-propyl alcohol.

Female rats and rabbits were exposed to 1500 ppm (7.05 mg/L) **n-butyl acetate** vapour for varying intervals during pregnancy. In rats, maternal food consumption and body weight gains were decreased. Foetal body weights and crown-rump measurements were reduced in exposed animals. There was no increase in the incidence of malformations among exposed rats nor treatment-related anomalies. In the rats administered n-butyl acetate prior to mating and through gestation/lactation, an increased incidence of hydronephrosis was seen. In rabbits, maternal food consumption and body weight gains were reduced. There was no effect on foetal body weights or measurements and there was no increase in malformations. There was an increase in two minor anomalies (misaligned sternbrae and retinal folds) as well as increased incidence of clear gall bladders. Both studies resulted in LOAECs for developmental toxicity of 1500 ppm (7.05 mg/L). Based on data for the analogue substances (**n-propyl alcohol** and **n-butyl acetate**), n-propyl acetate has the potential for reproductive and developmental toxicity at high doses.

n-Propyl acetate may present a hazard for human health (skin and eye irritation and potential reproductive/developmental toxicity at high doses). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

n-Propyl acetate is a naturally-occurring material and has been detected but not quantified in surface waters in the United States and Europe. The stability of n-propyl acetate in water is pH dependent. Hydrolysis is expected to occur slowly at neutral or acidic pH, but increase at pH > 8. The half-lives of n-propyl acetate in water at 25 °C and at pH 7, 8 and 9 are 3 years, 119 days and 12 days, respectively, as calculated using measured data. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a calculated half-life of 75 to 80 hours. A ready biodegradation test using a closed bottle method resulted in 72% biodegradation after 20 days. n-Propyl acetate is readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that n-propyl acetate will partition primarily into water (42.7%) and soil (42.6%), with a smaller amount in air (14.6%). A Henry's law constant of 22.3 Pa·m³/mol at 25 °C suggests that volatilisation of n-propyl acetate from water bodies may not be rapid but could be significant. Koc values of 11.2 and 100 were estimated, indicating a low sorption potential to organic content of soil.

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The bioaccumulation potential is estimated to be low based on the log Kow of 1.24, which is supported by a calculated BCF of 1.8 estimated with BCFWIN.

Fish	<i>Pimephales promelas</i>	OECD TG 203	96 h LC ₅₀ = 60 mg/L
Invertebrate	<i>Daphnia magna</i> Straus	OECD TG 202	48 h EC ₅₀ = 91.5 mg/L
Algae	<i>Pseudokirchnerilla subcapitata</i>	OECD TG 201	72 h ErC ₅₀ = 672 mg/L (growth rate method) 72 h EbC ₅₀ = 366 mg/L (biomass/area under growth curve) 72 h NOEC = 83.2 mg/L (growth rate, biomass)

The following acute toxicity test results* have been determined for aquatic species:

*all results are based on measured test concentrations

n-Propyl acetate may present a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). However, the chemical biodegrades rapidly and exhibits limited potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

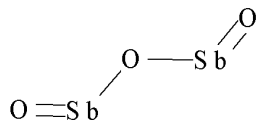
In 2006, consumption of n-propyl acetate in North America was estimated to be 29,000 metric tons; in Western Europe consumption was estimated to be 5,000 metric tons; and in Japan consumption was estimated to be 7,700 metric tons. In the United States, n-propyl acetate is manufactured by three producers.

n-Propyl acetate is used as a raw material in the chemical and pharmaceutical industry and as a solvent in the manufacture and use of liquid flexographic and rotogravure inks. n-Propyl acetate is used to control viscosity and modify the drying rate of ink, and to prevent smearing and ink accumulation on printing presses. The use of n-propyl acetate as an ink solvent is decreasing as water-based inks are developed. n-Propyl acetate is also used in the production of nitrocellulose lacquers, resins and waxes, and in the manufacture of artificial fragrances. n-Propyl acetate is an ingredient used in the manufacture of some consumer products including nail polish and glue. It is found naturally in fruits and is used as a synthetic flavouring substance and adjuvant.

In occupational settings, enclosed equipment and engineering controls are used during production, transfer and loading operations to minimize exposure and flammability hazards. The 8-h occupational exposure limit for n-propyl acetate in the U.S. is 200 ppm (835 mg/m³). Exposure to the general population or consumers to n-propyl acetate occurs naturally in a variety of foods that are consumed by the general population. Exposure can also occur through fugitive emissions from manufacturing sites, landfills, and sewers, or during the use of consumer products such as nail polish and glues. Considering the many uses of the substance in different industrial sectors, the potential for dermal and inhalation exposure should be anticipated and monitored by industrial health and safety professionals.

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SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1309-64-4 (same as 12412-52-1 and 1317-98-2)
Chemical Name	Diantimony trioxide, Sb ₂ O ₃
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue/Category rationale**

For the environment, data on antimony trichloride and antimony hydroxide have been used in the aquatic ecotoxicity assessment, since they all release the biologically active form, i.e. antimony ion. An important difference between different antimony compounds, as observed in toxicity tests, is the time needed to dissolve and liberate ions able of exerting toxicity. Antimony chlorides, being more soluble, will dissolve faster than oxides (the liberation of ions will be slower for oxides). Dissolution of antimony compounds will be faster in the aquatic compartment, as compared to the terrestrial compartment. Since most toxicity tests of antimony are performed under oxygenated conditions using trivalent antimony compounds such as SbCl₃ and Sb₂O₃, the toxicity exerted will, depending on the duration of the test, reflect a mixture of toxicity from trivalent and pentavalent antimony ions. There is no conclusive evidence supporting a significant difference in toxicity between the two valencies, and it is decided not to differentiate between relevant and reliable toxicity results originating from toxicity studies with tri- or pentavalent antimony studies. It however needs to be recognised in this context that for human health, there are discrete differences in toxicokinetics and toxicity between tri- and pentavalent antimony species.

Physical-chemical properties

Diantimony trioxide (Sb₂O₃) is solid and is commercialized as a white, odourless, crystalline powder. Based on handbook-data, the melting point is 655°C and boiling point is 1550°C, and vapour pressure at ambient temperature is considered to be negligible. The solubility in reconstituted standard water (= ISO 6341 medium; temperature 22.2°C) is 2.76 mg Sb/L. Dissolution of the substance in reconstituted standard water decreases constantly from pH 1 to pH 7. Above pH 7, the trend changes and the solubility of diantimony trioxide increases rapidly to pH 8, where a new equilibrium is established and the increase in solubility becomes much slower. The octanol-water partition coefficient (log K_{OW}) is not relevant for this type of substance.

Diantimony trioxide has two molecular arrangements, Senarmontite (CAS No. 12412-52-1) and Valentinite (CAS No. 1317-98-2), under environmental conditions. Since no data are available to differentiate between the two as regards exposure and effects, the intent is to cover both with the CAS Number for diantimony trioxide, i.e. 1309-64-4.

Human Health

In a rat study, the oral absorption was 0.3% and 0.05% at 100 mg/kg bw and 1000 mg/kg bw, respectively. However, at relevant human exposure levels an oral absorption of 1% is assumed, acknowledging both the poor solubility of diantimony trioxide and the higher intestinal absorption (3-8% on average) reported for more soluble antimony compounds. Dermal absorption of diantimony trioxide is considered negligible based on an *in vitro* human skin percutaneous study which showed 0.26% absorption. Based on particle size, the deposition of inhaled diantimony trioxide in the airways is calculated by the MPPD model resulting in an estimated total absorption via inhalation of 6.82 %.

After oral exposure of rats to diantimony trioxide suspension, antimony is distributed to most organs with the

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highest concentrations found in whole blood, thyroid and bone marrow. Antimony is retained in the lungs for long periods of time (the biological elimination half time in humans has been estimated to 600-3700 days) and accumulates in lung tissue after repeated inhalation exposure to diantimony trioxide. Antimony has also been detected in low amounts in human foetal liver as well as in human breast milk, placenta, amniotic fluid and umbilical cord blood, indicating that antimony can be distributed to the foetus and excreted in breast milk. After oral exposure, most of the antimony is excreted in the faeces, due to low oral absorption. Antimony is excreted both in faeces and in urine, biliary excretion being higher than urinary excretion.

There is one acute inhalation toxicity OECD guideline study in rats, which shows no signs of toxicity for diantimony trioxide, indicating a 4-hour (nose-only) $LC_{50} > 5.20 \text{ mg/L}$ (5 200 mg/m^3). The animal studies on acute oral exposure do not comply with current standards. Still, they indicate that the oral LD_{50} was in excess of 20 000 mg/kg bw in rats. There is one study on dermal exposure in rabbits that indicates that the LD_{50} for dermal exposure is higher than 8 300 mg/kg bw . The overall conclusion is that, despite the poor quality of the available acute oral and dermal toxicity studies with diantimony trioxide in laboratory animals, diantimony trioxide is considered to be of low acute inhalation, oral and dermal toxicity.

No reliable data were available for skin irritation to diantimony trioxide. Several human case study reports indicate that diantimony trioxide may cause dermatitis on skin damp with perspiration and the lesions appear to be closely associated with sweat ducts. Two eye irritation studies in rabbits, show that diantimony trioxide causes mild eye irritation, which was reversible. There is one acute inhalation toxicity animal study available, which also assessed the irritation potential to the respiratory tract, indicating that diantimony trioxide was not irritating to the respiratory system.

A skin sensitisation study, performed according to TG 406, showed that diantimony trioxide was not skin sensitising in guinea pigs.

The repeated dose toxicity of diantimony trioxide has been investigated in several animal studies via the inhalation and oral routes of exposure. The majority of these studies are considered inconclusive because they do not comply with current test guidelines, but those that are conclusive showed that diantimony trioxide is toxic to lung. In an inhalation repeated dose toxicity study (not following OECD test guideline), the substance was administered via whole body inhalation to 65 rats/sex/dose at 0, 0.06, 0.51 or 4.50 mg/m^3 , for 5 days/week for 12 months, followed by a 12-month observation period. Interstitial fibrosis, granulomatous inflammation and bronchiolar/alveolar hyperplasia occurred in a number of animals during the observation period, most pronounced in the high-dose group. Increased numbers of alveolar/intraalveolar macrophages and particulate material in alveolar/intraalveolar macrophages were seen in all dose groups during both the exposure and the observation periods. The data showed a lung burden-dependent effect on the diantimony trioxide clearance rate in the high-dose group. It was calculated that with a lung containing approximately 2 mg of diantimony trioxide after 52 weeks of exposure, pulmonary clearance was decreased by 80% with an increase in the clearance halftime from 2 to 10 months. The clearance mechanism was significantly impaired at this exposure level and was interpreted as an intrinsic toxic effect of diantimony trioxide rather than a general effect due to particle overload. Absolute and relative lung weights were unaffected in all exposure groups. Based on impaired lung clearance, the LOAEC and NOAEC for repeated dose inhalation toxicity were considered to be 4.50 mg/m^3 and 0.51 mg/m^3 , respectively. The NOAEC was determined in a study with a high background incidence of lung inflammation in controls; therefore there is some uncertainty regarding the reliability of the numerical values. In an OECD guideline 90-day oral study, diantimony trioxide did not cause systemic toxicity at doses up to 1686 and 1879 mg/kg bw/day in male and female rats, respectively.

Diantimony trioxide is not considered to induce gene mutations *in vitro*, but induces structural chromosome aberrations in cultured mammalian cells *in vitro*. Oral *in vivo* studies on the induction of chromosome aberrations and micronuclei in the bone marrow and unscheduled DNA synthesis in the liver have produced negative results. It is believed that a possible local genotoxic effect of diantimony trioxide would only be biologically relevant at concentration levels that also cause particle overload. Therefore, there is also no concern for local genotoxicity of diantimony trioxide in the lung.

Three chronic toxicity/carcinogenicity studies in rats with inhalation exposure to diantimony trioxide were available. The exposure duration in all three animal studies was 12 months only. In the study by Watt, inhalation of 5.0 mg/m^3 diantimony trioxide produced lung neoplasms in 44% of the animals tested (only females were exposed). In the study by Groth et al., 45 mg/m^3 diantimony trioxide produced pulmonary

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neoplasms in 32% of the female rats exposed but none in the male rats. The study by Newton et al., showed no lung tumours at any dose level up to 4.5 mg/m³. A comparison of the histopathology tissue sections from the Watt- and the Newton-studies indicated higher lung deposition of antimony and more severe lung damage in exposed rats in the Watt-study than in the Newton-study, which allegedly were conducted at similar exposure levels (1.9-5.0 and 0.06-4.50 mg/m³, respectively). This suggests that the exposure levels in the Watt study were likely higher (5-fold) than those reported, and consequently make the study unsuitable for derivation of a NOAEC.

Based on these data it is concluded that diantimony trioxide induces tumours in rat lung. The most likely mechanism for the lung carcinogenicity is impaired lung clearance and particle overload followed by an inflammatory response, fibrosis and tumours. Consequently, diantimony trioxide can be regarded as a threshold carcinogen and the NOAEC of 0.51 mg/m³, derived for local repeated dose toxicity and based on impaired clearance of particles, is also used for carcinogenicity. The NOAEC was determined in a study with a high background incidence of lung inflammation in controls, therefore there is some uncertainty regarding the reliability of the numerical value.

No reproductive toxicity studies have been conducted for diantimony trioxide. However, detailed examination of male and female reproductive organs from repeated-dose toxicity studies via the oral route of exposure has been done. Testicular toxicity of diantimony trioxide has been investigated in male mice and male rats. In this 4-week study, diantimony trioxide was administered via gavage to 10 mice and 8 rats/dose at 0, 12.0 and 1 200 mg/kg bw/day, for 5 and 3 days/week, respectively. An oral NOAEL = 1 200 mg/kg bw/day for testicular toxicity was determined. In a rat 90-day oral feeding study performed according to OECD TG 408 no histopathological changes were observed in testes up to a dose of 1686 mg/kg bw/day, or in ovaries and uterus up to a dose of 1879 mg/kg bw/day. Based on these results, diantimony trioxide was not toxic to male or female reproductive tissues.

The developmental toxicity of diantimony trioxide has been investigated, following a test protocol based on the OECD TG 414. However, some alterations in the conduct of the study have been made. Twenty-six mated rats per group were exposed (nose-only) from day 0 to day 19 of gestation at concentrations of 0, 2.6, 4.4 or 6.3 mg diantimony trioxide/m³. No evidence of developmental toxicity was observed in rats at doses up to 6.3 mg diantimony trioxide/m³ and the NOAEC for developmental toxicity was 6.3 mg/m³, the highest exposure level tested. The LOAEC for maternal toxicity (acute pneumonia and significantly increased absolute and relative lung weights relative to controls) in this study was 2.6 mg/m³. However, body weight and food intake were not affected at any dose level.

Environment

In the environment diantimony trioxide will slowly dissolve and transform into Sb(OH)₃, which is oxidized to Sb(OH)₆⁻ under oxygenated (or oxic) conditions. Antimony, being a natural element, cannot by definition be degraded. However, it can be transformed between different binding/speciation forms and oxidation states.

Combustion/incineration processes transform antimony compounds to diantimony trioxide regardless of the pre-incinerated form of antimony. There are indications that diantimony trioxide may dissolve in the atmosphere and that the trivalent form will oxidize to the pentavalent form. Antimony is deposited from the atmosphere predominantly dissolved in rain, but also as particulate matter in wet and dry deposition.

In natural waters dissolved antimony exists almost exclusively in the two valency states +3 and +5 as Sb(OH)₃ and Sb(OH)₆⁻, respectively. According to thermodynamic calculations, antimony should almost exclusively be present as Sb(V) in oxic systems, and as Sb(III) in anoxic systems. Even though the dominant species in oxic waters is Sb(V), Sb(III) has been detected in concentrations much greater than predicted concentrations, and the reverse is true for Sb(V) in anoxic systems.

After slow dissolution and subsequent oxidation of Sb₂O₃ in soil, its fate is controlled by sorption of Sb(OH)₆⁻ on soil constituents and precipitation of Ca[Sb(OH)₆]₂. The solubility of antimony compounds depends on the soil conditions (Eh/pH) and the time given to dissolve. The most important soil characteristic as regards the mobility of antimony in soil (and sediments) appear to be pH and the presence of hydrous oxides of iron, manganese, and aluminium, to which antimony may adsorb with decreasing sorption at increasing pH. In addition, hydrous oxides seem to oxidise dissolved trivalent antimonite (Sb(OH)₃) to the pentavalent antimonate (Sb(OH)₆⁻). Due to the anionic character of the dissolved species (Sb(OH)₆⁻), antimony is expected to have a low affinity for organic carbon. However, there exist results that indicate that the sorption of Sb(V)

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by humic acid in acid soils with high proportions of organic matter may be more important than previously suspected, although the strong Sb(V) scavenging potential of $\text{Fe}(\text{OH})_3$ probably results in a diminished role of organic matter binding in soils with high amounts of non-crystalline hydroxides. The cationic exchange reactions, which are the main sorption reactions on clay minerals, are not expected to be important for the anionic antimony.

Antimony released to the environment will eventually end up in either of the two compartments soil or sediment, depending on the release, the form of antimony, meteorological conditions, etc. The distribution of antimony between aqueous phase and soil/sediment/suspended matter is described using the partitioning coefficients $\log K_{p_{\text{soil}}} = 1.98 \text{ L/kg}$, $\log K_{p_{\text{suspended matter}}} = 3.65 \text{ L/kg}$ and $\log K_{p_{\text{sediment}}} = 3.4 \text{ L/kg}$.

The bioaccumulation potential seems to be low to moderate. No reliable bioaccumulation studies were available and measured data from different aquatic organisms have been used to calculate tentative BCF values. For marine fish the BCFs vary between 40 and 15000 whereas for freshwater fish the BCF values are lower, the highest being 14. For invertebrates tentative BCFs below 1 up to 4000-5000 have been calculated. It should be noted that there is a considerable uncertainty in these BCF values. An assessment of secondary poisoning using the tentative BCF values raised no concern.

The lowest reliable acute and chronic toxicity data for different aquatic organisms are presented below. Except for the marine fish *Pargus major*, for which the source of antimony was $\text{K}[\text{Sb}(\text{OH})_6]$, all these data were obtained using SbCl_3 . The reported aquatic toxicity values are above the solubility limits of antimony when using diantimony trioxide at the pH levels used in these studies.

Acute toxicity test results:

Marine fish [<i>Pargus major</i>]	96 h LC50	= 6.9 mg Sb/L (measured total)
Freshwater fish [<i>Pimephales promelas</i>]	96 h LC50	= 14.4 mg Sb/L (measured filtered)
Invertebrates [<i>Chlorohydra viridissimus</i>]	96 h LC50	= 1.77 mg Sb/L (measured filtered)
Algae [<i>Raphidocelis subcapitata</i>]	72 h E_r C50	> 36.6 mg Sb/L (measured total)
	(growth rate)	

Chronic toxicity test results:

Fish [<i>Pimephales promelas</i>]	28 d NOEC/LOEC (growth; length)	= 1.13/2.31 mg Sb/L (measured total)
Invertebrates [<i>Daphnia magna</i>]	21 d NOEC/LOEC (reproduction)	= 1.74/3.13 mg Sb/L (measured total)
Algae [<i>Raphidocelis subcapitata</i>]	72 h NOEC/LOEC (growth rate)	= 2.11/4.00 mg Sb/L (measured total)

The lowest chronic toxicity data for sediment organisms were observed for the midge *Chironomus riparius*: 14-d NOEC (growth) = 78 mg Sb/kg ww (SbCl_3 used). The lowest reliable terrestrial toxicity data were determined in a soil spiked with Sb_2O_3 and aged for 31 weeks before testing.

Lowest chronic toxicity test results for terrestrial species:

Plants [<i>Hordeum vulgare</i>]	5 d NOEC (root elongation)	= 370 mg Sb/kg dw (measured*)
Invertebrates [<i>Folsomia candida</i>]	28 d NOEC (reproduction)	= 370 mg Sb/kg dw (measured*)
Microorganisms	7 d NOEC (nitrification)	= 710 mg Sb/kg dw (measured*)

*Recalculated in order to represent toxicity data in fully equilibrated diantimony trioxide amended soil (see below).

Since the equilibrium pore water concentration was not reached during the study period used, the NOEC values were recalculated using the pore water concentrations measured at the NOEC (9.7 mg Sb/L (plants and invertebrates) and 18.7 mg Sb/L (microorganisms)), and the equilibrium solid:liquid distribution coefficient (K_d) for antimony for this soil, i.e. 38 L/kg.

Exposure

Diantimony trioxide is commercially produced at four sites in the EU (2006). The annual production volume in year 2005 was 24 250 tonnes in the EU and approximately 120 000 tonnes worldwide. In 2002 the worldwide production was about 112 600 tonnes, with China producing the largest part (47%) followed by US/Mexico

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(22%), Europe (17%), Japan (10%), South Africa (2%) and other countries (2%). Diantimony trioxide is mainly produced by re-volatilizing of crude stibnite or oxidation of antimony metal, with the latter process dominating in the EU. In the EU in 2005, diantimony trioxide was used as flame-retardant in plastics (38%), PVC (36%), rubber (9%) and textiles (7%), as a catalyst in polyethylene terephthalate production (4%), additive in glass manufacture (1%) and in pigments in paint and ceramics (5%).

Occupational exposure through inhalation of airborne dust and dermal contact with powder, pellets, paste, granules or final products is possible. Consumer exposure may occur through inhalation, ingestion and dermal contact with articles containing diantimony trioxide or domestic dust, but the exposure levels are low. (~60.000 times lower than the NOAEC established in long-term repeated dose inhalation study).

Diantimony trioxide is released to the environment via emissions to air, waste water, surface water and soil from manufacture, formulation, processing, use and disposal of diantimony trioxide, but also via coal combustion and refuse incineration, non-ferrous metal production (e.g. Cu), and road traffic. Humans may be exposed via the environment by inhalation of particles in air or ingestion of contaminated food and water, but the exposure levels are low.

Total estimated emissions of antimony into the environment in the EU from production of Sb_2O_3 are 1.36 tonnes per annum (tpa) to air, 0.006 tpa to surface water, 1.79 tpa to industrial urban soil. Total antimony emissions from formulation/industrial use/service life (of flame-retardants in plastic and rubber, flame-retardants in textiles, use as catalyst in the polyethylene terephthalate industry, use in paint and use in glass), were estimated to be 0.43 tpa to air, 1.75 tpa to surface water, 29.75 tpa to waste water and 34.49 tpa to industrial urban soil. Antimony emissions from disposal (100% incineration/100% landfill) were calculated to be 4.5/0 tpa to air, 5.4/0.38 tpa to waste water and 0/0.05 tpa to surface water. Total estimated emissions of antimony from unintentional sources are 16.67 tpa to air, 0.8 tpa to surface water and 2.5 tpa to industrial urban soil. Overall exposure is considered to be low compared to mammalian toxicity effect levels.

Realistic worst case (RWC) ambient concentrations were calculated as the median of the country specific 90th percentile values using available ambient measured data from EU countries (and Norway). RWC ambient concentrations were derived for fresh water (0.72 $\mu\text{g Sb/L}$; dissolved), freshwater sediment (3 mg Sb/kg dw), soil (1.7 mg Sb/kg dw), air (2.6 ng Sb/ m^3), marine water (0.20 $\mu\text{g Sb/L}$; dissolved) and marine sediment (3 mg Sb/kg dw).

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (skin irritation, lung toxicity and lung carcinogenicity after repeated exposure). Member countries are invited to perform an exposure assessment for workers and if then indicated a risk assessment.

As all studies on chronic toxicity/carcinogenicity deviate from the OECD guideline, which prescribes an exposure period of 24 months for rats and because of other critical shortcomings in the data set on chronic toxicity/carcinogenicity, the US NTP (National Toxicology Program - see <http://ntp.niehs.nih.gov>) has initiated 2-year inhalation toxicology and carcinogenicity studies on diantimony trioxide in rats and mice.

Environment

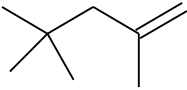
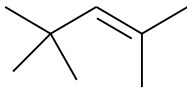
This chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). However, based on data presented by the Sponsor Country, relating to production by 4 producers in Europe which accounts for ~1/6 of the global production and relating to the use pattern in EU countries, exposure to the environment is expected to be low. Countries may desire to investigate any

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exposure scenarios that were not presented by the Sponsor country.

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SIDS INITIAL ASSESSMENT PROFILE

CAS No.	25167-70-8
Chemical Name	2,4,4-Trimethylpentene
Structural Formula	  2,4,4-Trimethylpent-1-ene 2,4,4-Trimethylpent-2-ene

SUMMARY CONCLUSIONS OF THE SIAR**Analogue rationale**

2,4,4-Trimethylpentene is a mixture of two isomers 2,4,4-Trimethylpent-1-ene (CAS-No.: 107-39-1) with a typical content of > 71.0 % (range 70 - 80%) and 2,4,4-Trimethylpent-2-ene (CAS-No.: 107-40-4) with a typical content of < 22.4 % (range 15 - 25%).

Physical-chemical properties

2,4,4-Trimethylpentene is a colourless liquid (relative density 0.7166 at 20 °C) with a melting point <-50 °C, a boiling point of 101.4-103.6°C (1013 hPa) and a measured vapour pressure of 57.90 hPa at 25 °C. The measured partition coefficient (log Kow) is 5.0, and the water solubility is 1.8 mg/L at 20 °C.

Human Health

No data regarding toxicokinetics, metabolism and distribution are available on 2,4,4-trimethylpentene.

There are no studies available on oral, dermal or inhalative absorption. From the physico-chemical data (log Pow 5.0, water solubility 1.8 mg/l, molecular weight 112 g/mol, vapour pressure 57.9 hPa at 25°C) it is expected that the substance shows a good oral and dermal bioavailability. In vitro studies on structurally similar compounds, e.g., short chain olefins (n-1-octene, n-4-octene, and 3-ethyl-2-pentene) with rat liver microsomes demonstrated the conversion of olefins to diols via epoxide intermediates. Similar reactions can be assumed for 2,4,4-trimethylpentene although the quantitative extent remains to be determined.

The acute toxicity of 2,4,4 trimethylpentene was low for the oral, dermal and inhalation routes of exposure in animal studies. Oral LD₅₀ values > 2 000 mg/kg bw for rats (OECD TG 401), inhalative LC₅₀ value of 31.5 mg/l for male rats and 30.0 mg/l for female rats and a dermal LD₅₀ value for rats >2000 mg/kg bw (OECD TG 402) were obtained. In compilation of all toxicological information on C6-C28 olefins it is stated that aspiration may be a hazard with C6-C14 olefins. Human data on acute toxicity of 2,4,4-trimethylpentene are not available.

Human data on local irritation of 2,4,4-trimethylpentene showed effects on the mucosa of nose and throat at a concentration of 465 mg/m³. In Draize tests with rabbits 2,4,4-trimethylpentene demonstrated moderate skin irritation (increasing irritation, eschar formation and exfoliation) after a 4-hours semi-occluded application (OECD TG 404) and mild eye irritation after instillation into the conjunctival sac (OECD TG 405).

In a guinea pig maximization test (OECD TG 406) a significant dermal response (a reaction more marked than the most severe among the control animals) were observed in 3/20 test animals following challenge application of the 75% substance formulation. Human data on sensitisation by skin contact or after inhalation as well as animal data on inhalation sensitisation are not available. Overall there is no convincing evidence that 2,4,4 trimethylpentene has skin sensitisation potential.

In a valid 28-day oral toxicity study according to OECD TG 407 (revised 1995) rats were administered by gavage 2,4,4-trimethylpentene (purity 99.1%) daily for 28 days at dosages of 0, 100, 300, 1 000 mg/kg bw/day. The liver and kidneys were identified as target organs. A significant increase in kidney weight (males) and liver weights (absolute and relative) were associated with significantly increased plasma proteins, albumin and urea in males at 1000 mg/kg bw/day and significantly decreased plasma glucose and urea in 1000 mg/kg bw/day females but without corroborating findings in histology. The increased urea concentration may be related to a minor alteration in renal function. The NOAEL in this study was considered to be 300 mg/kg bw/day derived from the effect on the liver at

the highest dose.

In an oral (gavage) reproductive developmental screening test according to OECD TG 421 rats were treated with 2,4,4-trimethylpentene (purity 99.1%) at 100, 300 and 1 000 mg/kg bw/day to groups of 10 males and 10 females for 15 days before mating. Treatment was continued throughout mating, gestation and lactation to day 3 of lactation for females and to termination after approximately 6 weeks of treatment for males. Relevant treatment-related effects were observed only in male rats. There were nephrotoxic effects, mainly in the cells of the proximal tubuli. After repeated oral exposure of 300 or 1000 mg/kg bw/day 2,4,4-trimethylpentene, an increased absolute and relative kidney weight was exhibited in male rats. Microscopy of the kidneys revealed basophilic cortical tubules at 100 mg/kg bw/day (LOAEL) and above, and proteinaceous casts and interstitial inflammatory cells at 300 mg/kg bw/day and above. Females that received 1 000 mg/kg bw/day had slightly elevated kidney weights without relevant microscopic changes. The kidney effects in male rats observed in the reproductive developmental screening test on 2,4,4-trimethylpentene are linked with the accumulation of α_{2u} -Globulin, detected by specific immunostaining of α_{2u} -Globulin, which resulted in the formation of hyaline droplets and kidney toxicity in male (not female) rats. α_{2u} -Globulin is a low molecular weight protein almost exclusively produced by the male rat, and are, therefore, not relevant to humans. For the calculation of an overall NOAEL the data of the 28-day toxicity study should be selected with the value of 300 mg/kg bw/day derived from the effect on the liver. There are no valid animal inhalation studies and at present, no studies with dermal administration of 2,4,4-trimethylpentene available.

On the basis of negative *in vitro* results from a bacterial mutation test (OECD TG 471) and a chromosomal aberration test with human lymphocytes (OECD TG 473) there is no evidence of a genotoxic potential of 2,4,4 trimethylpentene.

There are no cancer studies on 2,4,4 trimethylpentene available. Negative data from mutagenicity *in vitro* testing give no concern on genotoxic properties of the substance.

In a reproductive developmental screening test according to OECD Guideline 421 rats were administered 2,4,4-trimethylpentene by oral gavage at dosages of 100, 300 or 1000 mg/kg bw/day in maize oil at a volume-dosage of 5 mg/kg bw to groups of ten male and ten female rats for 15 days before pairing. Treatment was continued throughout mating, gestation and lactation to day 3 of lactation for females and to termination after approximately six weeks of treatment for males. All females were permitted to deliver and rear their offspring to postnatal day 4. Oral administration of 2,4,4-trimethylpentene to CD rats for 40 to 46 days (during premating, mating, gestation and up to lactation day 4) at dosages of up to 1 000 mg/kg bw/day did not reveal any indications for an impairment of reproductive performance and capability or peri/postnatal viability and performance of offspring up to postnatal day 4 at a screening level (NOAEL for reprotoxic effects: 1 000 mg/kg bw/d). Overall, 2,4,4 trimethylpentene is not a developmental toxicant.

Environment

Based on the molecular structure, hydrolysis of 2,4,4-trimethylpentene is not expected at environmental conditions. Tests concerning hydrolysis are not available. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 7.24 hours. A closed bottle test (OECD 301D) resulted in 0 % biodegradation after 28 days. 2,4,4-trimethylpentene is not readily biodegradable under aerobic conditions. A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that CBS will distribute mainly to sediment (62.9%) and water (27.5%), compartments with minor distribution to soil (8.04) the air (1.59%) compartment. A estimated Henry's law constant of $2.127 \cdot 10^5$ Pa.m³/mole at 25 °C suggests that volatilization of 2,4,4-trimethylpentene from the water phase is expected to be high. The adsorption coefficient log K_{oc} of 2,4,4-trimethylpentene was determined as 2.75 by the HPLC screening test method. Bioaccumulation potential seems to be high based on the log K_{ow} of 5.0. 2,4,4-trimethylpentene is expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor of 868.

The following acute toxicity test results (measured concentrations) have been determined for aquatic species:

e.g.,	Fish [<i>Oncorhynchus mykiss</i>]	96 h LC ₅₀ = 0.58 mg/L
	Invertebrate [<i>Daphnia magna</i>]	48 h LC ₅₀ = 1.2 mg/L
	Algae [<i>Selenastrum capricornutum</i>]	72 h ErC ₅₀ = 1.67 mg/L (growth rate method)
	Algae [<i>Selenastrum capricornutum</i>]	72 h EbC ₅₀ = 0.86 mg/L (area under growth curve method)

Exposure

2,4,4-trimethylpentene is commercially produced with an annual production volume of 40.000-50.000 tonnes in the EU. Worldwide production volume is not available. 2,4,4-trimethylpentene is produced via two production processes. Both processes are continuous and in both processes iso-butenes are used as feedstock. The complete process takes place in a closed system. 2,4,4-trimethylpentene is mainly used as chemical intermediate (> 99%) for

the production of 3,5,5-trimethylhexanal (Isononal), 3,5,5-trimethylhexanoic acid, 2,2,4-trimethylpentan and 3,5,5-trimethylhexanol. Less than 1% of the total production volume is also used as solvent for paints, lacquers and varnishes.

No monitoring data for effluents, surface water in occupational settings from are available from the production and processing sites in the EU.

Occupational exposure by inhalation or dermal contact is possible.

Consumer exposure is considered to be negligible, since there is no evidence available on the use of 2,4,4-trimethylpentene in consumer products.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

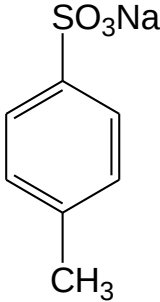
The chemical is of low priority for further work. The chemical possess hazards for human health (irritation). These hazards do not warrant further work as they are related to transient effects. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor Country.

Environment

The chemical is a candidate for further work. The substance has properties indicating a hazard for the environment (aquatic toxicity < 1 mg/l for fish. 1-10 mg/l for aquatic invertebrate and algae.). Member countries are invited to perform an exposure assessment and, if necessary, a risk assessment.

Note: A risk assessment performed in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union is available.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	657-84-1
Chemical Name	Sodium <i>p</i> -toluenesulfonate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue rationale**

At SIAM 21 in 2005, the Hydrotropes category was discussed and approved. The Hydrotropes category covers “toluene sulfonic acid, sodium salt”, “xylene sulfonic acid, sodium salt” and “cumene sulfonic acid, sodium salt”. This category also includes isomeric forms (ortho, meta, and/or para) of the respective sulfonic acid salts (sodium, ammonium, calcium and potassium). Although “sodium *p*-toluenesulfonate” is one of the category member, the SIDS documents of sodium *p*-toluenesulfonate are prepared separately as the sponsor country has obtained some new test (or experimental) data on this chemical. New SIDS information on sodium *p*-toluenesulfonate is introduced in this document, however, the evaluation of the endpoints of skin/eye irritation and sensitization were read across from the Hydrotropes category document.

Physical-chemical properties

Sodium *p*-toluenesulfonate is white crystal solid with a melting point of > 300 °C at 1013 hPa. Although an estimated boiling point is 533 °C, sodium *p*-toluenesulfonate may decompose before reaching this temperature. Vapour pressure and partition coefficient (Log K_{ow}) are estimated to be of 3.51×10^{-9} Pa at 25 °C and -2.40 respectively. Measured and estimated values for water solubility are > 250 g/L at 20 °C and 1000 g/L at 25 °C respectively.

Human Health

Sodium *p*-toluenesulfonate-³⁵S was rapidly absorbed and excreted by rats and dogs given an oral or intraperitoneal administration. Both species excreted the radioactivity primarily in the urine (82–85 % of the dose) and, to a lesser extent, in the feces (13–18 % of the dose). In dogs, sodium *p*-toluenesulfonate-³⁵S had a biological half-life in the plasma of 75 min. Only the unaltered *p*-toluenesulfonate-³⁵S moiety was detected chromatographically in the excreta of both species.

The oral LD₅₀ values in rats for sodium *p*-toluenesulfonate were greater than 2000 mg/kg bw in both sexes [OECD TG 401]. Sodium *p*-toluenesulfonate administered orally caused diarrhea at a dose of 2000 mg/kg bw. No valid studies were available for sodium *p*-toluenesulfonate for acute dermal and acute inhalation studies.

In the Hydrotropes Category, calcium xylene sulfonate and sodium cumene sulfonate are concluded to be non skin irritants. However, sodium *p*-toluenesulfonate may have a potential to cause skin and eye irritation in animals due to high pH(9.6) in aqueous solution, although no direct experimental data are available.

No studies of respiratory tract sensitisation on sodium *p*-toluenesulfonate are available. There is no indication of skin sensitization for toluenesulfonic acid, sodium salt (ortho, meta and/or para) in

guinea pigs according to the SIDS document of Hydrotopes category. It is therefore considered that sodium *p*-toluenesulfonate is not a skin sensitizer.

In a repeated-dose oral toxicity study in rats [OECD TG 407], sodium *p*-toluenesulfonate was administered orally by gavage to male and female rats (5 or 10 animals/sex/group) for 28 days at doses of 0, 100, 300 and 1000 mg/kg bw/day. As recovery groups, 5 animals/sex from the control and high-dose groups were sacrificed at the end of the recovery period (day 43). No deaths were observed in any group. There were no treatment-related changes in clinical signs, body weight, food intake and hematological or biochemical examination in either sex. An increase in urine specific gravity observed in male groups at 1000 mg/kg bw/day was considered to have no toxicological significance because no other relevant changes were found. Based on these results, the NOAEL for this repeated-dose oral toxicity study was found to be 1000 mg/kg bw/day in both male and female rats.

In an oral reproductive and developmental toxicity screening test (OECD TG 421: doses of 0, 100, 300 and 1000 mg/kg bw/day), diarrhea and soft feces were observed as systemic general toxicity at the dose of 1000 mg/kg in parental male and female animals. And inflammatory cellular infiltration of lamina propria and squamous cell hyperplasia in the stomach limiting ridge were observed in the male group at 1000 mg/kg bw/day. The NOAEL of systemic toxicity for this reproductive and developmental toxicity screening test was found to be 300 mg/kg bw/day.

The overall NOAEL of sodium *p*-toluenesulfonate for repeated dose oral toxicity was found to be 300 mg/kg bw/day in both male and female rats.

No data are available for the repeated-dose inhalation and dermal toxicity of sodium *p*-toluenesulfonate.

A bacterial reverse mutation assay using four strains of *Salmonella typhimurium* and an *Escherichia coli* strain, WP2 *uvrA* [OECD TG 471] on sodium *p*-toluenesulfonate was negative both with and without metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells [OECD TG 473] was also negative with or without metabolic activation. Although there are no data available for *in vivo* mutagenicity on sodium *p*-toluenesulfonate, the chemical is not considered to be genotoxic *in vitro* based on negative outcomes in *in vitro* assays.

No data are available for the carcinogenicity of sodium *p*-toluenesulfonate.

In a reproductive and developmental toxicity screening test in rats [OECD TG 421], sodium *p*-toluenesulfonate was administered orally by gavage at doses of 0, 100, 300 and 1000 mg/kg bw/day. Then both the reproductive performance of parental animals and the development and growth of F1 offspring were examined. There was no significant effect of sodium *p*-toluenesulfonate on the numbers of total offspring and live offspring, sex ratio, live birth index, viability index or body weight, and no compound-related abnormality was found in external features, clinical signs or autopsy findings of offspring up to 1000 mg/kg bw/day, the highest dose tested, while some toxic effects on parental animals (diarrhea, soft feces, etc.) were observed at 1000 mg/kg bw/day. Thus the NOAEL for reproductive and developmental toxicity was considered to be 1000 mg/kg bw/day in rats.

Environment

Sodium *p*-toluenesulfonate is dissociated into sodium ion and *p*-toluenesulfonate ion in water. Hydrolysis test of *p*-toluenesulfonate according to OECD Test-guideline 111 shows no hydrolysis at pH4, pH7 and pH9 at 50 °C for 5 days. *p*-Toluenesulfonate is readily biodegradable under aerobic conditions with BOD biodegradability of 93 % in 3 weeks (equivalent to OECD TG301C). Bioaccumulation potential of sodium *p*-toluenesulfonate seems to be low based on an estimated Log K_{ow} of -2.40, which is supported by a calculated BCF value of 3.16 with BCFWIN.

In the atmosphere, indirect photo-oxidation of sodium *p*-toluenesulfonate by reaction with hydroxyl radicals is estimated to result in a half-life of 8.8 days. However, photo-degradation as an environmental fate mechanism may not be important as sodium *p*-toluenesulfonate is not volatile.

Sodium *p*-toluenesulfonate has an estimated Henry's law constant of 2.83×10^{-4} Pa.m³/mole at 25 °C, which suggests that volatilization of sodium *p*-toluenesulfonate from the water phase is expected to be negligible. Level III fugacity model shows that sodium *p*-toluenesulfonate will distribute mainly to the water compartment (99.8 %) with minor distribution to the sediment compartment (0.18 %) and negligible amounts in the air and soil compartments if released only to the water compartment.

The following acute toxicity test results have been determined for aquatic species:

<i>Oryzias latipes</i> :	96 h LC ₅₀ >100 mg/L (nominal)
<i>Daphnia magna</i> :	48 h LC ₅₀ >1,000 mg/L (nominal)
<i>Pseudokirchneriella subcapitata</i> :	72 h ErC ₅₀ > 1,000 mg/L (growth rate method, nominal)
<i>Pseudokirchneriella subcapitata</i> :	72 h EbC ₅₀ > 1,000 mg/L (AUG method, nominal)

The following chronic toxicity test results have been determined:

<i>Daphnia magna</i> :	21 d NOEC = 100 mg/L (nominal)
<i>Pseudokirchneriella subcapitata</i> :	72 h NOErC = 10 mg/L (growth rate method, nominal)
<i>Pseudokirchneriella subcapitata</i> :	72 h NOEbC = 10 mg/L (AUG method, nominal)

Exposure

In Japan, sodium *p*-toluenesulfonate was commercially produced and/or imported with an annual production volume of 100 tonnes – 1,000 tonnes in the fiscal year 2004. According to the SPIN database, the total use of sodium *p*-toluenesulfonate was less than 10 tonnes in the Nordic countries in 2006. The worldwide production volume outside Japan is not available. Sodium *p*-toluenesulfonate is manufactured by neutralization of *p*-toluene sulfonate with sodium hydrate, here *p*-toluenesulfonate is made by sulfonation of *p*-toluene with sulphuric acid. Sodium *p*-toluenesulfonate is used as an anti-blocking agent in powder products, a solubilizer in detergents, and a dilution agent in dyes. No other information for the use pattern is obtained in the sponsor country.

In the sponsor country, manufacturing and formulation of sodium *p*-toluenesulfonate are conducted in a closed system. Even if a limited amount of sodium *p*-toluenesulfonate is released into the waste-water stream at production and processing sites, waste water stream is treated in the waste-water treatment plant. Furthermore, as sodium *p*-toluenesulfonate is readily biodegradable, emission of sodium *p*-toluenesulfonate from the production and processing sites into the environment is anticipated to be low. No monitoring data from production and processing sites are available in the sponsor country.

Sodium *p*-toluenesulfonate is used in consumer products, like detergents. Therefore, release from down-the-drain discharges following product use could lead to the environmental exposure into the surface water. However, as sodium *p*-toluenesulfonate is biodegradable and has limited potential for bio-accumulation, long-term environmental exposure is not foreseen.

Occupational exposure through an inhalation of aerosol may be a concern, and inhalation of vapor is negligible due to very low vapor pressure. Dermal intake may also be negligible due to low logK_{ow}.

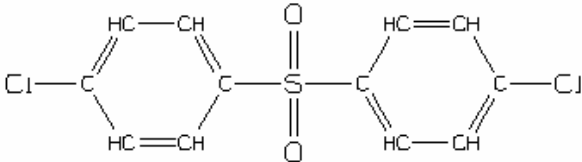
As sodium *p*-toluenesulfonate is used in consumer products, consumer exposure through dermal contact could exist. There are some potential intakes for incidental ingestion, inhalation and eye contact with sodium *p*-toluenesulfonate. However, these potential intakes may be mitigated by the fact that sodium *p*-toluenesulfonate is easily washed off through careful handling by consumers. No other information on consumer exposure is available.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: This chemical is currently of low priority for further work because of its low hazard profile.

Environment: This chemical is currently of low priority for further work because of its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	80-07-9
Chemical Name	4,4'-Dichlorodiphenyl sulfone
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

4,4'-Dichlorodiphenyl sulfone (DCDPS) is manufactured as an off-white powder or as solid pellets. Based on EPI Suite (version 3.20) calculations it has a melting point of 146 °C and a boiling point of 390 °C. The calculated vapour pressure at 25° Celsius was low (1.08E-06 hPa). The measured water solubility (at 20° Celsius) of DCDPS is 0.86 mg/l, while the measured log K_{ow} (at 22° Celsius) is 3.9.

Human Health

The fate of uniformly ^{14}C labeled DCDPS has been studied, in rats, both after intravenous administration and after repeated oral exposure. Based on the results the substance is readily absorbed from the gastrointestinal tract, distributed to all tissues examined, concentrated in adipose tissue mainly as parent compound, and reached steady state after ~2 weeks. Excreted DCDPS equivalents were primarily present as metabolites. Five metabolites have been found and two of these were identified: 3-hydroxy-4,4'-dichlorodiphenyl sulfone and its glucuronide.

The acute oral LD_{50} (rat) was higher than 2000 mg/kg bw. Valid acute toxicity studies, using dermal or inhalation exposure, were not available.

No valid irritation or sensitisation studies were available.

Data from five valid dietary repeated dose studies, including one chronic study on rats and one chronic study on mice, are available. The rats, in the chronic study, were exposed to DCDPS via the diet during 105 weeks and the mice during 105-106 weeks. Based on the results from these chronic studies, an overall No Observed Adverse Effect Level (NOAEL) of 1.5 mg/kg bw/day was established for repeated dose toxicity. The NOAEL is based on liver effects e.g. centrilobular hepatocyte hypertrophy, bile duct hyperplasia and centrilobular degeneration identified in chronic studies. Decreased body weight, increased liver and kidney weight, increased incidence of nephropathy and decreased thymus weight were other effects that were evident at higher doses. During a 28-day study on rats, a slight enzyme induction in the liver was observed at a dose of 0.8 mg/kg bw/day but with no marked liver weight increase or other effects apparent. This slight enzyme induction, without any other corroborative effects is, in this case, not considered as an adverse effect.

DCDPS did not induce gene mutations in bacterial assays. In studies with mammalian cells, weak responses (1.7 to 3.1 fold vehicle control values) were obtained in the mouse lymphoma L5178Y assay without S9. The study was conducted according to GLP and OECD Guideline 476. The result of the sister chromatid exchange study in CHO cells was equivocal in the absence of S9 and negative in the presence of S9. In a HGPRT gene mutation assay with Chinese hamster ovary (CHO) cells DCDPS was negative in both the absence and presence of metabolic activation (S9). In a chromosomal aberration test with CHO cells, no induction of chromosomal aberrations, in presence and absence of S9, was observed. Based on these results it is concluded that the mutagenicity of DCDPS is equivocal *in vitro*. *In vivo*, positive results were obtained in a mouse bone marrow micronucleus study after repeated i.p. injection over a dose range of 200 to 800 mg/kg bw/day. In this study, the positive results were confirmed in a second experiment. In another study, negative results were obtained after a single i.p. injection of up to 1960 mg

DCDPS/kg bw. However, in this study the bone marrow might not have been sufficiently exposed. During an Unscheduled DNA Synthesis (UDS) assay, done according to OECD Guideline 486, DCDPS did not cause DNA damage in the rat. From these results it can be concluded that DCDPS is mutagenic *in vivo*.

Two carcinogenicity studies, performed according to currently accepted guidelines and GLP standards, are available for rat and mouse (see paragraph on repeated dose toxicity). In these 2-year studies, there were no increases in the incidences of neoplasms in the liver or any other organ in rats or mice, which were related to DCDPS exposure. From these studies it can be concluded that DCDPS is not a carcinogen.

An oral reproduction/developmental toxicity screening test has been performed according to GLP and OECD Guideline 421. The daily administration of DCDPS to rats by gavage at dose levels of 5, 15 and 50 mg/kg bw/day resulted in centrilobular hepatocyte hypertrophy and liver enlargement in adult animals of either sex from all treatment groups. The dose of 5 mg/kg bw/day is regarded as a Lowest Observed Adverse Effect Level (LOAEL) based on liver effects, for adult toxicity. During repeated dose studies liver effects were also observed and used for establishment of the NOAEL. The results of the reproduction/developmental toxicity screening test revealed no effects on fertility or developmental toxicity and therefore the highest dose of 50 mg/kg bw/day was regarded as NOAEL for fertility and developmental toxicity. A reduction in bodyweight gain was observed in offspring from rats treated with 50 mg/kg bw/day but maternal toxicity was evident at this dose level. Histological examinations of the reproductive organs during the reproduction/developmental toxicity study and during four valid repeated dose studies did not reveal any effects on the reproductive organs. It can be concluded that DCDPS has neither an effect on developmental toxicity nor on fertility.

Environment

The substance is considered to be hydrolytically stable based on an expected half-life greater than one year at 25°C. DCDPS is not readily biodegradable. EPI Suite (version 3.20) was used to calculate the rate of photodegradation of DCDPS. The half-life was calculated to be 18 days based on a mean hydroxyl radical concentration of 1.5×10^6 OH-radicals $\cdot$ cm⁻³ over a 12-hour day. A level III fugacity model calculation, using a four compartment (air, water, soil and sediment) model has been conducted using EPI Suite version 3.20. An emission of 1.0 kg/h in the water compartment was hypothesized. Based on the results of the calculation, DCDPS is expected to partition to the aquatic compartment (80.8 %) with the remainder to sediment (18.9 %), soil (0.259 %) and air (0.00354 %). An emission of 1.0 kg/h to the soil compartment results in a partition to the soil compartment (99.7 %) with the remainder to water (0.221 %), sediment (0.0518 %) and air (0.00149 %). EPI Suite (version 3.20) calculations revealed a bioconcentration factor of 201. Measured BCF for fish of 75 and 82 (*Cyprinus carpio*) have been reported. There are, however, indications of biomagnification of DCDPS in air breathing organisms.

Aquatic ecotoxicity tests, which were performed according to GLP and standard guidelines, are available for fish, water fleas and algae. No mortality or effects on behaviour and general appearance were observed in a 96 hour limit test, performed at the water solubility limit, with zebra fish (*Brachydanio rerio*) at mean measured concentration of 0.98 mg/l. The acute EC₅₀ (48 h) for water fleas (*Daphnia magna*) was > 0.93 mg/l. The NOEC (21-day) for the water flea (*Daphnia magna*) for reproduction was calculated to be 0.32 mg/l. The EC₅₀ (72 h) based on biomass and growth rate for the algae (*P. subcapitata*) was > 0.80 mg/l. The NOEC (72 h) was 0.28 mg/l based on biomass. The LOEC was 0.49 mg/l which resulted in a biomass inhibition of 18 %. Terrestrial toxicity tests are not available for DCDPS.

Exposure

DCDPS is manufactured by Solvay in the USA and in India. The substance is also manufactured in the United Kingdom by Seal Sands Chemicals Ltd. The total production of these companies was estimated to be less than 18,000 tonnes in 2006.

DCDPS is manufactured also by other companies in China, India and the Russian Federation but the amount manufactured and the uses are unknown. However, Solvay is assumed to be the largest manufacturer of DCDPS. The information given below, regarding manufacturing and use, is based on data from the two Solvay production sites mentioned above.

DCDPS is used as starting material in the production of polysulfones, polyethersulfones and polyphenylsulfones. These polymers are a family of thermoplastics known as engineering plastics and are used in high-temperature applications. The polymers, which are thermally and chemically resistant, are used as coating on metals, as containers for holding food during heating or cooking and as components of food processing machinery and equipment. Recent analytical measurements showed that the residual

amount of DCDPS in these polymers ranged from 1.7 to 79 µg/g.

The majority (> 80 %) of DCDPS, produced by Solvay, is also polymerized by Solvay but it is also sold and transported in bulk quantities to customers (downstream users). However, for Solvay the global number of downstream users is limited (< 5). The downstream users of DCDPS are also using it for the production of polysulfones, polyethersulfones and polyphenylsulfones.

In Europe DCDPS has been detected both in the aquatic environment and in fish (1.8 – 190 ng/g fat), birds (5.2-2600 ng/g fat) and seals (21-700 ng/g fat) from the Baltic Sea. Based on a review of the available data from the Baltic region, it was suggested that DCDPS has a more local distribution than the more well-known long-range distributed PCB and DDT. The reason proposed was less distribution of DCDPS than of the POPs by the air pathway. A decreasing trend of the presence of DCDPS in the Baltic environment, as expressed in eggs of guillemot, could indicate historical sources to the contamination. However, the slow decrease of 1.6 % per year between 1971 and 2001 for DCDPS make ongoing emissions from current unknown uses seeming likely in the Baltic environment.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

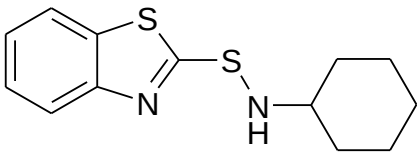
Human Health

The chemical is a candidate for further work. The chemical has properties indicating a hazard for human health (mutagenicity, repeated dose toxicity). Member countries are invited to perform an exposure assessment for workers, and if necessary a risk assessment.

Environment

The chemical is a candidate for further work. The chemical has properties indicating a hazard for the environment (, chronic toxicity to algae and to aquatic invertebrates between 0.1 -1 mg/l, lack of ready biodegradability and potential for persistency) and a potential for bioaccumulation. Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-33-0
Chemical Name	N-cyclohexylbenzothiazole-2-sulphenamide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue rationale**

The main hydrolysis products of N-cyclohexylbenzothiazole-2-sulphenamide (CBS) are mercaptobenzothiazole (MBT), CAS-No. 149-30-4, and cyclohexylamine (CHA), CAS-No. 108-91-8, had been used as supporting substances for the hazard identification in different toxicological endpoints, e.g. mutagenicity and reproductive toxicity.

Physical-chemical properties

CBS is a grey or yellow powder with a slight odour, a melting point of 97.5-105 °C and a measured vapour pressure of 1.5×10^{-8} hPa at 20 °C. Decomposition starts at 145 °C. The measured partition coefficient (log Kow) is 4.93, and the water solubility is 0.32 mg/L at 21 °C (pH 7).

Human Health

The results after oral administration to rats indicate that N-cyclohexylbenzothiazole-2-sulphenamide (CBS) is readily absorbed and that intensive metabolism of CBS takes place. As hydrolysis to 2-mercaptobenzothiazole (MBT) and cyclohexylamine (CHA) was shown *in vitro* and will occur in the gastrointestinal tract, presystemic metabolism may play a role in the fate of CBS with different kinetic fate of the metabolic breakdown products. For oral absorption a value of 100%, and for the inhalation absorption a value of 100% (defaults), are expected. Taking into account the available physical-chemical and toxicodynamic information, a dermal penetration value of 10% is proposed.

The acute toxicity of CBS in rats and mice is very low after oral and dermal administration; LD₅₀ values >5000 mg/kg bw were obtained. Dermal administration in rabbits led to a LD₅₀ value >7940 mg/kg bw. Data on inhalation toxicity and human data are not available.

CBS is not a corrosive substance. CBS has demonstrated few cases of skin irritation in human patch tests with the commercial product, when using petrolatum as a vehicle. CBS caused slight irritation on the skin in rabbits (Draize assay) and on the conjunctivae of the eye of rabbits (OECD TG 405). Occasional signs of mild nasal irritation were observed in rats immediately after the 6-hour exposure period with atmospheric concentrations up to 48 mg/m³ CBS 5 days per week in a 28-day inhalation toxicity study. The animals recovered from symptoms within 24 hours and these findings did not correlate to histopathologic effects. In light of the fact that CBS has shown slight irritations at the eye of rabbits it seems plausible that CBS leads also to slight irritations at the mucous membranes of the respiratory tract after inhalation.

Data on sensitisation caused by inhalation are not available. CBS did not cause skin sensitisation in guinea pigs (Buehler test). In contrast, there was one well conducted human patch testing study which clearly demonstrated contact sensitisation in humans. Data from epidemiological studies are difficult to assess, but also indicate some skin sensitising potential of CBS.

In a 28-day inhalation toxicity study groups of rats (10/sex/group) were whole body exposed to atmospheric concentrations of CBS of 4.3, 14.4 and 48 mg/m³ (analytic values which represent approx. 9% of the nominal values) for 6 hours per day and 5 days per week for a period of four consecutive weeks. There were no treatment-related premature deaths. No concentration dependent effects were noted for general appearance, behaviour, body weight, food consumption, hematology, urinalysis, gross pathology and absolute and relative organ weights. There were no toxicologically significant changes in clinical chemistry parameters, and no changes in organ weights and macroscopic examination that were considered to be an effect of exposition with CBS. Therefore, the no-observed-adverse effect-concentration (NOAEC) for systemic effects was 48 mg/m³.

In a 28-day (gavage) toxicity study mostly according to OECD TG 407 groups of rats (6 /sex/group) were tested at dosages of 0, 25, 80, 250, and 800 mg/kg bw/d CBS (purity 98.8%); additionally six animals per sex in the control and high dose groups were treated for 28 days and then allowed a 14-day treatment-free recovery period before sacrifice. CBS-related effects were present in males and females at ≥ 250 mg/kg bw/d. There were signs of a coagulopathy of the blood in males and females and effects in the kidney of male rats. No relevant CBS-related toxic effects were observed in animals of both sexes at 80 mg/kg bw/d. Therefore, the oral NOAEL in rats was 80 mg/kg bw/d.

In a dermal 21-day toxicity study according to OECD TG 410 CBS was applied daily to the intact and abraded skin at doses of 125, 500 and 2000 mg/kg bw/d to each of five male and female adult rabbits. The exposure time was 6 hours per day for a 7-day per week basis, for a period of 21 consecutive days. Two rabbits died during the course of study but neither death was attributable to CBS treatment. Experimental findings were present in both CBS treated animals and those of controls. Their incidence and severity did not distinguish CBS-treated rabbits from controls. Therefore, the NOAEL for systemic effects and local effects in rabbits after repeated dermal exposure was 2000 mg/kg bw/d.

Human toxicity data after repeated exposure to CBS is not available.

CBS was negative in well-conducted gene mutation assays employing various tester strains of *Salmonella* and one each of *E. coli* and *Saccharomyces*. A well-conducted mouse lymphoma assay was also negative. An *in vitro* chromosomal aberration test gave weak evidence for a clastogenic potential. Overall, CBS is not considered to be genotoxic which is in line with the overall negative genotoxicity data for the CBS hydrolysis products, MBT and CHA.

The existing two long-term studies on CBS in mice are not in accordance with the current testing procedures as proposed by OECD guidelines on carcinogenicity and/or combined chronic toxicity/carcinogenicity. However, they are performed in accordance with generally accepted scientific standards. The results have shown that CBS is not carcinogenic in mice at a dose of 95.3 mg/kg bw/d (time-weighted average dose). In addition, the carcinogenicity of both hydrolysis products, MBT and CHA, has been investigated in a number of long-term oral studies, involving a variety of strains of rats and mice. Results of these animal studies have clearly demonstrated that MBT and CHA are not carcinogenic in rats and mice. MBT is not carcinogenic in mice and male rats at a dose of 750 mg/kg bw/d and in female rats at a dose of 350 mg/kg bw/d. CHA is not carcinogenic in rats at doses up to 440 mg/kg bw/d and in mice up to 500 mg/kg bw/d, respectively.

Generation studies, respectively fertility studies are not available for CBS. Data from adequate repeated dose toxicity studies (90 days) to supplement the available developmental toxicity studies for hazard evaluation for reproductive toxicity at a screening level are neither available. Additional data were available from investigations on the hydrolysis products of CBS.

From the two-generation study with MBT no effects adverse to reproductive capability and capacity could be demonstrated for dietary exposures of up to and including 15000 ppm (corresponding to an intake of approximately 1200 mg/kg bw/day). Reductions in offspring body weights were correlated with the onset of food intake and were thus possibly related to a palatability problem. However, long-term dietary exposures revealed toxic effects at the liver and kidney organ systems which had been induced at even lower dosages of 8750 ppm (according to 700 mg/kg bw/day). Thus, from this study there was no indication for inherent reproductive toxicity of MBT even at systemic toxic dose levels.

CHA caused tubular atrophy and reductions in spermatogenesis in rats following oral administration at doses of approximately 200 mg/kg bw/day and above, in studies of 3-months to 2 years duration. NOAELs of 100 mg/kg bw/day and 82 mg/kg bw/day respectively were identified from a 3-month and 2-year study. These NOAELs are estimated to be equivalent to 276 and 218 mg/kg bw/day of CBS. As CBS is predicted to be metabolised rapidly and extensively to CHA, these findings suggest that CBS may cause similar testicular effects. The oral (gavage) 28-d study with CBS gave some limited support to the above findings due to the

induction of testicular effects in a single rat at a dose of 800 mg/kg bw/day and after recovery only that are absent at 250 mg/kg bw /day.

Results from oral developmental toxicity studies are available. Groups of 10-17 mated female Wistar rats were administered via diet with CBS at dosage levels of 0, 0.7, 7.1, 69.6 and 288.8 mg/kg bw/day from day 0 to day 20 of pregnancy. General toxicity was noted by significantly lower maternal body weight gain during pregnancy in the two highest dose group and reduced food consumption in the highest dose group.. Neither death nor clinical signs of toxicity were reported for the pregnant females of any group. Therefore the NOAEL derived from the results of this study for dams is 7.1 mg/kg bw/day in the diet based on reductions in body weight gain. There were no significant compound related effects on pre- and postimplantation losses, the number of live fetuses per litter or the sex ratio of live fetuses. However, significantly lower body weights of male and female fetuses and of the placentae were noted at the highest dose level. The NOAEL/developmental toxicity of 69.6 mg/kg bw/day is based on decreased mean fetal body weights at the highest dose level. These data were further supported by a guideline-compliant teratology study with rats groups of 20 to 25 pregnant females treated by gavage with CBS at dose levels of 100, 300, 500, and 900 mg/kg bw per day during gestation from day 6 to 15 and in a teratology study with groups of 17 to 22 mated females treated by gavage with CBS at dose levels of 50, 150, and 450 mg/kg bw/day during gestation days 6 to 15. Overall, fetal body weight impairment noted in the above studies was exclusively observed at oral dosages associated with significantly reduced maternal weight gain of 15-30%. Substance-related specific embryotoxic and/or teratogenic potential were not revealed from the available studies.

Environment

Hydrolysis of CBS was studied in deionized water at pH 7 using a phosphate buffer system. A half-life of 12.5 h was determined and hydrolysis was observed to be complete at the end of the study (24h). Benzothiazole was found to be the sole hydrolysis product, cyclohexylamine as a potential degradation product was not identified.

The UV spectrum of CBS indicates that photodegradation under environmental conditions is possible. In a photolysis screening test, a 1 mg/l solution in water containing 1% acetonitrile as a cosolvent was exposed to sunlight at midday in August. A half-life of 26 minutes was obtained (this value refers to the top millimetres of a water body in summer, because of factors like cloudiness, shadowing effects of vegetation, absorption and scattering of light by suspended solids etc. the actual environmental lifetime is substantially higher).

The indirect atmospheric oxidation rate by reaction with OH-radicals was estimated with $79.5 \cdot 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ by AopWin v1.91 and half-life thus 0.202 days.

The biodegradation of CBS has been determined in a shake flask procedure (draft method n° 2 for the proposed standard for the determination of the ultimate degradability of organic chemicals, August 1979, ASTM committee). An inoculum of a bacterial suspension originating from raw sewage, soil and activated sludge was incubated during 35 days with CBS concentrations of 20 and 30 mg/l. The CO₂ evolution was reported to be ca. 0% for the vessels with inoculum (duplicate) and 4 % for the sterile control. CBS is considered to be persistent to biological degradation

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that CBS will distribute mainly to the soil (71.1 %) and sediment (18.9%), compartments with minor distribution to the water (9.65%) and negligible amount in the air (0.3%) compartment.

The distribution of CBS between aqueous solutions and air can be calculated from water solubility and vapour pressure. Using the same values, a Henry's law constant of 0.0017 Pa.m³/mol is obtained, indicating that the substance is not volatile from aqueous solutions.

The distribution between the organic phase of soil or sediment solids and pore water can be calculated from the octanol/water partitioning coefficient. Using a log K_{ow} of 4.93, according to EUSES a K_{oc} value of 12 400 l/kg is calculated (class: predominantly hydrophobics).

According to the SIMPLETREAT model in EUSES 2.0, 33.9 % of CBS are directed to water, 54.7 % adsorbed onto sludge, and 11.4 % are degraded (hydrolysis half-life 12.5 h) in municipal stp.

There are no experimental data on bioaccumulation available. Using the equation $\log \text{BCF} = 0.85 \log \text{Kow} - 0.70$ and a log K_{ow} of 4.93, a BCF of 3094 l/kg is obtained. BCFWIN 2.15 gives a BCF of 1248 l/kg. The

results indicate high bioaccumulation potential for CBS.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Oryzias latipes</i>];	96 h LC ₅₀ = 2.1 mg/L (flow-through system, measured)
Invertebrate [<i>Daphnia magna</i>]	48 h EC ₅₀ = 0.79 mg/L (semistatic, measured)
Algae [<i>Selenastrum capricornutum</i>]	72 h E _r C50 > 0.15 mg/L ; NOEC=0.0084 mg/L(measured)

The following chronic test result has been determined for aquatic species:

Invertebrate [<i>Daphnia magna</i>]	21 d NOEC = 0.058 mg/L (reproduction, measured)

QSAR-Data (ECOSAR v0.99h)

Organism	Acute L(E)C50 (mg/L)	Chronic (mg/L)
Fish	0.345	0.071
Daphnid	0.453	
Algae	0.335	0.182

The effect values are above or in the range of the water solubility of 0.32 mg/L. for the effects assessment of CBS on aquatic organisms. The test substance concentrations were generally above the water solubility (0.32 mg/l). The observed effects in the static tests are thought to be caused partly by the degradation products rather than the parent substance.

Exposure

CBS is commercially produced with an annual production volume of 16000 tonnes in the EU 15. Worldwide production volume is estimated to be around 53000 tonnes in 1998. Total volume of manufactured and imported CBS in Japan seems to be 1000 – 10000 ton in 2004. The synthesis of CBS is carried out via 2-mercaptobenzothiazole (MBT). MBT is manufactured at temperatures ranging from 220-350°C and pressures up to approx. 13 MPa through the conversion of aniline, carbon disulphide (CS₂) and sulphur; benzothiazole and sulphur or aniline, carbon disulphide (CS₂), benzothiazole and sulphur.

CBS is exclusively used as vulcanization accelerator in rubber goods manufacture.

Production and use of CBS cause an environmental exposure of a number of benzothiazole derivatives which are formed as abiotic breakdown products in vulcanisation, waste water and in the environment. In addition, some of these derivatives are formed as metabolites in waste water and in the environment. Within the rubber industry releases into waste water occur only in parts. Tires and larger rubber articles are manufactured in a dry process, where the water used is not in contact with rubber. Wet process is used for extruded rubber, handmade rubber clothing, rubberised fabrics and some technical rubber products vulcanised in autoclaves. In such a process water normally contains special additives and the water is run in closed circuits where only evaporation losses are replaced by new water. Benzothiazole derivatives are released into the environment by tire tread particles. The particles accumulate in soil near roads, reach the hydrosphere via rainwater runoff, and occur as dust into the atmosphere. The particles were measured in all compartments. The benzothiazoles enter the environment from tire particles either by leaching with rainwater or by degradation of the rubber matrix. Consequently, the compounds have been detected in the hydrosphere and in soils. Releases of benzothiazole derivatives from rubber goods other than tires can be expected to occur by migration and leaching. Coming into contact with water, small-sized molecules like benzothiazole can cross the rubber surface into the environmental compartments. Because of the low vapour pressure, gaseous CBS releases into the atmosphere can be excluded. Some companies report about dust particle emissions into the atmosphere.

Occupational exposure by inhalation or dermal contact is possible.

Consumer exposure is considered to be negligible, since there is no evidence available on the use of CBS in consumer products.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

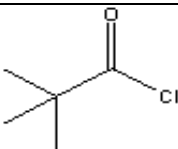
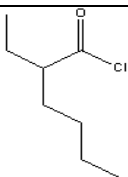
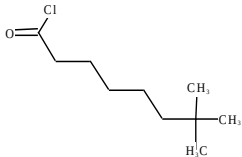
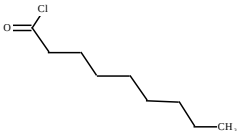
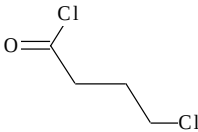
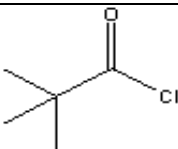
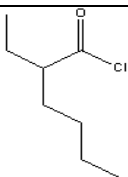
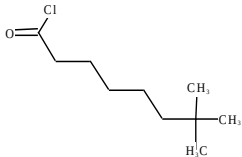
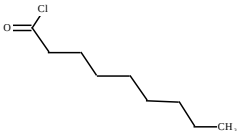
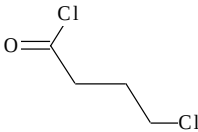
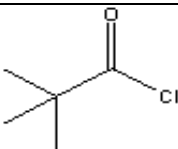
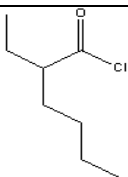
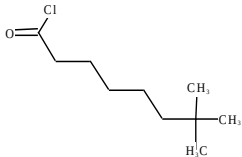
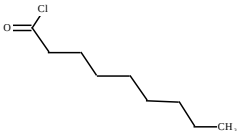
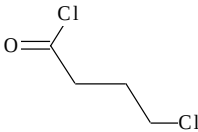
The chemical is of low priority for further work. The chemical possesses properties indicating a hazard for human health (skin sensitisation and repeated dose toxicity by inhalation). However, the

exposure situation at the workplace is controlled and adequate risk management measurements are in place. Individual countries may wish to carry out their own exposure assessments, relevant for their own industrial scenarios followed by a risk assessment.

Environment

The chemical is a candidate for further work. The substance has properties indicating a hazard for the environment (aquatic toxicity < 1 mg/l invertebrate and algae). Member countries are invited to perform an exposure assessment and, if necessary, a risk assessment (mainly needed for sites without a biological waste water treatment plant). If the exposure assessment shows significant exposure to the sediment, further testing of the toxicity on sediment dwelling organism is recommended.

Note: A risk assessment performed in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union is available.

<u>SIDS INITIAL ASSESSMENT PROFILE</u>											
Category Name	Acid Chloride Category										
CAS Nos and Chemical Names	Sponsored substances: 3282-30-2 Pivaloyl chloride (PCl) 760-67-8 2-Ethylhexanoyl chloride (EhCl) 40292-82-8 Neodecanoyl chloride (NdCl) 764-85-2 Nonanoyl chloride (NnCl) Analogue substance: similar structure 4635-59-0 Chlorobutyryl chloride (CCl2) Analogue substances: hydrolysis products 75-98-9 Pivalic acid 149-57-5 2-Ethylhexanoic acid 26896-20-8 Neodecanoic acid 112-05-0 Nonanoic acid										
Structural Formulae	<table> <tr> <td>3282-30-2</td><td></td></tr> <tr> <td>760-67-8</td><td></td></tr> <tr> <td>40292-82-8</td><td></td></tr> <tr> <td>764-85-2</td><td></td></tr> <tr> <td>4635-59-0</td><td></td></tr> </table>	3282-30-2		760-67-8		40292-82-8		764-85-2		4635-59-0	
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760-67-8											
40292-82-8											
764-85-2											
4635-59-0											

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The members of the Acid Chloride Category are listed above. The category consists of 4 sponsored acid chlorides (pivaloyl chloride; PCI, CAS No. 3282-30-2), 2-ethylhexanoyl chloride (EhCl; CAS No. 760-67-8), neodecanoyl chloride (NdCl; CAS No. 40292-82-8) and nonanoyl chloride (NnCl; CAS No. 764-85-2). These chemicals are grouped into a category based on similar molecular structure and functionality, high reactivity, physicochemical and toxicological properties.

Similar molecular structure and functionality : $R(C=O)Cl$ [where $R = \text{alkyl}$]

Similar high reactivity: The acid chloride group (i.e., $-(C=O)Cl$) is the most active functional group on these molecules and determines many aspects of the behaviour of the category members. Acid chlorides undergo various chemical reactions depending on the environment to which they are exposed. Hydrolysis is the primary reaction in aqueous systems and has been shown to occur very quickly for all compounds at pH 4 and 0 °C and/or pH 1.2 and 37 °C. Reactions with nucleophiles (such as $-NH_2$, $-SH$ and $-OH$) on biological macromolecules will also occur in mammalian tissues.

Similar chemical/physical properties: All category members are liquids with low melting points. Volatility and boiling points are largely dependent on molecular weight.

Similar toxicological properties: These category members are severely irritating and harmful at the site of contact (i.e., respiratory tract, skin, and eyes); systemic absorption at already severe local toxic effect concentrations (i.e. lethality via inhalation) is not expected.

The approach to address SIDS endpoints for the acid chloride category is to utilize data from the sponsored chemicals and the primary hydrolysis products. Chlorobutyl chloride (CCl2; CAS No. 4635-59-0), which is also an acid chloride with similar size and structure, has been used with respect to acute and repeated dose toxicity, and mutagenicity. The primary hydrolysis products for the sponsored acid chlorides are hydrochloric acid (HCl; CAS No. 7647-01-0) and an organic acid (pivalic acid (CAS No. 75-98-9), 2-ethylhexanoic acid (CAS No. 149-57-5), neodecanoic acid (CAS No. 26896-20-8), and nonanoic acid (CAS No. 112-05-0), respectively). These hydrolysis products can be used as analogues because of the rapid hydrolysis of acid chlorides to HCl and the organic acids. Repeated-dose, mutagenicity and reproductive toxicity endpoints for the acid chlorides category are fulfilled through the use of data from the primary hydrolysis products. Acute aquatic toxicity data are also fulfilled through the use of data from the primary hydrolysis products, HCl, pivalic acid, 2-ethylhexanoic acid, neodecanoic acid and/or nonanoic acid.

2-Ethylhexanoic acid and hydrogen chloride have previously been assessed in the OECD HPV Program. The SIDS Dossier for 2-Ethylhexanoic acid will be available for review on the UNEP website when published. The hydrogen chloride documents are available at <http://www.chem.unep.ch/irptc/sids/oecd/sids/7647010.pdf>. Pivalic acid has been assessed as part of the NeoAcids C5-C28 category in the U.S. HPV Challenge Program (http://www.epa.gov/hpvis/hazchar/Category_C5-C28%20%20Neoacids_HC_August%202007.pdf).

Physical-chemical properties

The acid chlorides are very reactive and hydrolytically unstable; they are liquids at normal temperature and pressure. PCI, EhCl and NdCl degrade spontaneously on contact with aqueous media; at pH 4 and 0 °C, > 50% hydrolysis occurred prior to analysis of the initial sample. The half-life of NnCl was 17 minutes at pH 7 and 0 °C. The acid chlorides hydrolyze to form one mole of their respective organic acids (pivalic, 2-ethylhexanoic, neodecanoic and nonanoic acids) and one mole of HCl. The melting points of the acid chlorides range from $<-60.5^{\circ}C$ (NnCl) to $11.6^{\circ}C$ (NdCl); boiling points range from $67.8^{\circ}C$ (EhCl) to $215.3^{\circ}C$ (NnCl). The melting point and boiling point of CCl2 are -49 and $173.5^{\circ}C$, respectively. Vapor pressures of the acid chlorides range from 0.22 hPa at $20^{\circ}C$ (NdCl; estimated based on measured) to 50.1 hPa at $25^{\circ}C$ (35.9 at $20^{\circ}C$) (PCI). The vapor pressure of CCl2 is 1.31 hPa at $20^{\circ}C$. The water solubility and partition coefficient estimates are not reliable because the acid chlorides are hydrolytically unstable. The water solubility values of the organic acid hydrolysis products range from 69 mg/L (estimated; un-dissociated neodecanoic acid) to 21,700 mg/L (measured; pivalic acid). The water solubility of HCl is 673 g/L at $30^{\circ}C$. The partition coefficients of the organic acid hydrolysis products in their neutral form range from 1.32 [estimated (un-dissociated); 4-chlorobutyric acid] to 3.9 [estimated (un-dissociated); neodecanoic acid].

Human Health

There are no data for toxicokinetics of the acid chlorides. Acute toxicity data are available for the inhalation, dermal and oral routes of exposure for the acid chlorides. The 1 and 4 hr-LC₅₀s in the rat range from 1.26 to 2.69 mg/L and

>0.31 to <3.58 mg/L, respectively. NdCl was the most toxic category member following acute inhalation. In the inhalation studies, eye irritation and respiratory irritation/distress were observed, with subsequent signs of generalized poor condition including decreased activity, rough fur, piloerection, emaciation, polyuria and wet fur. Observations at necropsy included discolouration of the lungs (gray, pale, red or dark, mottled) which were often edematous. Tracheal irritation and tracheal mucus, air-filled stomach and/or intestines (resulting from mouth-breathing) were also observed. The range of inhalation LC₅₀s for the analogue CCl₂ is 0.65-0.87 mg/L/4h. The organic acid six hr-LC₅₀s in the rat were all >2.36 mg/L. Observations in the acute inhalation studies with pivalic acid included piloerection, epistaxis, and dyspnea. No signs of toxicity were observed following exposure to neodecanoic acid at >3 mg/L, the highest dose tested.

Dermal LD₅₀s in rabbits for the acid chlorides were greater than 2000 mg/kg bw. Toxicological effects included decreased activity, ataxia, constricted pupils, decreased defecation and urination, diarrhea, emaciation, hemorrhaging (at exposure area), nasal discharge, polyuria and small feces. At necropsy findings included extensive ulceration throughout the exposure area, liver mottled pale red and red-brown, stomach distended with gas and almost empty, coloured material in the stomach, small intestine and/or cecum. Reliable acute dermal toxicity data were not located for the organic acids.

Oral (gavage) LD₅₀'s for the acid chlorides ranged from 683 to 1410 mg/kg bw when applied neat (without vehicle) or from 1470-2500 mg/kg bw when applied in olive oil. PCl was the most toxic category member following acute oral gavage. The acute toxicity of NnCl has not been investigated; however, a similar order of toxicity is expected as found with other category members. Toxicological effects of the acid chlorides observed during acute oral (gavage) studies in rats included decreased activity, muscle weakness, ataxia, agitation, slow, short, gasping, or noisy, breathing patterns, clear or coloured discharge from the eyes and/or nose, constricted and/or dilated pupils, reduced corneal reflexes, exophthalmos, red or black discoloured urine, polyuria, and general signs of poor condition including rough coat, piloerection, ptosis, diarrhea, emaciation, salivation and/or swollen tongue. Necropsy findings included extensive ulceration, hemorrhage or necrosis in the stomach and intestine, and edema in the lung. The oral LD₅₀ of the analogue CCl₂ is 1510 mg/kg (without vehicle).

The oral LD₅₀s for the organic acids range from >1600 to < 3200 mg/kg bw. Clinical signs included muscle weakness, CNS depression, dyspnea, and ataxia. Necropsy findings in high dose animals indicated congestion of lungs, liver, kidneys, and adrenals. The oral LD₅₀ value of HCl is reported to be 238-277 mg/kg bw for female rats.

PCl, EhCl and NdCl are corrosive to skin. PCl and EhCl are moderate to severely irritating to the eye. NdCl was not irritating to the eyes. Data are not available for NnCl, however it is assumed this substance may be corrosive to the skin and severely irritating to the eyes. The acid chlorides are expected to be sensory irritants. NnCl was a sensitizer in a murine local lymph node assay. Sensitization data were not located for PCl, EhCl or NdCl.

Repeated-dose toxicity studies are not available for the sponsored acid chlorides; data are available for the hydrolysis products, the analogue substance, CCl₂ and HCl. Rats exposed to the analogue substance CCl₂ by inhalation at 0, 0.002, 0.012, and 0.059 mg/L for 4 weeks (6h/day; 5 days/week) showed clinical symptoms linked to respiratory tract inflammation and irritation. Growth retardation, changes in blood parameters clinical chemistry, and organ weights were secondary to effects on the respiratory tract. The LOAEL for respiratory tract effects was 0.002 mg/L. Based on histology findings, there was no other target organ than the respiratory tract in concentrations up to 0.059 mg/L. Irritation was observed in all the treatment groups in a 90-day inhalation study using HCl. The NOAEL (except for the effects of irritation) was 20 ppm (0.03 mg/L) for rats and mice. Repeated-dose dermal toxicity studies (14 days) with rabbits with pivalic, neodecanoic, and nonanoic acid indicate a low order of systemic toxicity in the presence of moderate to severe skin irritation at the site of contact. The NOAELs for systemic toxicity were 300 mg/kg bw/day (pivalic acid), 2280 mg/kg bw/d (neodecanoic acid) and 500 mg/kg bw/d (nonanoic acid) [highest doses in each study]. Observations of toxicity were limited to local irritation effects in rats in a 28-day oral gavage study with pivalic acid; the NOAEL was 300 mg/kg bw/day. A diet containing 0.5 % 2-ethylhexanoic acid caused no adverse effect in rats in a 13 week feeding study (calculated NOAEL ca. 300 mg/kg bw/day). No adverse effect was observed in mice receiving a diet containing 0.5 % 2-ethylhexanoic acid in a 13 week feeding study. The NOAEL was calculated to be 200 mg/kg bw/day. In both studies, all toxicity observed at higher concentrations (changes in clinical chemistry, absolute and relative organ weights, microscopic changes in kidney liver and fore stomach) was reversible within 28 days after exposure ceased.

PCl and NnCl were weakly positive for mutagenicity in *S. typhimurium* strain TA 100 in OECD TG 471 studies; EhCl, NdCl and analogue substance, CCl₂ were negative in these studies. The organic acids (pivalic, 2-ethylhexanoic and neodecanoic acid) were negative for mutagenicity in standard bacterial reverse mutation assays. The hydrolysis product, HCl, was also negative in the Ames test. The analogue CCl₂ was negative for the induction of chromosome aberrations in human lymphocytes (*in vitro*). Pivalic acid (rat liver cells), neodecanoic acid (human lymphocytes), and HCl (CHO cells) were negative in *in vitro* chromosome aberration assays. Positive results have been obtained in the *in vitro* chromosome aberration test with HCl; however, the positive result was considered to be

the effect of low pH. 2-Ethylhexanoic acid was negative in an *in vivo* mouse micronucleus assay. Therefore, based on the current available data, the acid chlorides are not expected to be genotoxic.

Reproductive toxicity data are not available for the acid chlorides. Data are available for the hydrolysis products (2-ethylhexanoic acid, neodecanoic acid, nonanoic acid, and HCl). The reproductive toxicity of 2-ethylhexanoic acid has been investigated in a one generation study in rats [OECD TG 415] and the NOAEL for reproductive effects in parental animals was 300 mg/kg-bw/day; this effect occurred in the presence of maternal toxicity. The NOAEL for F1 offspring was 100 mg/kg-bw/day. The developmental toxicity of 2-ethylhexanoic acid has been investigated in a standard study in rabbits [USEPA TSCA Health Effects Testing Guidelines CFR 798.4900 (similar to OECD TG 414)] and the NOAEL for maternal animals was 25 mg/kg-bw/day and the NOAEL for offspring was 250 mg/kg-bw/day (the highest dose tested). In a guideline study [OECD TG 414] 2-ethylhexanoic acid was administered via drinking water to an unspecified number of Wistar rats at 0, 100, 300, or 600 mg/kg-bw/day, for days 6-19 of gestation. Clubfoot was the only skeletal malformation; changes in skeletal variations were also noted (wavy ribs, reduced cranial ossification, and twisted hind legs). However, wavy ribs and delayed ossification were not dose dependent. There is a high background incidence of wavy ribs in Wistar rats and the incidence observed was within the background range. Therefore, the NOAEL for offspring was 100 mg/kg-bw/day and the NOAEL for maternal animals was 300 mg/kg-bw/day. The developmental toxicity of 2-ethylhexanoic acid has also been investigated in another study in Fischer rats [USEPA TSCA Health Effects Testing Guidelines CFR 798.4900 (similar to OECD TG 414)]. The NOAEL for maternal animals was 250 mg/kg-bw/day and the NOAEL for offspring was 100 mg/kg-bw/day as well. Based on these results, 2-ethylhexanoic acid is not likely to cause effects on fertility but is likely to be a developmental toxicant.

The reproductive toxicity of neodecanoic acid has been investigated in a three generation study in rats. In this study, neodecanoic acid was administered via the diet to 10 males/20 females/dose (P1) at 0, and approx. 5, 25 and 75 mg/kg-bw/day for 9 weeks prior to mating to produce F1A and F1B (P2) generations. No adverse effects on reproductive or developmental parameters were observed up to the highest dose tested. There were no treatment related effects on parental animals observed at any dose. The NOAEL for parental, F1 offspring, and F2 offspring was 1500 ppm (75 mg/kg-bw/day). Based on these results, neodecanoic acid is considered not to be a reproductive/developmental toxicant.

The reproductive toxicity of nonanoic acid has been investigated in two standard developmental toxicity studies in rats. In both studies, nonanoic acid was administered via gavage to an 11 pregnant animals/dose at 0 or 1500 mg/kg-bw, for gestational days 6 through 15. No adverse effects on development were observed. There were no treatment related effects on parental animals. The NOAEL for developmental toxicity from these studies is 1500 mg/kg-bw/day. Based on these results, nonanoic acid is considered not to be a developmental toxicant. As stated in the Hazard Characterization for Neoacids C5 to C28 (http://www.epa.gov/hpvis/hazchar/Category_C5-C28%20Neoacids_HC_August%202007.pdf): "The potential health hazard of the neoacids C5 to C28 category is moderate based on the limited data available for repeated-dose and reproductive toxicity and the findings in the developmental studies." As such, a potential hazard for reproductive toxicity cannot be excluded for pivalic acid. As stated in the SIAR for HCl, no reliable studies were identified regarding reproductive toxicity in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. However, based on a weight of evidence analysis, conclusions from two studies suggest HCl is not a reproductive toxicant.

In summary, there is no indication of reproductive effects for the acid chlorides based on the available data. 2-Ethylhexanoyl chloride is likely the only category member with a potential for developmental toxicity; however, there is a potential concern for developmental effects associated with pivaloyl chloride.

The chemicals possess properties indicating a hazard for human health (lethality from acute inhalation, localized irritation of skin, eye and respiratory tract, potential for sensitization, toxicity at the site of contact or entry, liver and kidney toxicity, developmental toxicity for EhCl). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The overall OH rate constant for the acid chlorides and resulting half-life and rate constant due to indirect photolysis are estimated to range from 1.6×10^{-12} cm³/molecule-sec (PCL) to 11.5×10^{-12} cm³/molecule-sec (NnCl) and 0.9 d (EhCl and NnCl) to 6.7 d (PCL). Photodegradation as a mode of removal is unlikely as the AC are hydrolytically unstable. It is assumed that reaction with water vapor is the predominant degradation process for acid chlorides in air. The products resulting from acid chloride hydrolysis (organic acids) in the atmosphere are expected to further react with hydroxyl radicals. The half-lives due to the atmospheric oxidation from indirect photolysis of the organic acids were determined to range from 1.1 d (nonanoic acid) to 10.5 d (pivalic acid); the overall OH rate constants ranged from 1.02×10^{-12} cm³/molecule-sec (pivalic acid) to 9.8×10^{-12} cm³/molecule-sec (nonanoic acid). HCl can react with hydroxyl radicals to form chloride free radical and water and its half-life time is calculated as 11 d. Level

III Fugacity modeling, using loading rates of 1000 kg/h each for air, soil, and water, shows the following percent distribution range for the acid chlorides: Air = 7.5 (NdCl) to 35 (PCl); Soil = 11.3 (PCl) to 62.3 (NdCl); Water = 29.2 (NdCl) to 53.6 (PCl); Sediment = 0.11 (PCl) to 1.0 (NdCl). However, because the acid chlorides are very reactive and hydrolytically unstable, the substances are unlikely to be found in the environment. Therefore, Level III Fugacity modeling for the hydrolysis products (organic acids) was conducted using loading rates of 1000 kg/h each for air, soil, and water. The model estimated the following percent distribution ranges, when the organic acids are released simultaneously to all three compartments: Air = 2.2 (neodecanoic acid) to 6.1 (pivalic acid); Soil = 57.5 (pivalic acid) to 72.1 (neodecanoic acid), Water = 23.3 (neodecanoic acid) to 36.4 (pivalic acid); and Sediment = 0.09 (pivalic acid) to 2.4 (neodecanoic acid). These hydrolysis products will also exist as ionised substances (anion) under environmental conditions based upon calculated pKa values ranging from 4.69 to 4.75 for the category member hydrolysis products, and fugacity modelling may not be appropriate. The Fugacity model cannot be applied for ionized substances such as HCl. The biodegradation of the acid chlorides has not been determined due to their rapid hydrolysis; any expected biodegradation is likely reflective of the corresponding organic acid hydrolysis product. Studies with pivalic and neodecanoic acid indicate these organic acids are not readily biodegradable. 2-Ethylhexanoic acid and nonanoic acid are readily biodegradable. Bioaccumulation is not anticipated since these materials are very reactive and hydrolytically unstable. BCFwin modelling indicates the organic acids are not likely to bioaccumulate.

Acute toxicity studies with fish have been conducted with acid chlorides (sponsored substances and the hydrolysis products). The 96-hr LC₅₀'s of the acid chlorides ranged from 66.3 mg/L (not neutralized, measured, EhCl) to 287 mg/L (not neutralized, measured, PCl) in *Brachydanio rerio*. The 96-hr LC₅₀'s of the hydrolysis products were 104 mg/L (neutralized measured nonanoic acid; *Pimephales promelas*), 91 mg/L (nonanoic acid, *Oncorhynchus mykiss*) and 4.92 mg/L at pH 4.3 (HCl, *Cyprinus carpio*). Acute aquatic invertebrate tests have not been conducted with acid chloride category members. The 48 hr EC₅₀ values for the hydrolysis products in the water flea (*Daphnia magna*) were 203 mg/L (nominal, pivalic acid), 85.4 mg/L (neutralized, nominal, 2-ethylhexanoic acid), 47 mg/L (nominal, neodecanoic acid), 96 mg/L (nonanoic acid), and 0.492 mg/L (at pH 5.3; HCl). The 72-hr EC₅₀s for the hydrolysis product pivalic acid with *Pseudokirchneriella subcapitata* was E_bC₅₀ = 878 mg/L (E_rC₅₀ = 979 mg/L, measured), and 2-ethylhexanoic acid with *Scenedesmus subspicatus* were E_bC₅₀ = 60.5 mg/L and E_rC₅₀ = 49.3 mg/L (not neutralized, nominal). The 72-hr EC₅₀ value for HCl with *P. subcapitata* was 0.492 mg/L (at pH 5.3). The hazard of HCl for the environment is caused by the proton (pH effect). For this reason the effect of HCl on the organisms depends on the buffer capacity of the aquatic ecosystem. HCl has been previously discussed and agreed upon in the OECD HPV Programme.

The chemicals have properties that result in moderate toxicity to aquatic organisms, mainly due to acidification of the test medium. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

Acid chlorides are prepared through the reaction of carboxylic acids and phosgene in the presence of catalysts such as N,N-dialkylcarbamides or tertiary amines. Given the high reactivity and toxicity of reactants and reaction products, the synthesis is conducted in closed-systems under strictly controlled conditions. The following summarizes the 2005 production volumes in tonnes of the acid chlorides for the sponsor country, Europe and Japan; ranges are provided in order to protect confidential business information.

	Sponsor country		Europe	Asia
PCl	ca. 4536-22680	ca. 0-4536		ca. 0-4536
EhCl	ca. 4536-22680		ca. 0-4536	ca. 0-4536
NdCl	ca. 4536-22680	ca. 0-4536		ca. 0-4536
NnCl		0		0

NnCl is produced in batch such that it may not be produced every year: production volume for 2002 was > 1,000,000 pounds (ca 454 tonnes). All category members are used solely as industrial intermediates and are sold only to industrial customers.

Acid chlorides are manufactured within enclosed reactors and are filled into drums through closed systems. There are no intentional releases to the environment. The reactive nature of the acid chlorides destroys the parent material in water, thus limiting environmental exposure. Acid chlorides hydrolyze rapidly; resulting in the production of one mole of HCl and one mole of an organic acid.

In order to limit exposures due to the irritating nature of these substances and their high acute toxicity, these chemicals are manufactured within enclosed reactors and are filled into drums through closed systems. Engineering controls (such as room air exchange, local exhaust) and personal protective equipment (respirators) are also used as standard industry practice to further prevent exposure. Additionally, due to the highly irritating nature of these

materials and their high vapor pressure, employees are trained on the safe use and handling as well as emergency procedures in the event of an accident. Inhalation is the route of exposure with the greatest concern in the occupational setting due to the relatively high vapor pressures of these materials.

Customers of these materials use acid chlorides solely as chemical intermediates due to their high reactivity. As first step intermediates, these materials are reacted with nucleophiles containing various functional groups such as oxygen, sulfur, and nitrogen. Available analytical information indicates the residue concentration of acid chlorides in final products is expected to be extremely low due to their reactivity. As demonstrated for the nucleophile “water”, hydrolysis is complete in less than 24 h with remaining residual acid chlorides in amounts below detection limit.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Ethyl Silicates
CAS No.	78-10-4, 11099-06-2 and 68412-37-3
Chemical Name	Tetraethyl orthosilicate (TEOS), Silicic acid, ethyl ester (PEOS) and Silicic acid (H ₄ SiO ₄), tetraethyl ester, hydrolyzed (PEOS)
Structural Formula	$ \begin{array}{c} \text{R}-\text{O} \quad \text{O}-\text{R} \\ \quad \\ \text{R}-\text{O}-\left[\text{Si}-\text{O} \right]_n-\text{Si}-\text{O}-\text{R} \\ \quad \\ \text{O} \quad \text{O} \\ \quad \\ \text{R} \quad \text{R} \end{array} $ 78-10-4 R = ethyl and n = 0 R = ethyl or hydrogen terminated for 68412-37-3 and 11099-06-2; where n=4 is a representative example for the polymer composition

SUMMARY CONCLUSIONS OF THE SIAR**Category Justification**

Tetraethyl orthosilicate (TEOS) and silicic acid, ethyl ester (PEOS) (same as silicic acid (H₄SiO₄), tetraethyl ester, hydrolyzed) hydrolyse on contact with water, and are expected to release either metasilicic acid (CAS No. 10193-36-9) or silicic acid (CAS No. 7699-41-4), respectively, and ethanol (CAS No. 64-17-5). TEOS (CAS No. 78-10-4) may also hydrolyse to form PEOS. Ethanol has previously been assessed in the OECD HPV Programme. Metasilicic acid and silicic acid are expected to react to form oligomers and homopolymers of various chain lengths and degrees of cyclization and branching. These oligomers and homopolymers are represented in this assessment by PEOS and are described by two CAS numbers that are used interchangeably: CAS No. 11099-06-2 and CAS No. 68412-37-3. Based on similarities in chemical structures, physicochemical (hydrolysis) and toxicological properties, and based on the principle that data from the monomer is likely to indicate a higher toxicity than that of the polymerised form, the grouping of TEOS and PEOS, and the use of data for TEOS to supplement data for the human health endpoints for PEOS is appropriate.

Physical-chemical properties

TEOS and PEOS are liquids. TEOS and PEOS have melting points of -82.2°C (measured) and -62.37°C (estimated), boiling points of 166.5°C (measured) and 124.66 °C (estimated) at 1013 hPa and vapor pressures of 2.51 hPa (measured) and 7.25 hPa (estimated) at 20 °C, respectively. By the chemical reactivity nature of the Si-O-Et bonds, quantitative estimates for water solubility are substituted with qualitative analysis of the hydrolysis products and observations with environmental test data. TEOS and PEOS are expected to be sparingly soluble with TEOS followed by PEOS as being the most sparingly soluble.

Human Health

No data are available on the toxicokinetics, metabolism or distribution of either TEOS or PEOS. However, observation of degenerative/necrotic nephropathy in a repeated dose oral and inhalation studies indicates that TEOS is systemically absorbed. In an OECD TG 403 study, the 4-hr LC₅₀ of TEOS was 10.0 mg/L (males) and 16.8 mg/L (females) in Wiskf (SPF71) rats, when exposed nose only to an aerosol atmosphere. Clinical signs of toxicity included mortality, motor behaviour and respiration, palpebral stenosis extending to full lid closure with encrusted blood covered eyelid rims, shivering and tonic cramping. Cyanosis and decreased reflexes occurred in individual animals. Necropsy findings included red and orange lung coloration. The oral LD₅₀ of TEOS and PEOS is greater than 2000 mg/kg bw in male and female rats (WISW (SPF Cpb) and Sprague-Dawley), respectively, in studies following OECD TG 401. Clinical signs of toxicity were unremarkable. TEOS was moderately irritating to the skin in rabbits (OECD TG 404). PEOS is not irritating to the skin in rabbits (FIFRA/TSCA test guideline). TEOS was not irritating to the eyes in standard irritation studies (OECD TG 405) in animal tests, but was a moderate/severe eye irritant in an *in vitro* assay and caused eye irritation during a four hour inhalation toxicity study in Wiskf (SPF71) rats. PEOS was a minimal eye irritant in rabbits (FIFRA/TSCA test guideline). Respiratory irritation data were not

available for TEOS or PEOS. However, in an acute inhalation toxicity study with TEOS, signs indicative of respiratory irritation were observed. TEOS and PEOS were not skin sensitising in guinea pigs following either the Buelher test or OECD TG 406.

The repeated-dose toxicity of TEOS has been investigated by the oral route in a seven-day range-finding study and combined repeated-dose/reproductive/developmental toxicity screening study. Daily oral exposures of Sprague-Dawley rats (3/sex/dose) to 0, 200, 600 or 1000 mg/kg bw/day TEOS for seven days resulted in mortality in males (2 out of 3) at the highest dose tested. Clinical findings included significant body weight loss or decreased body weight gain in both sexes. At necropsy, enlargement and abnormal coloration of the kidneys was noted in both sexes in a dose-dependent manner and correlated with high kidney weights. In males, the prostate and seminal vesicles were reduced in size. The dose levels of 600 and 1000 mg/kg-bw/day were considered to exceed the maximum tolerated dose in males. Repeated oral exposure of Sprague-Dawley rats [following OECD TG 422] to 0, 10, 50 or 100 mg/kg bw/day TEOS (10/sex/dose) from the pre-mating period, during mating and until sacrifice (males) or during gestation and lactation until day 4 post-partum (females) (at least four weeks total), induced a transient decrease in body weight gain during lactation at 100 mg/kg bw/day. No change in body weight was noted in males at any dose. In males at 100 and 50 mg/kg-bw/day there was treatment-related degenerative/necrotic nephropathy (9/10 at 100 mg/kg-bw/day; minimal in 4/10 at 50 mg/kg bw/d) and in the females at 100 mg/kg-bw/day there was a slight degenerative/necrotic nephropathy in 3/10 females; there were no findings at 50 or 10 mg/kg-bw/day in females. This was associated with slightly lower plasma levels of sodium, potassium and glucose. Based on the observation of tubular nephropathy and associated clinical chemistry changes, the NOAEL was 10 mg/kg-bw/day and 50 mg/kg-bw/day in male and female rats, respectively. The LOAEL was 50 and 100 mg/kg-bw/day for males and females, respectively. Groups of ten ICR male mice were exposed to TEOS at 50 or 100 ppm for 6 hrs/d, 5d/week for 2 or 4 weeks. Microscopic changes of the nasal mucosa were observed in all exposed mice. Tubulo-interstitial nephritis was observed in mice exposed to 100 ppm (but not 50 ppm) for 2 or 4 weeks. Groups of ten ICR male mice were exposed to TEOS at 200 ppm for 6 hrs/d, 5d/week for 2 or 4 weeks. Decreased body weights of the exposed mice were observed after 2 or 4 weeks exposure; animals in the 2 week (but not 4 week) exposure groups recovered during the two week observation period. Tubulo-interstitial nephritis was observed in mice exposed for 2 or 4 weeks, however clinical chemistry did not confirm renal dysfunction. Infiltration of polymorphonuclear neutrophils into the nasal mucosa was also observed immediately following 2 or 4 week exposure. The NOAEC for systemic renal effects was 50 ppm. The LOAEC for local respiratory effects was 50 ppm.

In bacterial reverse mutation assays with multiple strains of *Salmonella typhimurium*, TEOS and PEOS were negative both with and without metabolic activation (Directive 84/449/EEC, B.14 and Directive 92/69/EEC, B. 14). An *in vitro* chromosomal aberration test using TEOS was negative both with and without metabolic activation (OECD TG 473). Based on these results, TEOS and PEOS are considered to be non-genotoxic *in vitro*.

No data were available regarding the carcinogenicity of TEOS or PEOS.

In the aforementioned screening study [OECD TG 422] with TEOS, no adverse effects on reproduction or development of Sprague-Dawley rats were observed up to the highest dose tested. The NOAEL for reproductive/developmental toxicity for TEOS was 100 mg/kg-bw/day in rats. The NOAEL for maternal toxicity was 50 mg/kg-bw/day. Based on these results, TEOS is considered not likely to be a reproductive or developmental toxicant.

Chemicals in this category possess properties indicating a hazard for human health [skin, eye and respiratory tract irritation (TEOS) and eye irritation (PEOS), and repeated-dose toxicity (kidney and respiratory tract). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The EPISuite program developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure; therefore there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported below.

All chemicals are subject to hydrolysis. The hydrolysis half-life for TEOS is 4.4 hours at pH 7. For PEOS, the hydrolysis is dependent on the solubilities of the individual components. Other hydrolysis products are expected to be metasilicic acid or silicic acid and ethanol. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.4 days for TEOS and 1.1 days for PEOS. A DOC-die away test with TEOS resulted in 98% biodegradation in 28 days. TEOS is readily biodegradable under aerobic conditions. A modified Sturm test with PEOS resulted in 47% biodegradation in 28 days. PEOS is not readily biodegradable under aerobic conditions.

A level III fugacity model calculation (Epiwin v 3.20) with equal and continuous distributions to air, water and soil

compartments suggests that TEOS will distribute mainly to soil (74.1 51%), with lesser amounts to air (17.6 %) and water (8.3 %) and negligible amounts to sediment (0.0 %); PEOS will distribute more evenly between water and soil (46.4 and 51%, respectively), with lesser amounts distributed to air (2.5%) and sediment (<1%). The bioaccumulation potential is considered to be low based on the chemical reactivity for these chemicals. Because TEOS and PEOS react to form different substances through hydrolysis, the BCF for the ethyl esters cannot be predicted, but is expected to be below if hydrolysis products predominate.

An LC_0 of 245 mg/L (measured) was determined in a 96-hr study with TEOS and *Brachydanio rerio*. An LC_0 of 119 mg/L (measured) was determined in a 96-hr study with PEOS and *Brachydanio rerio*. The 48-hr EC_{50} of TEOS under flow-through conditions was > 75 mg/L (expressed as measured concentrations) for the water flea (*Daphnia magna*). The 48-hr EC_{50} of PEOS was > 193 mg/L (measured) for the water flea (*Daphnia magna*). There were no effects observed in these studies. The 72-hr ErC_{50} and EbC_{50} values for TEOS and *Pseudokirchneriella subcapitata* were >100 mg/L (expressed as nominal concentrations due to rapid hydrolysis of the substance). The 72-hr NOEC for growth rate or biomass was determined to be 100 mg/L. *Scenedesmus subspicatus* was exposed to TEOS and PEOS for 72 hrs; on the basis of cell growth, the 72-hr E_bC_{50} was 889.2 and >207 mg/L, respectively; on the basis of growth rate, the 0-72 hr E_bC_{50} was >1039.3 and >207 mg/L, respectively. The NOEC was 115.5 and 115 mg/L for TEOS and PEOS, respectively.

The chemicals in this category have a low hazard profile for the environment. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

The 2005 production volumes in tonnes by region for TEOS and PEOS are:

Region	TEOS	PEOS
North America	ca. 380.4	< 0.45 (produced) < 453.6 (imported)
Europe	ca. 2948.4	ca. 7810.9
Japan	ca. 399.2	ca. 562.5

Traditional application areas for ethyl silicates are:

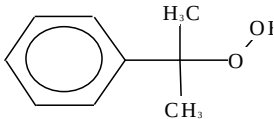
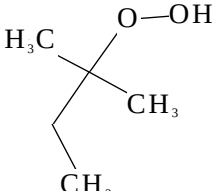
- Binders for zinc-rich paints in heavy-duty corrosion protection
- Binders for precision castings and refractory materials
- Formation of SiO₂ layers on silicon chips
- Modification of organic polymers in the chemical industry
- Binders for stone consolidation
- Marine and protective coatings
- Clear coupling agent for textile coatings.

Ethyl silicates are increasingly used in sol-gel processes for the manufacture of modern materials: via hydrolysis and condensation processes, liquids (called "sols") are converted into solids (called "gels"). By using alkoxysilanes or organofunctional silanes it is possible to produce submicron or spherical silica powders, thin-film coatings, fibers, porous (aerogels) or dense materials. These materials are used in many sectors, e.g. for chromatography, for the surface coating of glass and pigments, in the ceramics industry, for the production of catalysts and for polymer modification. In paints, industrial customers generally make a hydrolysate of PEOS before adding it to the formulation; at this point in the process the parent substance has already been changed. Use levels of the PEOS hydrolysate in paints range from 10-20%. TEOS is also used as a raw material in semiconductor manufacture. TEOS and PEOS are shipped by road and marine routes in drums and cans.

There are no intentional releases to the environment during manufacturing and any exposure to the parent compounds would be limited due to hydrolysis of both chemicals. TEOS is manufactured in both open and closed systems where engineering controls are routinely used. TEOS and PEOS are stored on-site in drums and cans. The Occupational Safety and Health Administration (OSHA) in the Sponsor country has set a permissible exposure limit (PEL), for an 8-hour time weighted average period, of 100 ppm (850 mg/m³). In addition, OSHA has issued guidance on minimizing exposure to ethyl silicates that discusses appropriate engineering controls. Occupational exposure via the inhalation and dermal routes is possible but would be controlled by use of these engineering controls and adherence to the PEL.

TEOS is used in consumer sealants and in some mold-making products with indirect food contact at levels < 6%.

PEOS is used in consumer sealants and adhesives at levels $< 0.1\%$. The consumer sealants and adhesives contain unreacted PEOS by design, as the products are developed so that upon use (as soon as the product is exposed to air/moisture), PEOS will crosslink as the sealant cures, releasing ethanol. Thus, the sponsored substances are reacted during use and are not expected to be present in the final sealant or adhesive product.

<u>SIDS INITIAL ASSESSMENT PROFILE</u>	
CAS Nos.	80-15-9 3425-61-4
Chemical Names	hydroperoxide, 1-methyl-1-phenylethyl (CHP) hydroperoxide, 1,1-dimethylpropyl (TAHP)
Structural Formulae	 CHP  TAHP
SUMMARY CONCLUSIONS OF THE SIAR Category/Analogue Rationale 1-Methyl-1-phenylethylhydroperoxide (cumene hydroperoxide; CHP, CAS No. 80-15-9) and 1,1-dimethylpropylhydroperoxide, (<i>tert</i>-amyl hydroperoxide; TAHP, CAS No. 3425-61-4) are monosubstituted derivatives of hydrogen peroxide with the general molecular formula ROOH. These compounds are further classified together as tertiary hydroperoxides as they share the general molecular formula R-C(CH₃)₂-O-OH. TAHP is a low molecular weight saturated aliphatic hydroperoxide. CHP is an aryl hydroperoxide. They are members of a category because the functional characteristic is the reactivity of the hydroperoxide moiety; the aryl/alkyl group is not expected to contribute to the toxicity of the category members as much as the reactivity of the hydroperoxide moiety. Differences in their physical states and some physical-chemical properties are believed to be relevant for exposure scenarios but the common element, the hydroperoxide moiety, is most relevant for toxicity. 1,1-Dimethylethyl hydroperoxide (<i>tert</i>-butyl hydroperoxide; TBHP, CAS No. 75-91-2) has previously been assessed in the OECD HPV Programme. Data for TBHP are referenced to provide support for TAHP and CHP. Biodegradation and acute aquatic toxicity endpoints for TAHP are fulfilled using data for TBHP and CHP. Repeated-dose toxicity, chromosomal aberrations, fertility and developmental effects data for TBHP are used to fulfill these endpoints for TAHP and CHP. The reactivity of organic peroxides is related to their half-lives at a given temperature. When measured at a 0.2 molar concentration in benzene, the temperatures for a 1-hour half-life for CHP, TAHP, and TBHP are 190, 183, and 200 °C, respectively. The similarity of the activation energies required to decompose these hydroperoxides supports their inclusion as a category because the hydroperoxide moiety is believed to be the primary determinant of the biological effects observed. According to the draft EU Risk Assessment Report on TBHP for human health, the initial decomposition of these substances is expected to be at the peroxide bond. A key decomposition pathway involves formation of free radicals,	

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expected at the site of first contact. The major decomposition product is the rapid formation of t-butanol, which is subsequently metabolized. TBHP is rapidly metabolized *in vivo* to t-butyl alcohol (TBA) by glutathione peroxidase. Cumyl alcohol is the anticipated metabolite of CHP.

CHP, TAHP and TBHP are irritants at the point of administration by ocular, dermal and inhalation routes. A comparison of available subchronic data (TBHP and TBA; CHP) supports the assertion that the toxicity profile for this category of materials is dominated by the irritating to corrosive nature of the peroxide functionality.

The physical properties, reaction profiles and toxicity supports our decision to treat these hydroperoxides as a category, although differences due to different rates of reaction, by-products and chemical structure may be expected.

Physical-chemical properties

CHP, TAHP and TBHP are liquid preparations at room temperature and pressure. The melting points of **CHP**, **TAHP** and **TBHP** are -9°C, -28.8°C and -8°C, respectively. The reported boiling points are 100 - 101 °C at 10.6 hPa and 96 °C at 1013 hPa for **CHP** and **TBHP**, respectively. **TAHP** decomposes at 1013 hPa; TBHP has a decomposition point of 13°C. The density of **CHP**, **TAHP** and **TBHP** are 1.1 g/cm³, 0.91 g/cm³ and 0.90 g/cm³ at 20 °C, respectively. The vapour pressure of **CHP** is 0.02 hPa at 25 °C. The vapour pressure of **TAHP** and **TBHP** are similar (23 hPa at 26°C and 27 hPa at 20°C, respectively). The hydroperoxides are very water soluble, with values ranging from 143,000 (**CHP**) to ≥100,000 (**TBHP**) mg/L. The n-octanol/water partition coefficients (log value) of **CHP**, **TAHP** and **TBHP** are 1.6 at 25 °C (measured), 1.4 (estimated; temperature not specified) and 0.7 at 25 °C (measured), respectively.

Human Health

No data on toxicokinetics are available. Acute toxicity testing has been performed by various routes of exposure for **CHP** (oral), **TAHP** (oral, dermal) and **TBHP** (oral, dermal and inhalation). The inhalation 4-hr LC₅₀ (combined sexes) value for **TBHP** in rats was 1.85 mg/L. At all exposure levels, clinical signs of respiratory and ocular irritation were observed, with recovery occurring at the lowest exposure concentration. Lung discoloration was observed during gross necropsy. Valid acute inhalation studies were not available for **TAHP** or **CHP**. The dermal LD₅₀ of **TAHP** (OECD TG 402) in rats was 354 mg/kg bw/day (females) and 492 mg/kg bw/day (males). Exposure was 24 hours. Clinical observations included staining around the mouth and on the fur, decreased activity, wobbly gait, reddish colored urine and decreased food consumption. Necropsy of deceased animals revealed congested meningeal vessels in the brain, mottled livers, abnormal contents in the digestive tract, reddened mucosa in urinary bladder and cervical lymph nodes, reddened thymus, and discolored kidneys and spleen. Irritation was observed at the application site. Valid acute dermal toxicity studies were not available for **CHP**. The oral LD₅₀ of **TAHP** (OECD TG 401) in rats was 483 mg/kg bw/day (females) and 518 mg/kg bw/day (males). Salivation, abnormal breathing and urine stain were observed in all groups. Necropsy of deceased animals revealed congested meningeal vessels in the brain, mottled livers, abnormal contents in the digestive tract, linear striations and dark red foci in stomach, reddened mucosa in small intestines, dark red and thickened serosa in the stomach, discolored thymus, and abnormally colored contents in urinary bladder and thoracic cavity. The oral LD₅₀ for **CHP** was 382 mg/kg bw/day; practically all deaths occurred within 5 days. Extensive urinary bleeding in the rats exposed to 400 mg/kg bw/day was observed during clinical observations.

TAHP is a severe skin irritant that caused necrosis and corrosion in rabbits in a study consistent with OECD Test Guidelines; **TAHP** is a severe eye irritant in rabbits. **CHP** is expected to exhibit similar irritation properties. There are no data available on sensitization for TAHP and CHP.

A repeated-dose inhalation toxicity study is available for **CHP**. Repeated-dose toxicity studies were not available for **TAHP**. However, repeated-dose toxicity studies by the inhalation, dermal and oral route of exposure were available for **TBHP**. In a repeated-dose inhalation toxicity study, rats (10/sex/concentration) were exposed to **CHP** for 6 hrs/day, 5 days/week for 3 months at 0, 1, 6 or 31 mg/m³ (0, 0.001, 0.006 or 0.03 mg/L, respectively) as an aerosol. The clinical signs of exposure included skin and respiratory irritation. Changes in relative organ weights (heart, liver and kidney) were not considered toxicologically relevant. The NOAEL was 31 mg/m³ (0.03 mg/L) in this study.

In a repeated-dose toxicity study, rats (12/sex/dose) were exposed by the dermal route to **TBHP** at 0, 22, 44, 88, or 175 mg/kg bw/day for 12 applications over 17 days. Dermal irritation (confirmed by histopathological findings) was observed. No other clinical signs of toxicity were observed. The NOAEL for dermal toxicity for **TBHP** in rats was 88 mg/kg bw/day (males) and 44 mg/kg bw/day (females). Due to the limited number of systemic endpoints measured, this is primarily a NOAEL for dermal effects. In a similar study, mice (5/sex/dose) were administered 0, 22, 44, 88, 176 or 352 mg/kg bw/day for 13 applications over 18 days. Dermal irritation at the application site was the only clinical sign of toxicity; confirmed by histopathological findings. The NOAEL for **TBHP** for dermal toxicity in mice was 44 mg/kg bw/day (males) and 88 mg/kg bw/day (females).

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In a combined repeated-dose/reproductive/developmental (OECD TG 422) toxicity study, rats (12/sex/dose) were administered **TBHP** by oral gavage for 41-45 days at doses of 0, 3, 10 and 30 mg/kg bw/day. Treatment-related changes in the form of tubular nephrosis, as well as multifocal, increased accumulation of tubular proteinaceous material, were observed in kidneys of male rats at 10 and 30 mg/kg bw/day. This accumulation of intratubular protein is considered a male rat characteristic. In males, the bilirubin level increased but was decreased in females at doses of 10 mg/kg bw/day and above. The reported NOAEL for systemic toxicity was 3 mg/kg bw/day based on kidney effects attributed to alpha-2 μ -globulin accumulation as previously concluded in the OECD HPV Programme.

In a reverse mutation assay in several *S. typhimurium* strains, **CHP** was mutagenic or weakly mutagenic. **CHP** was mutagenic in strain TA98 at one dose level with rat S9, in a single run with mouse S9 and in one of two experiments without activation. **TAHP** (OECD TG 471) did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for strains TA1537, TA1535, TA1538, and TA98 with or without metabolic activation. However, for TA100 there was a slight increase (less than 2 fold) in the number of revertants. In a mouse lymphoma study, **TBHP** induced a dose-dependent increase in the mutant frequency of cultures treated both with and without metabolic activation. In a mammalian cell gene mutation assay, **TAHP** did not induce mutations at the HGPRT locus in CHO cells. **TBHP** was positive in several chromosome aberration studies with cultured mammalian cells. *In vitro* chromosome aberration studies were not located for **TAHP** and **CHP**. In a mouse micronucleus test, **TBHP** did not result in chromosomal damage and/or damage to the mitotic apparatus in bone marrow cells of mice *in vivo*. In an *in vivo* mammalian bone marrow chromosome aberration test, **TBHP** did not induce chromosomal damage when administered to rats by inhalation for 5 d. *In vivo* genotoxicity studies were not located for **TAHP**. In studies with mice, similar to OECD TG 478, repeated intraperitoneal injection of **TBHP** for males resulted in a significant increase in DNA damage in the testicular tissue at doses of 27 and 54 mg/kg bw/day and above; injection of **CHP** for males resulted in the same effects at doses of 23 and 46 mg/kg bw/day and above. Based on these results, **TAHP** and **CHP** are considered to be potentially genotoxic *in vitro*. **TBHP** is considered genotoxic *in vitro*, and potentially genotoxic *in vivo*.

Reliable carcinogenicity studies were not available for **CHP** or **TAHP**.

No reproductive/developmental toxicity data are available for **TAHP** or **CHP**. In an OECD TG 422 study with **TBHP** in rats described above, the body weight of pups, clinical and macroscopic observations were comparable to controls. No treatment related effects were observed. Based on these data, the NOAEL for reproductive toxicity was 30 mg/kg bw/day (the highest dose tested). The NOAEL for developmental toxicity was 30 mg/kg bw/day as previously concluded in the OECD HPV Programme.

In a developmental toxicity study (OECD TG 414), rats (24 females/dose) were exposed to **TBHP** at 0, 5, 15 and 50 mg/kg bw/day by oral gavage once/day from days 6 to 15 of gestation. There was a slight decrease in maternal body weight gain and food intake at 50 mg/kg bw/day. The NOAEL for developmental toxicity was 50 mg/kg bw/day (highest dose tested). Overall, **TAHP** and **CHP** are not likely to exhibit reproductive/developmental toxicity based on available information.

The available data suggest chemicals in this category possess properties indicating a hazard for human health (acute inhalation toxicity, corrosivity, genotoxicity, repeated-dose toxicity for the oral, dermal and inhalation exposure routes). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

Photodegradation half-lives for **CHP**, **TAHP** and **TBHP** range from ca. 1 to 5 days. **TBHP** was photolysed (250 - 390 nm) in a quartz cell alone or in 2.5% solution of aliphatic solvents; a high **TBHP** radical concentration formed during photolysis alone or in solvent. EUSES calculations suggest a first-order degradation rate constant of 0.13/day for **TBHP** in air.

The stability of hydroperoxides in pure water does not represent the situation under real-world conditions. In the presence of transition metals or other reducing agents, hydroperoxides rapidly decompose. In natural waters containing transition metals and organic matter, hydroperoxides, and organic peroxides in general, are not expected to be stable.

An abiotic degradation study with **TBHP** (similar to OECD TG 111) did not show an appreciable degradation during the 5-d test period at a temperature of 50 °C and pH values of 4, 7 and 9, respectively. The abiotic degradation of **TBHP** was studied in 10-d tests in ultra-pure water and in sterilised (thus abiotic) activated sludge; the results show up to around 5% degradation of **TBHP** in ultra-pure water and up to around 25% degradation in sterilised sludge.

Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 1000 kg/h for each medium, shows the

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following percent distribution: **CHP**: Air = 1.1%; Soil = 65%; Water = 34%; Sediment = 1.5%; **TAHP**: Air = 6.7%; Soil = 47%; Water = 46%; Sediment = 0.09%; **TBHP**: Air = 7.7%; Soil = 42%; Water = 51%; Sediment = 0.88%.

CHP did not readily degrade over 28 days under the test conditions of an OECD TG 301 B. In OECD TG 301 B and D tests, there was no biodegradation of **TBHP** over 28 days. No measured data are available for **TAHP**, but based on its structural similarity to **TBHP**, it is not likely to be readily biodegradable.

The estimated BCF for **TBHP**, **TAHP** and **CHP** are 3.2, 2.5 and 9.1, respectively; these materials have minimal potential for bioaccumulation.

The toxicity of **CHP** to groups of *Oncorhynchus mykiss* was evaluated in an OECD TG 203 study. The interpolated LC_{50} value was 3.9 mg/L and the 96-h NOEC (behavioural changes) was < 1.5 mg/L. Because the last fish in the 6 mg/L group died in the last 24 hours of the study, the reported LC_{50} may not be asymptotic. In an OECD TG 202 study with **CHP**, where the test article was shown by measurements to be stable over the 24-hour renewal period, the 48-hr EC_{50} for *Daphnia magna* was 18 mg/L and the 48-hr NOEC was 10 mg/L. In an OECD TG 201 study, *Pseudokirchneriella subcapitata* were exposed to **CHP** for 72 hours; the EC_{b50} was 1.6 mg/L and the 72-hr EC_{r50} was 3.1 mg/L. The reported LOEC and NOEC for biomass and growth rate were 1 and 2.2 mg/L (biomass), and 0.46 and 1.0 mg/L, respectively. Reported values were nominal concentrations.

The toxicity of **TBHP** was evaluated in OECD TG 203 studies with *Pimephales promelas* or *Poecilia reticulata* exposed under measured semi-static conditions for 96 hours. The 96-hr LC_{50} and NOEC for *Pimephales promelas* were 42.3 and 32 mg/L, respectively. In the second 96-hr fish study, the LC_{50} and NOEC values for *Poecilia reticulata* were 57 and 30 mg/L, respectively. In an OECD TG 202 study, the 48-hr EC_{50} for *Daphnia magna* exposed to **TBHP** was 20 mg/L and the NOEC was 10 mg/L. Reported values were nominal concentrations. In an OECD TG 201 study, *Pseudokirchneriella subcapitata* were exposed to **TBHP** for 72 hours; the EC_{50} with respect to growth rate and biomass were 2.1 and 1.2 mg/L. The NOEC for growth rate and biomass was 0.32 mg/L. Reported values are nominal concentrations.

ECOSAR estimations of toxicity to fish, daphnia and algae are available. **CHP**: LC_{50} for fish = 0.26 mg/L, daphnid = 5.1 mg/L; **TAHP**: LC_{50} for fish = 0.14 mg/L, daphnid = 7.1 mg/L; **TBHP**: LC_{50} for fish = 0.11 mg/L, daphnid = 9.8 mg/L. There are no predicted values for algae.

The available data suggest chemicals in this category are not readily biodegradable and possess properties indicating a hazard for the environment (acute toxicity to fish, invertebrates and algae between 1 and 100 mg/L). However, they possess a minimal potential for bioaccumulation with estimated BCFs less than 10. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

Worldwide production of neat **CHP** in 2006 was in the range of 1,000-10,000 tonnes. **CHP** is used as a modifier with certain resins, a polymerization initiator and as a raw material to make other organic peroxides and resins. Approximately 790 tonnes of neat **TAHP** and approximately 26,400 tonnes of neat **TBHP** were produced worldwide in 2006. Both are used as a source of free radicals in polymerization and other reactions, in the manufacture of other peroxides, and as an emulsion polymerization initiator.

Releases to the environment and potential industrial worker exposure can occur during handling in industrial settings, including manufacture (open vessel), use and spills. Exposure limits have not been established, but internal industrial hygiene limits are used within industrial facilities.

Consumer exposure is expected to be extremely low because only negligible amounts of hydroperoxide are expected to remain after its use in processing of materials based on application of the Arrhenius equation. During manufacturing processes in which hydroperoxides are used, the process materials are typically held at a thermal decomposition temperature for many half-lives, and therefore only negligible amounts of the hydroperoxides are expected to remain. Manufacturers provide customers with data sheets showing half-lives as a function of temperature so they can select appropriate process temperatures and holding times. It is important to manufacturers of articles using hydroperoxides to ensure the hydroperoxides are reacted, until only negligible amounts remain, to avoid post-processing changes in material properties.

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SIDS INITIAL ASSESSMENT PROFILE

CAS No.	68515-32-2, 68855-24-3, 84961-70-6, 85117-41-5, 151911-58-9, 129813-62-3, 68515-34-4, and 94094-93-6
Category Name	Linear Alkylbenzene (LAB) Alkylate Bottoms Category
Structural Formula	[See Figure 1 of SIAR]

SUMMARY CONCLUSIONS OF THE SIAR**Category/Analogue Rationale**

The linear alkylbenzene (LAB) alkylate bottoms are best described as a category of Class 2 substances. Class 2 substances are generally ones that may have variable compositions or be composed of a complex combination of different molecules. Therefore, they cannot be represented by unique chemical structures or molecular formulae. This Class 2 category is process based, and represents co-products of the LAB manufacturing process. Analysis of LAB alkylate bottoms samples from all member companies shows that the mixtures are predominantly comprised of di- and trialkylbenzenes, alkyl tetralins/indanes and diphenylalkanes, with lesser amounts of other constituents (e.g. LAB) and only trace amounts of other component classes. The analytical characterization demonstrates that composition is relatively consistent across production processes as well as among all LAB alkylate bottoms category members. No single product represents the extremes of the ranges determined. This includes the light and heavy ends, which are produced by distillation of whole bottoms into two subfractions, and which fit in the range of values found for the whole bottoms.

The LAB alkylate bottoms products manufactured and tested are 100% LAB alkylate bottoms, with no additives. GC-MS analyses of LAB alkylate bottoms samples indicate that PAH compounds of concern are not detected.

Based on the similarity of the chemical structural compositions and physico-chemical properties, a predictable pattern in environmental fate properties, environmental effects and mammalian toxicity is anticipated for the chemicals in this category. Therefore, they can be grouped and evaluated together.

Data are available for various preparations of LAB alkylate bottoms and for analogues (discussed below) that are used as supporting evidence and to fill data gaps.

C10-C14 dialkylbenzenes comprise the largest single component of LAB alkylate bottoms. A C10-C14 dialkylbenzene (CAS No. 85117-31-3) is used as an analogue for LAB alkylate bottoms for the biodegradation endpoint.

Data for benzene, C10-C13 alkyl derivatives (LAB, CAS No. 67774-74-7) and benzene, C10-C16 alkyl derivatives (C10-14 LAB, CAS No. 68648-87-3) are used to fill data gaps for LAB alkylate bottoms, e.g. acute inhalation toxicity and *in vivo* genotoxicity. LAB has been previously assessed in an EU Risk Assessment (http://ecb.jrc.it/home.php?CONTENU=/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/) and C10-C14 LAB has previously been assessed in the OECD HPV Programme. LAB/C10-C14 LAB is a component (approximately 0.75%) of LAB alkylates bottoms.

Data from lab-synthesized LAB homologues, such as phenyl-C10 (C10 LAB) or phenyl-C12 (C12 LAB) as well as homologues such as phenyl-C18, which are outside the alkyl chain range for LAB are provided to illustrate how the aquatic toxicity of linear alkyl benzenes vary with alkyl chain length.

Physical-chemical properties

The LAB alkylate bottoms are all liquids at ambient temperatures. The density ranges from 0.89-0.92 at 15-20 °C, with higher average molecular weights (318-480) than LAB (218-274 for C10-C14 LAB). The melting points range (based on weight-of-evidence) is -70 to $\leq$ -33 °C and boiling point ranges overlap or are higher than that of LAB (278-314 °C for LAB; 270-500 °C for LAB alkylate bottoms). The range of vapour pressures is <0.01 to ≤ 7.5 hPa at 21-25 °C (weight-of-evidence) and suggests limited volatility. Further, these compounds have low water solubility (<0.004 to <0.021 mg/L) and high estimated log K_{ow} values (9.5 to 13.7).

Human Health

No specific data are available on the absorption, distribution or elimination of LAB alkylate bottoms. Metabolism on linear alkyl chains includes conversion of the terminal carbons of linear alkyl chains (alkanes) to carboxylic acids followed by metabolism of the resulting fatty acids. The carboxylic acid serves as a substrate for acyl-CoA synthetase, and the resulting acyl-CoA enters the β -oxidation pathway. Metabolism and biodegradation data on linear alkyl chains, LAB and linear alkylbenzene sulfonates (LAS) suggest that LAB alkylate bottoms will undergo metabolism and degradation in biological systems.

Inhalation studies in rats with the analogue substance LAB (CAS No. 67774-74-7) resulted in an LD₅₀ of 71 mg/L. The dermal rat LD₅₀ was >5000 mg/kg bw for CAS No. 68515-32-2 and >2000 mg/kg bw for the analogue substance LAB (CAS No. 67774-74-7). No clinical signs of toxicity were observed. The dermal rabbit LD₅₀s for CAS Nos, 129813-61-2 and 68855-24-3 were >2010 and >7940 mg/kg bw, respectively. Rabbits showed signs of reduced appetite and activity. The oral rat LD₅₀s for the LAB alkylate bottoms were >2000 mg/kg bw and for the analogue substance LAB (CAS No. 6774-74-7) >5000 mg/kg-bw. The only clinical sign of toxicity observed was a reduced appetite in one study.

LAB alkylate bottoms are slightly irritating to the skin (OECD TG 404) and not irritating to the eye of rabbits (OECD TG 405). LAB alkylate bottoms are not skin sensitisers in guinea pigs (OECD TG 406) and analogue LAB (CAS No. 67774-74-7) is not a sensitiser in humans.

Repeated-dose studies were available via inhalation for LAB, via the dermal exposure route for one LAB alkylate bottom and via oral feed for an LAB alkylate bottoms blend and LAB. In a repeated-dose inhalation toxicity study, Sprague-Dawley rats (15/sex/concentration), were exposed to LAB (respirable particles) at 0, 102, 298 or 580 mg/m³ (~ 0 , 0.102, 0.298 or 0.580 mg/L, respectively) for 6 hours/day, 5 days/week for 14 weeks. No deaths were observed, but respiratory effects (irritation and difficulty breathing) were evident in the mid- and high exposure concentrations. Body weights were depressed and liver weights and serum levels of hepatic enzymes were elevated at these levels, although no gross or histopathological changes were observed. Based on respiratory effects, body weight changes and changes in clinical chemistry, the NOAEL for repeated-dose inhalation toxicity was considered to be 102 mg/m³ (respirable particles).

In a repeated-dose dermal toxicity study, Wistar rats (6/sex/dose) were treated with 2000 mg/kg-bw/day (limit dose) LAB alkylate bottoms (CAS No. 68515-32-2) for 5 days/week for 28 days. No mortality was observed; however, a significant weight decrease was observed in female rats and acute multifocal hepatitis was observed in both sexes. The NOAEL for repeated-dose dermal toxicity was not established.

In a combined repeated-dose/reproductive/developmental toxicity screening study [OECD TG 422], an industry blend (containing all LAB alkylate bottoms products mixed in proportion to their production volume, as summarized in the table below) was administered by oral gavage to 60 male and 80 female Crl:CD(SD) rats at 0 (corn oil vehicle), 250, 500 and 1000 mg/kg-bw/day.

Component Class	Individual Products, weight %		Industry Blend, weight %
	Minimum	Maximum	Day 0
CnH _{2n-6}	43.4	94.3	73.5
CnH _{2n-8}	4.4	32.0	11.6
CnH _{2n-10}	0.0	7.0	2.4
CnH _{2n-12}	0.6	10.7	4.8

CnH2n-14	0.8	12.1	5.2
CnH2n-16	0.0	7.5	2.5

Clinical observations included body weight gain differences and changes in the thyroid of both sexes at all dose levels and in the thymus of the 1000 mg/kg-bw/day female rats. The significance of the effects seen in the thyroid at all dose levels is uncertain as it is generally accepted that humans are less susceptible than rats in relation to thyroid effects. The overall NOAEL for repeated-dose oral toxicity was considered to be 500 mg/kg-bw/day based on body weight reductions at 1000 mg/kg-bw/day. In a repeated-dose oral toxicity study, rats were administered 0, 2500, 5000, 7500 or 20000 ppm (~0, 125, 250, 375 or 1000 mg/kg-bw/day) LAB in the diet for 4 weeks. No deaths were observed. Body weights and food consumption were reduced at all exposure levels. No gross pathological changes were observed. The NOAEL was not established.

For LAB alkylate bottoms (CAS Nos 84961-70-6 and 85117-41-5) and LAB, *in vitro* bacterial reverse mutation assays (Ames test) using multiple strains of *Salmonella typhimurium* were negative for gene mutations, both with and without metabolic activation. An *in vitro* chromosomal aberration test with LAB alkylate bottom (CAS No. 85117-41-5) tested up to 80 nL/mL in Chinese hamster ovary (CHO) cells was negative with and without metabolic activation. LAB did not cause gene mutations *in vitro* in CHO cells and was not genotoxic in an *in vivo* rat bone marrow chromosome aberration test. Based on these data, LAB alkylate bottoms are considered not to be genotoxic *in vitro* or *in vivo*. No carcinogenicity data are available.

Reproductive toxicity data are available for an LAB alkylate bottoms blend and LAB. In a combined repeated-dose/reproductive/developmental toxicity screening study [OECD TG 422] with the LAB alkylate bottoms blend described above, no reproductive effects were observed at any dose up to the highest dose tested (1000 mg/kg-bw/day). Based on the lack of effects on reproduction parameters, the NOAEL for reproductive toxicity for LAB alkylate bottoms blend was 1000 mg/kg-bw/day. In a two-generation reproductive toxicity study, CD rats were given a single daily dose of LAB via gastric intubation at 5, 50 or 500 mg/kg-bw/day over a 35-week period. Evidence of toxicity was observed at the 500 mg/kg-bw/day dose level, with the most consistent effects being depressed weight gains in adults, smaller litters, fewer live pups, and decreased pup survival. At 50 mg/kg bw/day, the only effect was a temporary reduction in pup weight gain at day 7 that returned to normal at days 14 and 21. This temporary reduction occurred in one generation only, and thus was not consistent across generations. Based on decreased litter size and pup survival, the NOAEL for reproductive toxicity for LAB was 50 mg/kg-bw/day.

Developmental toxicity data are available for an LAB alkylate bottom (CAS No. 68855-24-3), the LAB alkylate bottoms blend and LAB. Pregnant Sprague-Dawley rats were administered 400, 800 and 1600 mg/kg-bw/day LAB alkylate bottom (CAS No. 68855-24-3) from gestation day 6 to day 15. On day 20 of gestation, the surviving animals were sacrificed and effects on the adults and fetuses were evaluated. No mortality was observed. Changes in maternal weight were observed at the two higher dose levels; however, no fetal effects were observed at any dose level. The NOAEL for developmental toxicity is 1600 mg/kg-bw/day. In a combined repeated-dose/reproductive/developmental toxicity screening study [OECD TG 422] with a LAB alkylate bottoms blend described above, no developmental effects were observed at the highest dose tested (1000 mg/kg-bw/day). The NOAEL for developmental toxicity was 1000 mg/kg-bw/day. Pregnant CD rats were administered 125, 500 and 2000 mg/kg-bw/day LAB on days 6 through 15 of gestation via oral gavage. Depressed maternal food consumption and weight gains were observed at 500 and 2000 mg/kg-bw/day during treatment which significantly increased in the post-treatment period. No treatment related increases were observed in soft-tissue malformations and variations; however, some skeletal variations (wavy ribs) and ossification variations were observed at the higher doses. Based on these effects, the NOAEL for both maternal and developmental toxicity was 125 mg/kg-bw/day. These results show that a minor component of the LAB alkylate bottoms exhibited reproductive/developmental toxicity at high doses; however, based on data for the LAB alkylate bottoms blend, this toxicity is not representative of the LAB alkylate bottoms mixture. Based on these screening-level data LAB alkylate bottoms are considered to have a low potential for reproductive/developmental toxicity.

The LAB alkylate bottoms possess properties indicating a low hazard profile for human health. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

Based on studies conducted at concentrations greatly exceeding water solubility, LAB alkylate bottoms are not readily biodegradable. For C10-C14 dialkylbenzene, a major component (over 70%) of LAB

alkylate bottoms, biodegradation ranged from 28-41% in 28 days and 43-54% in 48 days. These tests were conducted at concentrations higher than the water solubility of the materials and biodegradation may be more rapid at lower concentrations (as observed with LAB). Biodegradation for LAB at concentrations far exceeding the water solubility concentration ranged from 56 to 67%. Studies carried out in more natural systems (using concentrations ranging from 0.1 to 0.5 mg/L) showed LAB primary biodegradation greater than 90% with half-lives of 4-15 days. Based on structural similarities to LAB, LAB alkylate bottoms are also expected to undergo faster biodegradation at water soluble concentrations.

Level III fugacity modeling with equal and continuous distributions to air, water and soil compartments of representative LAB alkylate bottoms constituents (di- and trialkylbenzenes and diphenylalkanes) predicts predominant distribution to sediments (64-67%) and soil (28-30%) and lesser amounts to water (3.4-7.2%).

Predicted BCFs are 3.2 (estimated using EPI Suite v.3.20). In addition, because of the rapid metabolism of linear alkyl chains, LAB and LAS, and the presence in all LAB alkylate bottoms component structures of linear alkyl chains with unblocked terminal carbons, LAB alkylate bottoms are likely to show low bioaccumulation, similar to LAB and LAS.

Acute toxicity to several species of fish, *Daphnia*, and algae has been evaluated for LAB and two of the LAB alkylate bottoms. Studies conducted with fish using solvents to facilitate accurate dosing of the test media resulted in no effects at nominal concentrations up to 1000 mg/L. Similarly, new studies conducted on alkylate bottoms using water accommodated fractions (WAF) demonstrated no adverse effects at 100% WAF (loading rate = 1000 mg/L, measured = 0.024 and 0.020 mg/L). In addition to WAFs (NOECs = 0.0098 to >0.019 mg/L), studies on *Daphnia* and algae demonstrated no effects at saturation. Studies with C₁₀-LAB, the most water soluble component of LAB alkylate bottoms, show that these materials are not toxic at the limits of water solubility. ECOSAR modeling of key constituents also confirms that LAB alkylate bottoms are not predicted to be toxic at saturation. The lack of acute aquatic toxicity at water soluble concentrations has been confirmed with the most water soluble component of the LAB alkylate bottoms, C₁₀ LAB.

There are no chronic aquatic toxicity data on LAB alkylate bottoms. A 21-day *Daphnia* chronic study conducted on LAB indicated that reproduction and growth were affected at concentrations of 15 (LOEC) and 30 µg/L with a NOEC of 7.5 µg/L. ECOSAR-modeled LAB values are consistent with the potential for chronic toxicity below the water solubility limit. EPISuite modelling predicts that the LAB alkylate bottoms have higher Log Kows (>9.0), hence lower water solubility than LAB. Although no measured chronic toxicity data are available for LAB alkylate bottoms, these predicted data suggest that chronic effects would not be observed up to the water solubilities of the LAB alkylate bottoms. Because the LAB components make up less than 1% of the LAB alkylate bottoms, the LAB components are unlikely to produce chronic aquatic toxicity at the low water solubility of the LAB alkylate bottoms.

LAB alkylate bottoms have a low hazard profile for the environment. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

A survey of consortium members determined that total LAB alkylate bottoms production volume in 2005 in North and South America and Europe was between 50 and 100 kilotonnes. There are four primary processes by which LAB can be manufactured, and by which the LAB alkylate bottoms category co-products may be formed. In the final step of each process, the LAB alkylate bottoms are separated from the LAB by distillation. The LAB alkylate bottoms are predominantly used in non-consumer applications such as lubricating, transformer and other oils, as well as in auxiliary and marine diesel fuels and other miscellaneous uses. Some of the miscellaneous uses (e.g., car wash rust proofing, solvent cleaning bases for asphalt) may result in environmental releases to water and soil.

Occupational worker exposure is limited by engineering controls and the proper use of personal protective equipment, which are strict product stewardship requirements for LAB manufacture. For the closed system oils use (refrigeration/heat transfer fluids, transformer/dielectric oil), workers are protected from exposure by facility engineering controls for closed system processing and standard use of safety shoes, fire retardant clothing, safety glasses, gloves and other personal protective equipment (PPE). When used in auxiliary and marine diesel fuels, workers again use standard PPE to protect them from exposure. For sulfonated oil additives, the sulfonation reactions are conducted in closed manufacturing systems (reactor vessels) that are designed to limit any occupational exposure. However, given the widespread and dispersed use of these substances, proper use of PPE and other protective measures cannot be assured in all situations. Therefore, there is potential for some human

(dermal and inhalation) exposure and environmental exposure.

The LAB alkylate bottoms are used primarily in closed system oils (refrigeration/heat transfer fluids, transformer/dielectric oil), lubricating oils, marine fuels and other occupational settings. Furthermore, LAB alkylate bottoms are considered additives and thus generally make up small proportions of the final product, e.g. <1% of automobile or marine oils containing detergents. Therefore, consumer exposure to LAB alkylate bottoms is expected to be low.

<u>SIDS INITIAL ASSESSMENT PROFILE</u>	
CAS Nos	74-93-1 5188-07-8
Chemical Names	Methanethiol Sodium Methanethiolate
Structural Formulae	$\text{H}_3\text{C}-\text{SH}$ $\text{H}_3\text{C}-\text{S}^- \text{Na}^+$
SUMMARY CONCLUSIONS OF THE SIAR Category Rationale Sodium methanethiolate (CAS No. 5188-07-8) is the sodium salt of methanethiol (CAS No. 74-93-1) and is safer and easier to handle. Upon addition to water, sodium methanethiolate dissociates to the methanethiolate anion and sodium cation. Depending on pH, equilibrium then exists between the methanethiolate anion and methanethiol itself (protonated, neutral form). At environmentally relevant pHs, the substance exists almost entirely in the protonated form, methanethiol. Because the compounds are identical at environmental and biological pH values, toxicity and fate data from either compound can be used to read across to the other compound. Physical-chemical properties Methanethiol is a gas and sodium methanethiolate is a solid at room temperature. The melting points of methanethiol and sodium methanethiolate are -123.1 and 40 °C and the boiling points are 5.95 and 69 °C, respectively. The vapor pressure of methanethiol is 1650 hPa at 20 °C. The water solubility of methanethiol is 2.33×10^4 mg/L (20 °C) while sodium methanethiolate completely dissociates in water. The estimated log K_{ow} values for methanethiol and sodium methanethiolate are 0.78 and -2.33, respectively. Human Health <i>In vitro</i> metabolism studies that investigated the fate of methanethiol in blood indicated that it becomes extensively oxidized to formic acid and sulfite or sulfate upon entry into the blood stream. In rats, the 4-hour inhalation LC_{50} of methanethiol was 675 ppm. The dermal LD_{50} (OECD TG 402) of sodium methanethiolate was > 84.8 mg/kg-bw, the highest dose that could be tested based on corrosivity. At this dose, one female exhibited reversible body weight loss and clinical signs that included hypoactivity and tremors. The oral LD_{50} (OECD TG 401) of sodium methanethiolate in rats was 116 (when diluted in water) and 109 mg/kg body weight (when in methanol). In the oral studies, rats exhibited significant decreases in spontaneous activity and dyspnea, tonic-clonic convulsions, ataxia and coma at the higher doses. Sodium methanethiolate was corrosive (necrosis and blanching up to grade 4, eschar up to grade 3) to rabbit skin (OECD TG 404). Based on the corrosive properties observed in the primary skin irritation/corrosion studies, no eye irritation studies were performed. Sodium methanethiolate is presumed to be corrosive to the eye. Sodium methanethiolate was not a skin sensitizer in guinea pigs (OECD TG 406). Repeated-dose toxicity has been investigated in a 3-month inhalation toxicity study with methanethiol and an oral combined repeated-dose/reproductive/developmental toxicity study with sodium methanethiolate. In the 3-month inhalation study with methanethiol, Sprague-Dawley rats (31 males/concentration) were exposed to concentrations of 0, 2, 17 or 57 ppm (0, 0.0039, 0.033 or 0.118 mg/L) for seven hours per day, five days per week. A statistically-significant reduction in body weight at 57 ppm with a statistically-significant dose-related trend among all treated groups was observed. Significant changes in average organ weights (spleen and adrenals) were not considered relevant by the study authors. Average albumin concentration was lower for all exposed groups. Reduced inorganic phosphate and elevated total bilirubin occurred in the 2 and 17 ppm groups and cholesterol was slightly elevated in the 2 ppm group. Blood urea	

nitrogen was lower in the 57 ppm group and lactate dehydrogenase was lower in all exposed groups. However, there were no dose-related trends in these parameters or any exposure-related histopathological effects. The authors determined the NOAEC and the LOAEC to be 17 and 57 ppm (0.033 and 0.118 mg/L), respectively.

In the oral repeated-dose toxicity study (OECD TG 422), Sprague-Dawley rats (10/sex) were dosed by gavage with 0 (water), 5, 15 or 45 mg/kg-bw/day sodium methanethiolate for 8 or 9 weeks (males and females, respectively). Treatment-related effects at 45 mg/kg bw/day included low muscle tone, incoordination and excessive salivation; reduction in body weight gain and food consumption for females and/or males; decreased hemoglobin concentration (both sexes) with reduced mean and packed cell volumes, red blood cells and/or mean cell hemoglobin concentrations (females); higher absolute and relative spleens weights with increased incidence and/or severity of extramedullary hematopoiesis and hemosiderosis in the spleen (both sexes) and sinusoidal ectasia (males); higher incidence of extramedullary hematopoiesis in the liver with associated greenish pigment in a few Kupffer's cells (females). The NOAEL and the LOAEL for sodium methanethiolate in rats were considered to be 15 and 45 mg/kg bw/day, respectively.

Sodium methanethiolate was not mutagenic in a bacterial reverse mutation assay (OECD TG 471) *in vitro* either with or without metabolic activation. In a mammalian cell cytogenetic assay (OECD TG 473) using human lymphocytes, sodium methanethiolate did not induce structural chromosome aberrations but did induce polyploidy. Neither methanethiol (via inhalation) nor sodium methanethiolate (oral) resulted in increased chromosomal mutations in the Mammalian Erythrocyte Micronucleus Test (OECD TG 474). Overall, it is concluded that these compounds are not associated with gene mutations in bacteria or chromosomal aberrations *in vivo*. No data are available on the carcinogenicity of methanethiol or sodium methanethiolate.

There were no effects following oral exposure to sodium methanethiolate on reproductive performance, fertility or development in pups in the OECD TG 422 study, described previously. The NOAEL for reproductive performance and developmental toxicity was 45 mg/kg bw/day (the highest dose tested). Based on these screening-level results, sodium methanethiolate or methanethiol is not likely to result in reproductive/developmental toxicity.

These chemicals possess properties indicating a hazard for human health (lethality from acute inhalation and oral exposures, skin corrosion and repeated-dose toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The EPISuite program developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for sodium salts of organic acids; therefore, there is uncertainty associated with the estimated values and they should be used with caution whenever they are reported below.

The estimated Henry's Law constant for methanethiol is 2.84 hPa m³/mol, suggesting that volatilization from water is expected to be significant.

Sodium methanethiolate will dissociate in water and exist as methanethiolate. At environmental pH, methanethiolate will typically exist as methanethiol (>99.9%), as methanethiol has an acid dissociation constant of 10.7. Hydrolysis of methanethiol does not occur under normal environmental conditions. Because it is a gas and has a high vapor pressure, methanethiol is expected to volatilize in the environment. In the atmosphere, indirect photo-oxidation of methanethiol is predicted to occur. Measurement of reaction with hydroxyl radicals led to half lives ranging from less than 4 to 46 minutes; an estimated half life of 4 hours was obtained using EPISuite. Measurement of the reaction with NO_x resulted in a half life of 2 hours. The half life resulting from indirect photo-oxidation of sodium methanethiolate with hydroxyl radicals is estimated to be 10 days. A test conducted according to OECD TG 301D with sodium methanethiolate resulted in 64% degradation over 21 days, and the 10-day window was met. Based on these results sodium methanethiolate is considered to be readily biodegradable.

The level III fugacity model calculation with equal and continuous distributions of methanethiol to air, water and soil is 9.8% to air, 79% to water, 11% to soil and 0.1% to sediment. A low bioaccumulation potential is expected based on the log partition coefficient (log K_{ow}) of 0.78 for methanethiol (sodium methanethiolate dissociates in water and, at environmentally relevant pH, is present almost entirely as methanethiol). The estimated BCF for methanethiol is 3.16.

The following acute toxicity test results have been determined for aquatic species using sodium methanethiolate as a starting material:

Fish [<i>Danio rerio</i>] - (OECD TG 203)	96-h LC ₅₀ = 1.8 mg/L (measured)
Invertebrates [<i>Daphnia magna</i>] - (OECD TG 202)	48-h EC ₅₀ = 1.32 to 2.46 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i>] - (OECD TG 201)	72-h ErC ₅₀ = 15 mg/L (growth rate) (measured)
	72-h EbC ₅₀ = 6.3 mg/L (biomass) (measured)

72-h NOEC (biomass) = 0.81 mg/L (measured)

72-h NOEC (growth rate) = 4.11 mg/L (measured)

These chemicals possess properties indicating a hazard for the environment (acute toxicity to fish, invertebrates and algae from 1 to 100 mg/L). However, the chemicals are readily biodegradable and have a limited potential for bioaccumulation. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

In the United States, companies produced or imported > 450,000 metric tons (> 1 billion pounds) of methanethiol and 450 - 4500 metric tons (1 – 10 million pounds) of sodium methanethiolate in 2002.

During manufacture and use, methanethiol and sodium methanethiolate are primarily handled in closed systems. For example, use of process equipment and venting to a scrubber system are designed to limit release and exposures inside and outside plants that manufacture or use these compounds.

Methanethiol is used exclusively as a chemical intermediate by the submitting companies, with a primary use for the manufacture of methionine for animal nutrition. Other uses for the submitting companies include the use of methanethiol and sodium methanethiolate as intermediates for additives, modifiers and solvents, agricultural intermediates, biocides, health care products and pharmaceuticals. It may be used as an odorant for hazardous/odorless gases, although the submitting companies do not sell in this market. Other minor industrial uses, natural sources and production from fermentation processes may occur.

Methanethiol is also a natural substance found in certain foods, such as some nuts and cheese. Methanethiol is found endogenously in the blood, brain and other tissues of humans. Further, methanethiol is released from decaying organic matter in marshes and is present in the natural gas of certain regions in the United States, in coal tar and in some crude oils. It is also released as a decay product of wood in pulp mills, petroleum refining and sewage treatment plants.

Monitoring in two U.S. plants indicated that exposures over several years exceeded the TLV only once (3 ppm) and were generally less than 0.5 ppm with most exposures less than 0.05 ppm. Over the past several decades, emissions of methanethiol to air from chemical facilities in some locations have been recorded; however, only occasional measurements of low levels of methanethiol in water sources and air have been identified.

Although occupational exposure is possible, it is likely to occur more often as a result of chemical or microbiological reaction in certain settings (e.g., sewage treatment plants) than from production or use of the industrially-manufactured gas. An 8-h TWA-TLV of 0.5 ppm (1 mg/m³) was adopted for methanethiol by the American Conference of Governmental Industrial Hygienists (ACGIH). Due to the low odor threshold and extremely disagreeable odor even small leaks can be detected and facilities are expected to limit exposure to well below the TLV to avoid odor complaints.

For most uses, consumer exposure is not likely because methanethiol and sodium methanethiolate are used mainly as intermediates and the odor can be detected at low levels. Further, residual levels of methanethiol from its use as an intermediate are unlikely, because of the compound's volatility. For uses where methanethiol may be added specifically to alert individuals to a hazardous/odorless material, some exposure to the compound may occur. As noted above, the submitting companies do not participate in the gas odorant market.

Environmental exposure through air may be possible as a result of plant emissions, natural sources or as a result of chemical or microbiological reactions described above. However, methanethiol has not been found in groundwater or surface water at hazardous waste sites or in public or private wells.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	CAS-No.: 7440-02-0, 7786-81-4, 3333-67-3 (12122-15-5, 12607-70-4), 7718-54-9, 13138-45-9
Chemical Name	Nickel (metal), Nickel Sulphate, Nickel Carbonate (2:3 basic nickel carbonate, 1:2 basic nickel carbonate), Nickel Chloride, Nickel Dinitrate
Structural Formula	Ni, NiSO ₄ , NiCO ₃ , Ni(OH) ₂ , NiCl ₂ , Ni(NO ₃) ₂

SUMMARY CONCLUSIONS OF THE SIAR**READ ACROSS JUSTIFICATION FOR HUMAN HEALTH**

This group of five nickel chemicals, nickel, nickel sulphate, nickel chloride, nickel dinitrate and nickel carbonate are presented in this SIAP together as read across has been done in a number cases where available test data alone did not fulfill the SIDS requirements. Data from other nickel compounds than the five nickel substances covered by this SIAP have been used where relevant to support the conclusions concerning the hazard identification of the five selected nickel substances. It is expected that the nickel cation is the determining factor for systemic toxicity and toxicity to environmental organisms.

The conclusions of the SIAR for nickel chloride (CAS No. 7718-54-9) do not apply to a second compound, nickel chloride, (CAS No. 37211-05-5) as this substance is a Ni¹⁺ compound.

The conclusions of the SIAR for nickel dinitrate also apply to a second compound, nitric acid, nickel salt (CAS No. 14216-75-2).

CATEGORY JUSTIFICATION FOR ENVIRONMENT

Nickel and the four nickel salts are HPV chemicals prioritized for comprehensive risk assessment within the EU Existing Substances Regulation. Apart from the administrative and legal purpose, the main reason for providing a background SIAP and SIAR on all of these nickel compounds are that they release the biologically active form, i.e. ionic Ni²⁺ in the environment and in the tissues of organisms. Therefore, ecotoxicological effects and systemic effects in organisms can be considered together for these substances.

BACKGROUND

A large amount of information was provided by industry for the compilation of the data presented in the SIAR. Additional data on nickel from published literature have been reviewed in good quality reviews including UK HSE (1987), IARC (1990), IPCS (1991, 1996), US ATSDR (1995) and a Nordic Expert Group (Aitio, 1995) [See reference list in full SIAR]. The effects of nickel on the skin have also been reviewed (Maibach & Menné, eds. 1989, Hostýnek and Maibach, 2002). NiPERA in collaboration with Eurométaux have also produced a criteria document for nickel and nickel compounds for the European Commission (NiPERA, 1996). Toxicology Excellence for Risk Assessment (TERA) has prepared a toxicological review of soluble nickel salts for Metal Finishing Association of Southern California Inc., US-EPA and Health Canada (TERA, 1999).

These health reviews plus (where considered relevant) the primary literature, have been used widely in assembling the SIAR as it was determined that much of the essential data to establish possible hazards and risks of nickel for human health has already been adequately evaluated. This implies that not all the studies cited in the SIAR have been checked and studies have often been described in a summary form. To ensure transparency in the SIAR, when information was cited from reviews, the primary source was given with the notation "quoted from".

The ecotoxicological data in this report were derived from comprehensive new research activities and from

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original papers on the subject, published in international journals. Databases searched for literature included NiPERA CAB abstracts (1972-2006), Current Contents, Science Direct, IS Web of Science, and AGRICOLA. Review articles covering nickel in the environment were also searched for data sources, as were draft Effects Assessments for Water, Sediment, and Soil that were prepared by the Danish Rapporteur in 2004. Only original literature was quoted.

This document provides relevant hazard information for all nickel substances which release Ni^{2+} and where the effects can be attributed to this nickel ion.

Nickel metal is commonly divided into two product categories. Class I nickel products are metallic nickel with a nickel content of 99% or more. Class II nickel products include metallic nickel of lower purity as well as nickel oxides and ferronickel. The conclusions of the SIAR covers metallic nickel (CAS No.: 7440-02-0) of both Class I and II.

The CAS numbers shown above for the four nickel salts refer to the anhydrous compounds, and follow the EU convention in relation to EINECS numbers of including both the anhydrous and hydrated forms of the compound under the same number. The conclusions of the SIARs apply to all the hydrated forms of the four salts.

The identity of the nickel carbonates covered by the SIAR is particularly complex. The name "nickel carbonate" is most often used as a common class name rather than to identify the simple salt NiCO_3 , and most of the commercial "nickel carbonates" are described more appropriately as basic nickel carbonates with a general formula $x\text{NiCO}_3 \cdot y\text{Ni(OH)}_2 \cdot z\text{H}_2\text{O}$. The SIAR refers to "nickel carbonate" throughout, although this also covers both the 2:3 basic carbonate (CAS No. 12122-15-5) and the 1:2 basic carbonate (CAS No. 12607-70-4) which are regarded as the commercial product.

PHYSICAL-CHEMICAL PROPERTIES

Nickel chloride: exists as a hydrated crystalline powder. The solubility of nickel chloride hexahydrate at 20°C is 2540 g/L. Vapour pressure for nickel chloride is 1 mm Hg at 671°C. Octanol-water partition coefficients for nickel sulphate are not relevant.

Nickel dinitrate: exists as a hydrated crystalline powder. The solubility of nickel dinitrate at 0°C is 2385 g/L. No data are available on the vapour pressure for nickel dinitrate. Octanol-water partition coefficients for nickel dinitrate are not relevant.

Nickel hydroxycarbonate: exists as a hydrated crystalline powder. The solubility of nickel oxycarbonate in water is rather low, with the solubility product KSP ranging from 10^{-7} to 10^{-8} . No data are available on the vapour pressure for nickel oxycarbonate. Octanol-water partition coefficients for nickel oxycarbonate are not relevant.

Nickel sulphate: exists as a hydrated crystalline powder. The solubility of nickel sulphate hexahydrate at 0°C is 625 to 655 g/L. No data are available on the vapour pressure of nickel sulphate. Octanol-water partition coefficients for nickel sulphate are not relevant.

Nickel metal: exists in virtually all forms, shapes and particle sizes. Nickel metal can be regarded as insoluble in water. Vapour pressure for nickel metal is 133 Pa at 1810°C.

The Octanol-water partition coefficients are not relevant for inorganic substances.

HUMAN HEALTH

The following Table shows the availability of human health effect data for the five nickel compounds.

Nickel compound	Human Health effects						
	Table of data availability						
	Acute	Irritation	Sensitisation	Repeated dose	Mutagenicity	Carcinogenicity	Reproductive toxicity
nickel metal	☐	☐	☐	☐	(☐)	(☐)	-

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nickel sulfate	□	□	□	□	□	□	□
nickel chloride	□	(□)	□	□	□	□	□
nickel dinitrate	□	□	(□)-	-	□	-	-
“nickel carbonate”	□	(□)	-	(-)	(□)	-	-

Key: “□” denotes sufficient data were available for the substance/endpoint. “(□)” indicates that there was some data, but not enough to draw a direct conclusion “(-)” indicates only very limited data from which no conclusions can be drawn. “-” denotes no data available.

In all cases except for “□” read across has been performed to varying extents as described in more detail in the SIARs

Toxicokinetics

The available data on nickel sulfate and nickel chloride indicate that the absorption of nickel following inhalation of the respirable fraction (particulates with an aerodynamic diameter below 5 µm) might be as high as up to 97-99% in experimental animals. No human data were available. The fraction absorbed apparently depends on the concentration of the nickel compound in the inhaled air as well as on the duration of exposure. No data regarding the absorbed fraction of nickel in humans or experimental animals following inhalation of nickel dinitrate or nickel carbonate have been located.

The absorbed fraction of nickel from the respiratory tract following exposure by inhalation of nickel sulfate, nickel chloride, nickel dinitrate and nickel carbonate for the respirable fraction is considered to be 100%.

No data regarding the absorbed fraction of metallic nickel in humans following inhalation of nickel metal have been located. Data from a 13-week inhalation study in rats exposed to nickel powder with a mean particle size of 1.2 µm showed pulmonary accumulation of nickel particles. The particles were found to be slowly eliminated following pulmonary absorption, as decreases in nickel lung burden and increases in nickel blood level were found in the animals throughout a 90-day exposure free recovery period. As a rough upper estimate, an absorbed fraction of 6% (pulmonary + gastrointestinal absorption) has been calculated based on data from repeated inhalation exposure of 1 mg/m³ of nickel powder in the 13-week study in rats.

For nickel particulates with aerodynamic diameters above 5 µm (non-respirable fraction), the absorption of nickel from the respiratory tract is considered to be negligible as these particles predominantly will be cleared from the respiratory tract by mucociliary action and translocated into the gastrointestinal tract and thus absorbed according to the absorption rate for oral exposure.

Other data on nickel oxide indicate that the absorption of nickel from the respiratory tract following inhalation of insoluble nickel compounds is very limited.

The absorbed fraction of nickel following oral ingestion can be as high as 27% when nickel sulfate is administered in drinking water to fasting individuals while the absorbed fraction seems to be around 1 to 5% when nickel sulfate is administered together with food and to non-fasting individuals based on studies with human volunteers. The absorbed fraction of nickel following oral ingestion of nickel chloride was up to about 10% and for nickel dinitrate up to 34% in studies in rats. No human data were available. The fasting status of these animals was not reported but the compounds were administered in a 5 % starch saline solution by gavage. No data were available for nickel carbonate, although there was a study in rats which demonstrated that appreciable quantities of nickel from diets containing nickel carbonate were retained and tissue accumulation was significant. Based on human data for nickel sulfate, the absorbed fraction of nickel following oral ingestion of nickel sulfate, nickel chloride, nickel dinitrate and nickel carbonate is considered to be 30% for fasting individuals and 5% in all other situations.

The absorbed fraction of nickel following oral administration of nickel metal in 5% starch saline solution by gavage was about 0.09% in a study in rats. No human data were available. Based on

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this study in rats, which indicates a 100-fold lower absorption of nickel following administration of nickel metal than for soluble nickel compounds (by direct comparisons of the absorbed fractions), the absorbed fraction of nickel following oral ingestion of nickel metal is considered to be 0.3% for fasting individuals and 0.05% in all other situations.

Other data on insoluble nickel compounds (nickel oxides and nickel sulphides) indicate that absorption of nickel from the gastrointestinal tract may occur following oral exposure; however, the data were too limited for an evaluation of the absorbed fraction of nickel.

The available data indicate that absorption of nickel following dermal contact to various nickel compounds can take place, but to a limited extent with a large part of the applied dose remaining on the skin surface or in the stratum corneum. The data were too limited for an evaluation of the absorbed fraction of nickel following dermal contact to the five nickel compounds. A recent *in vitro* study with human stratum corneum indicated an absorbed fraction of about 1-1.5% for nickel sulfate, nickel chloride and nickel dinitrate. Thus, the absorbed fraction of nickel following dermal contact to nickel sulfate, nickel chloride, nickel dinitrate, and nickel carbonate is considered to be 2%. A recent human *in vivo* study with nickel metal showed that around 0.2% remained in the stratum corneum. The absorbed fraction of nickel following dermal contact to nickel metal is therefore considered to be 0.2%.

Upon entry into the bloodstream, the nickel ion is bound to specific serum components and rapidly distributed throughout the body. In serum, nickel is present in three forms: 1) as a complex associated with albumin; 2) as a complex associated with a nickel-metalloprotein (nickeloplamin); and 3) as ultrafiltrable material. In human serum, 40% of the nickel is present as ultrafiltrable material, 34% is associated with albumin, and 26% is associated with nickeloplamin. Absorbed nickel is widely distributed in the body with tissue levels generally below 1 ppm; elevated tissue levels of nickel have been observed in the kidney, liver and lung. Generally, nickel tends to deposit in the lungs of workers occupationally exposed to nickel compounds and in experimental animals following inhalation or intratracheal instillation.

Nickel has been shown to cross the human placenta. Transplacental transfer has also been demonstrated in rats administered nickel carbonate or nickel metal catalyst in the diet, in mice following administration of nickel chloride by intraperitoneal injection, and in rats following administration of nickel by intramuscular injection.

The cellular uptake of soluble and insoluble nickel compounds are different as insoluble nickel compounds enter the cell via phagocytosis, while soluble nickel compounds are not phagocytised, but enter the cell via metal ion transport systems, particularly the magnesium transport system or through membrane diffusion. The latter two processes are much less efficient implicating that the same extracellular levels of soluble and insoluble nickel compounds lead to lower nickel levels intracellularly for soluble nickel compounds. Soluble forms of nickel interact with the cell in a way that maximises cytotoxicity and minimises nickel delivery to the nucleus, while insoluble forms of nickel interact with cells in a way that decreases the cytotoxic potential while increasing the delivery of nickel to the nucleus.

Absorbed nickel is excreted in the urine, regardless of the route of exposure; the half-life for urinary excretion in humans has been reported to range from 17 – 29 hours. Most ingested nickel is excreted via faeces due to the relatively low gastrointestinal absorption. In humans, nickel excreted in the urine following oral intake of soluble nickel compounds accounts for 20-30% of a dose when the nickel compound is administered in drinking water to fasting subjects or to fasting subjects compared with 1-5% when administered together with food or in close proximity to a meal. Small amounts of absorbed nickel can also be excreted through other routes, including hair, saliva, sweat, tears, and milk. Inhaled nickel particles that are deposited in the respiratory tract can be eliminated from the airway by absorption from the lung or by removal via the mucociliary action. This latter fraction may subsequently be swallowed and enter the gastrointestinal tract. An elimination half-life of 30-60 days has been estimated for metallic nickel particles accumulated in lung tissue. The elimination is dependent on dissolution of the accumulated nickel particles followed by absorption and elimination of nickel from the blood.

Acute toxicity

There were no data for acute inhalation toxicity from properly conducted Guideline inhalation tests for any of the nickel compounds. Considering the acute oral toxicity of the soluble nickel

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compounds (see below), the potential for an almost complete absorption via the respiratory tract of nickel from respirable nickel particulates, and observed lethality in rats in a 16-day inhalation study with nickel sulfate, there is a concern for acute inhalation toxicity. In the absence of acute inhalation toxicity data, data from repeated dose inhalation studies is used for the evaluation of acute inhalation toxicity. These data do not indicate a solubility-related difference in toxicity. A LOAEC of 0.7 mg Ni/m³ for reduced body weight and adverse local effects in the respiratory tract (atrophy and inflammation) is determined for acute inhalation toxicity of nickel sulfate, nickel chloride, nickel dinitrate, and nickel carbonate from the 16-day rat inhalation study with nickel sulfate. The use of results from the repeated dose study is considered to be a conservative approach, since greater toxicity is expected from repeated exposure compared to a single 4-hour exposure as in the Guideline acute inhalation test. Data from an acute inhalation study in rats with nickel metal indicate a low order of toxicity via inhalation, however an acute inhalation LC₅₀ value cannot be estimated from that study. For metallic nickel a NOAEC for acute inhalation toxicity of 10200 mg Ni/m³ based on a 1-hour exposure duration is determined for mortality and signs of toxicity.

The five nickel compounds have been tested in acute oral toxicity tests.

	nickel sulfate	nickel chloride	nickel dinitrate	nickel carbonate	<u>nickel metal</u>
<u>LD₅₀</u> <u>mg Ni/kg bw</u>	61-72 to 112	43-51 to 105-130	<u>330</u>	402 - 625	> 9000
<u>LD₅₀</u> <u>mg salt (hydrate) /kg bw</u>	275-325 to 500 mg nickel sulfate hexahydrate /kg bw	175-210 to 432-535 mg nickel chloride hexahydrate /kg bw	1620 mg nickel dinitrate hexahydrate /kg bw	812 - 1263 mg nickel carbonate/kg bw	
<u>Acute toxic class</u>			range between 200 and 2000 mg/kg bw		

The results show that soluble nickel compounds are more toxic by the oral route than the insoluble salts. However, the very soluble nickel dinitrate appears to be less toxic than the other two soluble nickel compounds, with an LD₅₀ value (1620 mg/kg bw) comparable to that for nickel carbonate. The nickel dinitrate LD₅₀ study was reported in 1969 and may not be comparable to more recent studies, as the study was carried out in non-fasted animals and is probably an underestimate of the acute toxicity. However, a more recent toxic class method study with nickel dinitrate showed no mortality or signs of toxic symptoms at 200 mg nickel nitrate hexahydrate/kg bw.

Other data for nickel acetate show LD₅₀ values of 350-360 mg /kg bw (115-118 mg Ni/kg bw) and for nickel hydroxide LD₅₀ values of 1500-1700 mg /kg bw (915-1037 mg Ni/kg bw). The insoluble oxides and sulphides show LD₅₀ values above 5000 mg /kg bw.

No data for acute dermal toxicity of the five nickel compounds were available. There is no concern for acute systemic effects following dermal exposure to nickel compounds due to poor absorption of nickel by this route.

Irritation/Corrosivity

The available data for skin irritation produced by the nickel salts indicate that they are skin irritants, although the data were not entirely consistent. Nickel sulfate caused only a slight degree of skin irritation in a Guideline study, whilst skin irritation was seen in humans following dermal exposure in concentrations above 20%. There is some evidence that nickel chloride is also an irritant in humans, possibly at lower concentrations. Nickel dinitrate was a skin irritant in an Guideline animal study. No data were available for nickel carbonate. On the basis of the human data for nickel sulphate, nickel carbonate is also considered a skin irritant.

The insoluble nickel metal did not cause skin irritation in a Guideline study and nickel metal is not

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considered as a skin irritant.

The more limited data for eye irritation produced by the nickel salts were not consistent. Nickel sulfate caused only a slight degree of eye irritation in a Guideline study, whilst nickel dinitrate was a severe eye irritant in a Guideline study as irritation persisted at the end of the observation period. No data were available for nickel chloride, nickel carbonate or nickel metal. Based on the animal data nickel dinitrate is considered as a severe eye irritant whereas the other nickel compounds (nickel sulfate, nickel chloride, nickel carbonate, nickel metal) are not considered as eye irritants. However, mechanical irritation of the eye from nickel metal powder might occur.

Short-term repeated inhalation of soluble as well as insoluble nickel compounds is associated with lesions in the olfactory and lung epithelium. No data were found regarding respiratory irritation following a single inhalation exposure for any of the five nickel compounds. Based on the repeated dose toxicity data, there is a concern for respiratory irritation of nickel compounds although the available data do not allow a firm conclusion on acute respiratory irritation.

Sensitisation

All five compounds are regarded as skin sensitisers in humans. Nickel sulfate is a skin sensitiser in humans and in experimental animals. Nickel chloride is a skin sensitiser in experimental animals and can elicit an allergic reaction in nickel sensitive humans. Nickel dinitrate can elicit an allergic reaction in nickel sensitive humans. Nickel metal is a skin sensitiser in humans. No data were available for nickel carbonate. The Ni^{2+} ion is considered exclusively responsible for the immunological effects of nickel.

For nickel metal, the experience in Denmark following the introduction of legislation with a cut-off release rate of $0.5 \mu\text{g Ni/cm}^2/\text{week}$ suggests that limiting the release to this level is sufficient to protect against sensitisation of non-sensitised individuals in a substantial part of the population exposed to direct and prolonged contact with nickel and nickel alloys. The release rate of $0.5 \mu\text{g Ni/cm}^2/\text{week}$ after direct and prolonged contact is also considered sufficient to protect against elicitation in a significant proportion of nickel sensitized individuals. There were no data from skin exposure to nickel sulfate, nickel chloride, nickel carbonate or nickel dinitrate to allow an estimate of the dose of these salts that may cause skin sensitisation. Based on elicitation testing of nickel sensitised patients an empirical elicitation threshold of $0.3 \mu\text{g Ni/cm}^2$ for nickel sulfate is suggested as the best estimate of a threshold for sensitisation. As sensitisation is assumed to require higher doses than elicitation, this estimate for sensitisation is more conservative than the estimate for elicitation.

It was not possible to establish a NOAEL for oral challenge in patients with nickel dermatitis. The LOAEL established after provocation of patients on an empty stomach is $12 \mu\text{g Ni/kg bw}$. It should be noted that the dose of $12 \mu\text{g Ni/kg bw}$ is the acute LOAEL in fasting patients on a 48-hour diet with reduced nickel content. A LOAEL after repeated exposure may be lower and a LOAEL in non-fasting patients is probably higher because of reduced absorption of nickel ions when mixed in food.

Nickel sulfate is considered to be a respiratory sensitiser in humans, based on a limited number of cases. There were no data for nickel chloride, nickel dinitrate or nickel carbonate. The Ni^{2+} ion is considered exclusively responsible for the immunological effects of nickel. As nickel sulfate is considered to induce respiratory sensitisation it must be assumed that nickel chloride, nickel dinitrate and nickel carbonate also may have the potential to induce respiratory sensitisation and thus, should be regarded as respiratory sensitisers. Metallic nickel has also been reported to cause respiratory sensitisation, but the available data do not allow a firm conclusion. It is not possible to set a threshold for sensitisation or elicitation.

Repeated exposure

Following repeated exposure by inhalation of nickel sulfate and nickel chloride the main target is the respiratory tract (both the lungs and the nose) in experimental animals. For nickel sulfate, lung inflammation and fibrosis were observed, while for nickel chloride apparently less severe effects were seen. A LOAEC of 0.056 mg Ni/m^3 ($0.25 \text{ mg nickel sulfate hexahydrate/m}^3$ with a mean particle diameter of $1.8\text{--}3.1 \mu\text{m}$ for lung inflammation and fibrosis is determined from a 2-year study in F344 rats. It should be noted that data from this study indicate that adverse effects possibly occur at lower exposure levels. With nickel chloride, the LOAEC for local lung effects

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(adverse effects on lung macrophages) in rabbits exposed for up to 8 months was 0.2 mg Ni/m^3 ($0.8 \text{ mg nickel chloride hexahydrate/m}^3$). There were no data on repeated dose toxicity of nickel dinitrate or nickel carbonate following inhalation.

Following repeated exposure by inhalation of nickel metal, the main target is the lung where serious effects were induced in the form of chronic inflammation and fibrosis in experimental animals. A LOAEC of 1 mg Ni/m^3 (nickel powder, mean particle diameter of $1.2 \mu\text{m}$) for changes in lung weight and relative lung weight, alveolar proteinosis and granulomatous inflammation, accumulation of nickel particles in the lung and increased nickel blood levels is determined from a 13-week study in rats.

Other data on insoluble nickel compounds show that repeated exposure by inhalation also results in lung inflammation and fibrosis. For the two insoluble compounds nickel subsulphide and nickel oxide, inflammatory lung lesions were observed at all concentration levels in two-year studies in rats.

Thus it appears that the effects following repeated inhalation exposure to nickel compounds do not depend on the solubility characteristics. Chronic lung inflammation and lung fibrosis were serious and potentially irreversible effects.

Since nickel sulfate and nickel chloride have not been tested in a parallel manner, it is not possible to carry out a direct comparison of the potency. For the three compounds tested by NTP in a similar protocol, the following order of toxic potency, based on mg Ni/m^3 , could be determined: Nickel sulfate hexahydrate > nickel subsulphide > nickel oxide.

In the absence of adequate repeated inhalation toxicity data for nickel chloride, and no data for nickel dinitrate and nickel carbonate, the LOAEC of 0.056 mg Ni/m^3 for lung inflammation and fibrosis in the 2-year rat study for nickel sulfate hexahydrate is determined as a LOAEC for repeated dose toxicity via inhalation for nickel chloride, nickel dinitrate and nickel carbonate.

For metallic nickel, a LOAEC of 1 mg Ni/m^3 (for changes in lung weight and relative lung weight, alveolar proteinosis and granulomatous inflammation, accumulation of nickel particles in the lung and increased nickel blood levels) is determined from a 13-week study in rats.

Sufficient oral repeated dose toxicity data were only available for nickel sulfate and nickel chloride. In experimental animals administration of nickel sulfate via feed or drinking water was mainly associated with non-specific indications of toxicity, such as decreased survival and decreased body weight. In addition, increased urinary albumin (indicator of diminished kidney function), mild tubular nephrosis, as well as immuno-suppressive effects were observed. A NOAEL of $2.2 \text{ mg Ni/kg bw/day}$ for reduced body weight and increased mortality is determined for nickel sulfate from a 2-year carcinogenicity study (OECD TG 451) in rats. Reduced survival was also found with gavage administration of nickel chloride; however, when nickel chloride was administered in feed or drinking water at comparable doses no effects were found. There were no adequate data on repeated dose toxicity of nickel carbonate following oral administration and no data for nickel dinitrate and nickel metal as well as no data on effects following repeated oral exposure with insoluble nickel compounds.

In the absence of data for nickel compounds other than nickel sulfate as well as for insoluble nickel compounds, the values for nickel sulfate (oral LOAEL of $6.7 \text{ mg Ni/kg bw/day}$ based on reduced body weight and increased mortality and NOAEL of $2.2 \text{ mg Ni/kg bw/day}$) is determined for repeated dose oral toxicity for nickel compounds. Uncertainties remain whether this actually should be considered as a NOAEL as reduced body weight gain (both sexes) and increased mortality (females) occurred to a statistically non-significant extent in the 2-year carcinogenicity study in rats.

When using this NOAEL for nickel metal, consideration should be given to differences in bioavailability between nickel sulfate and metallic nickel.

Dermal repeated dose toxicity data were lacking for soluble as well as for insoluble nickel compounds. There is no concern for systemic effects following dermal exposure to nickel compounds, due to poor absorption of nickel by this route.

Genotoxicity

There is considerable evidence for the *in vitro* genotoxicity of nickel compounds. Positive effects

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were generally seen in studies of chromosomal effects (chromosomal aberrations, sister chromatid exchanges), cell transformation tests and tests for DNA damage and repair. Whilst there were positive results for gene mutations, particularly with nickel chloride, the positive results in at least some of these assays could possibly be due to genetic events other than point mutations.

Interpretation of the results of *in vivo* studies is more complicated. Most of the reviewed studies were carried out with nickel chloride, nickel sulfate and nickel dinitrate. There were little *in vivo* data on other soluble compounds, and *in vivo* data on sparingly soluble nickel compounds such as nickel carbonate, insoluble compounds such as nickel oxide and nickel sulphides as well as nickel metal were also very limited.

Of the individual compounds, the genotoxicity of nickel chloride has been the most extensively studied. In a recent and well-performed Comet assay (mice), there was clear evidence that nickel chloride induces DNA strand breaks *in vivo* in leukocytes after a single oral dose. Four studies showed chromosomal aberrations in somatic cells *in vivo* (three in mice and one in hamsters, three with intraperitoneal (ip) administration and one with oral administration). Data from four *in vivo* micronucleus studies in mice were conflicting. One of three i.p. studies was regarded as positive whilst two other studies were negative; the oral study was regarded as positive. There is no obvious explanation for the differences in the conclusions of the different studies. Some studies were carried out to see whether there are effects on germ cells. One bone marrow micronucleus test found morphological changes in spermatozoa after oral administration. There were two dominant lethal tests, one in mice and one in rats. In a dominant lethal test (mice), treatment decreased significantly the incidence of pregnant females and the mean number of implanted embryos, but did not increase the post-implantation loss. Pre-implantation losses have also been recorded in a dominant lethal test in rats. Studies in man indicate that nickel exposure might induce chromosomal aberrations in the exposed workers studied. Taken together, the evidence for an *in vivo* clastogenic effect of nickel chloride is convincing. There were no definitive studies on germ cells, and little evidence concerning heritable effects on germ cells. Evidence from human studies was limited.

The *in vivo* data on nickel sulfate were rather more limited than for nickel chloride. An *in vivo* inhalation study in rats showed that nickel sulfate seemed to induce DNA damage and inflammation in lung cells at approximately the same concentrations. The results from other *in vivo* studies (oral and intraperitoneal) were conflicting. One i.p. study for chromosomal aberrations was negative whereas one oral study was regarded as positive. Of the three micronucleus studies, one oral study was positive whilst two more recent studies an ip study and oral guideline study were both negative. Studies in man indicate that nickel exposure might induce chromosomal aberrations in the exposed workers studied. Taken together, there was evidence for an *in vivo* clastogenic effect of nickel sulfate in somatic cells. There were no definitive studies on germ cells, and little evidence concerning heritable effects on germ cells. Evidence from human studies was limited.

The evidence for nickel dinitrate was even more limited, and added little new information, as many of the studies included either nickel sulfate and/or nickel chloride, and were the same as the studies discussed above.

An *in vivo* inhalation study in rats showed that nickel subsulfide induced DNA damage in lung cells at lower concentrations than with nickel sulfate.

Overall, the soluble nickel compounds (nickel sulfate, nickel chloride, nickel dinitrate) as well as nickel carbonate, based on available information are regarded as being genotoxic in somatic cells *in vivo*; hence the possibility that the germ cells are affected cannot be excluded.

The available data on nickel metal were inadequate in order to draw any direct conclusion on the *in vivo* genotoxicity of nickel metal.

Carcinogenicity

There was no evidence of carcinogenicity in rats and mice following inhalation of nickel sulfate hexahydrate (mass median aerodynamic diameter of $1.8-3.1 \pm 1.6-2.9 \mu\text{m}$) in concentrations up to 0.11 mg Ni/m^3 or 0.22 mg Ni/m^3 , respectively for 2 years. No studies regarding carcinogenicity following inhalation exposure or intratracheal instillation of nickel chloride, nickel dinitrate, and nickel carbonate in experimental animals have been located.

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The studies in experimental animals on the carcinogenicity of nickel metal following inhalation or intratracheal instillation suffer from inadequacies and were considered inadequate for an evaluation of the carcinogenic activity of nickel metal following inhalation.

Other inhalation studies on nickel oxide and nickel subsulphide showed some evidence and clear evidence, respectively, for carcinogenic activity following inhalation in rats, and there was equivocal evidence for nickel oxide in female mice.

The epidemiological data for nickel sulfate and nickel chloride were considered to be sufficient to establish a causal association between the human exposure to the substances and the development of lung cancer. There was supporting evidence for this conclusion from more limited data on nasal cancer. No epidemiological data were available for nickel dinitrate and nickel carbonate.

Epidemiological evidence for carcinogenicity in humans exposed to nickel metal and nickel-containing alloys alone has not been found. However, epidemiological studies have shown elevated risks of cancer in workers that were known or supposed to be exposed to nickel metal together with other nickel compounds. Further, there was epidemiological evidence to regard both nickel oxide and nickel sulfide as human carcinogens.

Overall, the four nickel salts are considered as human carcinogens by inhalation.

The available data on nickel metal do not provide evidence on which to draw a firm conclusion about the carcinogenicity following inhalation. A study to evaluate the inhalation carcinogenicity of nickel metal has been initiated.

There were sufficient oral carcinogenicity data, including a well-conducted OECD TG 451 study in rats, to show that nickel sulfate does not have any carcinogenic potential in experimental animals following oral administration. No data regarding carcinogenicity of nickel chloride, nickel dinitrate, nickel carbonate, and nickel metal in experimental animals following oral administration have been located. No human data were available.

Overall, there was evidence for lack of a carcinogenic potential following oral administration based on the OECD TG 451 study with oral administration of nickel sulfate to rats. Based on the data on nickel sulfate, the other nickel compounds are considered to be without carcinogenic concern by the oral route.

No data regarding carcinogenicity following dermal contact to nickel sulfate, nickel chloride, nickel dinitrate, nickel carbonate, and nickel metal in experimental animals or in humans have been located. No tumours developed in the buccal pouch, oral cavity, or intestinal tract of male hamsters painted on the mucosa of the buccal pouches with α -nickel subsulphide.

Overall, although the available data were sparse, the lack of a carcinogenic potential after oral exposure to nickel sulfate indicate that carcinogenic effects are very unlikely to occur systemically following dermal exposure to nickel sulfate, nickel chloride, nickel dinitrate, nickel carbonate, and nickel metal. However, data were too limited for an evaluation of local carcinogenicity following dermal contact to nickel compounds.

Reproductive toxicity

Experimental animal data on nickel chloride and nickel sulfate were used for the evaluation of the reproductive toxicity of nickel compounds. The basic assumption is that that it is the nickel ion that is the determining factor for the reproductive and developmental toxicity.

No effects on fertility were seen in animal studies following oral administration of nickel sulfate or nickel chloride. The most reliable NOAEL for effects on fertility for nickel sulfate is 2.2 mg Ni/kg bw/day (the highest dose in a recent OECD TG 416 two-generation study in rats); it should be noted that the NOAEL for fertility is possibly higher. Based on the available studies on nickel chloride, it was not possible to consider a NOAEL for effects on fertility for nickel chloride.

Additional data on the effects on male reproductive organs in experimental animals have been reported in other studies on nickel sulfate following oral or inhalation exposure. A NOAEC for effects on male reproductive organs of 0.45 mg Ni /m³ is determined for inhalation exposure and a NOAEL of 2.2 mg Ni/kg bw/day for oral administration. Based on the available studies on nickel chloride, it was not possible to reach a conclusion for effects on reproductive organs. The potential for effects on reproductive organs has not been sufficiently investigated, as sperm quality and

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oestrus cyclicity either were not investigated or the highest dose level did not induce any signs of toxicity in the adult animals. Therefore, to be able to draw clear conclusions regarding the potential for effects on reproductive organs further studies using higher dose levels and including these end-points would be relevant.

No standard prenatal developmental toxicity studies via either the oral or inhalation routes were located. The available studies on nickel sulfate, nickel chloride and an unspecified nickel salt provide consistent evidence of increased postimplantation / perinatal lethality in rats after oral exposure. Based on increased postimplantation / perinatal lethality in F1 generation in an OECD TG 416 two-generation study at 2.2 mg Ni/kg bw/day a NOAEL of 1.1 mg Ni/kg bw/day for nickel sulfate was determined in rats. For nickel chloride, a definite NOAEL could not be determined.

No data regarding reproductive effects in experimental animals of nickel carbonate, nickel dinitrate, metallic nickel or other nickel compounds have been found.

There were no conclusive studies regarding reproductive toxicity in humans.

Overall, based on the recent oral OECD TG 416 two-generation study in rats with nickel sulfate, a NOAEL of 2.2 mg Ni/kg bw/day is determined for effects on fertility and on male reproductive organs and a NOAEL of 1.1 mg Ni/kg bw/day for developmental toxicity following oral ingestion of nickel sulfate, nickel chloride, nickel dinitrate, nickel carbonate as well as for nickel metal. It should be noted that the NOAEL for fertility is possibly higher. When applying this oral NOAEL for nickel metal, consideration should be given to the lower bioavailability of metal compared to nickel sulphate.

For inhalation, a NOAEC for effects on male reproductive organs of 0.45 mg Ni/m³ is determined for nickel sulfate, nickel chloride, nickel dinitrate, nickel carbonate as well as for nickel metal based on the data for nickel sulfate. No data on fertility and developmental toxicity following inhalation were available; a NOAEC of 0.55 mg Ni/m³ for fertility and of 0.277 mg Ni/m³ for developmental toxicity was estimated from the oral NOAELs for nickel sulfate.

For dermal contact, no data were available, but there is no concern for reproductive effects following dermal contact to nickel compounds, due to poor absorption of nickel by this route.

ENVIRONMENT

The Effects Assessments for the Aquatic, Terrestrial, Sediment, and Marine compartments, and the Secondary Poisoning (accumulation through the food chains), and Indirect Human Exposure Assessments are comprised of an Effects Database, Implementation of Bioavailability, and determination of Predicted No Effects Concentrations (PNECs).

Environmental Fate:

All five nickel compounds (nickel chloride, nickel dinitrate, nickel hydroxycarbonate, nickel sulphate, nickel metal) release Ni²⁺ into the environment, and partitioning coefficients for this ionic form are therefore relevant for all five substances. Ni²⁺ partitioning coefficient for solid-water in suspended matter (Kp susp) is 26,303 (log Kp susp = 4.42). Ni²⁺ partitioning coefficient for sediment-porewater (Kp sed) is 7,079 (log Kp sediment = 3.85). Ni²⁺ partitioning coefficient for soil-water (Kp soil) is 726 (log Kp soil = 2.86). Ni²⁺ partitioning coefficients were based on 50th percentiles of distributions of values from available high quality data.

Common effects assessment basis: The ecotoxicity databases on the effects of soluble nickel compounds to aquatic, soil- and sediment-dwelling organisms are in general extensive. It should be noted that the effects assessments of Ni metal and for Ni compounds is based on the assumption that adverse effects to aquatic, soil- and sediment-dwelling organisms are a consequence of exposure to the (bio)available Ni-ion, as opposed to the parent substances. The result of this assumption is that the ecotoxicology will be similar for the five priority nickel substances (i.e., nickel metal, nickel sulfate, nickel chloride, nickel carbonate, and nickel dinitrate). Therefore, data from soluble nickel salts are used in the derivation of chronic ecotoxicological NOEC and L(E)C₁₀ values. If both NOEC and L(E)C₁₀ data are available, the L(E)C₁₀ value was used in the effects assessment. The soil database includes data on Nickel acetate (a soluble nickel substance) as the inclusion of these data increase the breadth of the database that will be applied to all soluble and sparingly soluble nickel substances.

Application of metal-specific risk assessment methodologies: Recognition of metal-specific ecotoxicological and geochemical characteristics led to several modifications of risk assessment approaches for

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metals which have been employed in the past. These modifications are related to the treatment of extensive data sets also used in the past (cf. SIARs of Zn and Cd), but furthermore also includes further advancements of approaches to incorporate bioavailability corrections, and implementation of the Ecoregion Approach to derive PNECs at the regional scale. Extensive sensitivity analyses were conducted to justify the selection of approaches, methods and critical parameters.

Aquatic

One generic goal of the nickel risk assessment is to express the chronic toxicity of Ni in the bioavailable form. Bioavailability models were subsequently used to normalize the ecotoxicity data to sets of standard physicochemical conditions for important abiotic factors (i.e., pH, hardness, and dissolved organic carbon (DOC)). This approach allows for the comparison of intrinsic toxicity among organisms on an equal basis.

For the aquatic compartment, Biotic Ligand Models (BLMs; cf. SIAR for Zn) were used to normalize the ecotoxicity data. BLMs were developed and validated for two invertebrates (*Ceriodaphnia dubia* and *Daphnia magna*), an alga (*Pseudokirchneriella subcapitata*), and a fish (*Oncorhynchus mykiss*). Appropriate use of this bioavailability normalization necessitates that the geochemical boundaries of the BLMs are defined relative to the environmental conditions considered. In general, the BLMs cover between 10 and 90% of the pH, hardness, and DOC observed in EU surface waters (Table 1). Only reliable ecotoxicity data from tests conducted within the boundaries of the BLMs have been used for establishment of the PNEC. Definition of the relevant environmental conditions and the exclusion of otherwise reliable ecotoxicity data relative to these conditions may need to be adapted for other regions.

Table 1: Ranges of pH and hardness used for data selection

Test organism	pH range	Hardness range (mg/l CaCO ₃)
Algae – <i>P. subcapitata</i>	5.7-8.2	(20-480)
Higher plants – <i>H. vulgare</i>	4.1-7.5	NA
Invertebrates – <i>D. magna</i>	5.9-8.2	6-320
Invertebrates – <i>C. dubia</i>	6.5-8.2	6-320
Fish – <i>O. mykiss</i>	5.4-8.5	20-310

Effects data sets selected: More than 250 individual NOEC/EC₁₀ values were collected and screened for quality and relevancy, which yielded 193 individual high quality data covering 30 different species. The selected data set covers 16 different families, different trophic levels and feeding patterns and is so far the largest data set on a metal. It should be noted that some reliable aquatic ecotoxicity data that passed the relevancy criteria were set aside because they were obtained from tests in which the geochemical parameters were outside of the BLM boundaries. These otherwise high quality data were listed in separate tables in the SIAR, some of which will be used in a special scenario to assess risk of Ni exposure in particular alkaline waters (i.e., pH = 8.3 – 9.0) that are outside of the BLM boundary.

For algae, EC₁₀ values of Ni for chronic exposures conducted with *Pseudokirchneriella subcapitata* ranged from 25.3 to 425 µg Ni L⁻¹, with a median value of 88.2 µg Ni L⁻¹ (n = 47). Chronic growth inhibition data (EC₁₀) were available for nine additional **freshwater algae species**. These EC₁₀ values ranged from 12.3 µg Ni/L for *Scenedesmus accumulates* to 51.8 µg Ni/L for *Coelastrum microporum*. For higher aquatic plants, chronic effects to *Lemna gibba* and *Lemna minor* ranged between 8.2 and 80 µg Ni L⁻¹.

Chronic nickel toxicity data were available for fifteen **invertebrate species**. The large majority of data were from crustaceans, but data from insects, hydrozoans, and molluscs were also available. The NOEC/L(E)C₁₀ varied between 2.8 µg/l for *Ceriodaphnia dubia* and 1193.3 µg/l for *Chironomus tentans*.

Chronic nickel toxicity data were available for three species of **fish**, with NOEC/LC₁₀ values ranging from 40 µg Ni L⁻¹ for *Brachydanio rerio* to 1,100 µg Ni L⁻¹ for *Oncorhynchus mykiss*. NOEC/L(E)C₁₀ data were available for three species of amphibians, with values ranging from 84.5 µg Ni L⁻¹ to 13,147 µg Ni L⁻¹, both values from *Xenopus laevis*.

In summary, NOEC/L(E)C₁₀ values for chronic nickel toxicity to aquatic organisms ranged from 2.8 µg Ni L⁻¹ (*C. dubia*) to 13,147 µg Ni L⁻¹ (*X. laevis*).

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Bioavailability correction: Many of the aquatic toxicity data were obtained from experiments designed to determine effects of water quality parameters on nickel toxicity. Factors identified to affect nickel toxicity included pH, hardness, and dissolved organic carbon (DOC). The use of the BLM performs two principal functions. First, it removes the influence of variable geochemical conditions when calculating species mean values from individual toxicity tests, which may have been performed using different combinations of pH, hardness, and DOC. Geochemical normalization is accomplished by the chemical speciation software within the BLM (WHAM VI, in the case of the nickel BLM), and ensures that all data within a given Species Sensitivity Distribution (SSD) are evaluated on an equivalent free nickel ion basis. Second, the BLM takes into account the competitive effects of positively-charged constituents of freshwater, such as Ca^{2+} , Mg^{2+} , and H^+ , on the uptake of Ni^{2+} at the assumed site of action on the organisms.

Biotic Ligand Models have been developed for the three standard trophic levels for bioavailability correction covering the algae *Pseudokirchneriella subcapitata*, the invertebrate *Daphnia magna*, and the fish *Oncorhynchus mykiss*. An additional BLM was developed for *Ceriodaphnia dubia* because intraspecies variability for this particular sensitive species could not be explained by the *D. magna* BLM. Recalibrating the speciation model to accurately estimate nickel speciation at the low nickel concentrations (e.g., $< 5 \mu\text{g Ni/L}$) that are relevant to *C. dubia* was required for the development of an accurate *C. dubia* BLM. Effects of DOC were evaluated in toxicity tests using natural waters that represented ranges of natural DOC type (e.g., streams and ponds) and quantity (low to high DOC concentration). Therefore, the effect of varying DOC quality on Ni toxicity was implicitly addressed in the BLM development. An additional BLM was developed under hydroponic conditions for the plant *Hordeum vulgare*, and this may be useful for normalizing nickel toxicity to aquatic vascular plants. Because the intra- and interspecies variability that are present among the data are largely influenced by the water quality parameters that were used in the toxicity tests, it is critical for the PNEC derivation to include a step that normalizes the NOECs/L(E)C₁₀ values to a set of standard water quality parameters, e.g., pH, hardness, and DOC. All individual toxicity data were normalized using BLMs. In most cases, BLMs from taxonomically similar group of organisms were used to normalize the NOEC/L(E)C₁₀ data, i.e., all fish and amphibian toxicity data were normalized by the *O. mykiss* BLM, invertebrate data were normalized by the more stringent of either the *C. dubia* or *D. magna* BLM, and algae were normalized by the more stringent of either the *P. subcapitata* or *H. vulgare* BLM. For certain groups of organisms with no BLM, the most stringent BLM was used even if it was not obvious that this BLM originated from the taxonomically most similar organism. For example, L(E)C₁₀ data for *Lemna minor*, a vascular plant, were normalized using the *D. magna* BLM because the *D. magna* BLM was shown to result in the most cautious predictions. Support for the cross-species extrapolation was provided by examples from the literature for phytoplankton and fish, and from a spot-check study for invertebrates and vascular plants. The spot check study was performed on three non-crustacean invertebrates (the midge larvae *Chironomus tentans*, the rotifer *Brachionus calyciflorus*, and the snail *Lymnaea stagnalis*) and one higher plant (duck weed, *L. minor*). The results of the spot check study indicated that the available BLMs were capable of predicting toxicity to the test species used in the spot testing exercise, within a factor of 2. It was based on this concluded that “full cross-species extrapolation” as described above was the preferred approach which was therefore taken forward as the basis for normalizing the SSD according to the abiotic factors hardness, pH and DOC concentration in freshwaters.

Ecoregion Approach: The use of statistically based scenarios to represent a “reasonable worst case” was not applied to the Ni case as the combination of water quality parameters used to define these scenarios very often do not occur in actual natural surface waters. The Ecoregion approach was developed as an alternative to calculate regional hazard concentration at the 5th percentile (HC5) and PNECs for a series of typical freshwater systems that cover at least 90 % of abiotic conditions ranges in EU freshwaters. The Ecoregion approach was developed for conditions typically found in EU freshwaters and its applicability for use in other jurisdictions should be evaluated on a case by case basis. Seven systems were chosen, and they include frequently occurring existing river/lake types of typical surface waters (i.e., “Ecoregions”) (Table 2). The systems ranged in pH from 6.7 to 8.2, in hardness from 28 to 273 mg CaCO_3/L , and in DOC from 2.5 to 12.0 mg/L (Table 2). The HC5s ranged from 7.1 $\mu\text{g Ni L}^{-1}$ (for a system with pH = 7.9, hardness = 48.3 mg $\text{CaCO}_3 \text{ L}^{-1}$ and DOC = 2.5 mg L^{-1}) to 43.6 $\mu\text{g Ni L}^{-1}$ (for a system with pH = 6.9, hardness = 260 mg $\text{CaCO}_3 \text{ L}^{-1}$, and DOC = 12.0 mg L^{-1}). The combination of high hardness and DOC together with low pH is equivalent to low bioavailability (low sensitivity), as exemplified by the scenario represented by the Small River scenario (Table 2). On the other hand, the combination of low hardness and DOC together with high pH is equivalent to high bioavailability (high sensitivity), as exemplified by the Lake (1) scenario (Table 2).

HC5 and PNEC derivation: For PNEC derivation, data for the most sensitive endpoint for a given species were aggregated to derive a species geometric mean ecotoxicity value. Species geometric mean values were

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used to establish a species sensitivity distribution (SSD), from which an HC₅ was derived. The Predicted No Effects Concentration (PNEC) was derived as a function of the HC₅ and an assessment factor covering residual uncertainty (PNEC = HC₅/Assessment Factor).

For each Ecoregion scenario, the HC₅ was determined by the full cross-species normalization approach, which resulted in HC₅ values ranging from 7.1 µg/l for the high pH low DOC scenario (Lake 1), to 43.6 µg/l for the low pH high DOC and hardness scenario (Small River) (Table 2).

Table 2. Physico-chemical characteristics for seven typical freshwater systems to which the nickel BLMs were applied. HC₅ values represent the 5th percentile of the Species Sensitivity Distribution based on BLM-normalized data assuming lognormal distributions.

<u>Selected example of typical surface water (ecoregion) Name</u>	<u>Bioavail-ability</u>	<u>pH</u>	<u>Hardness (mg/l CaCO₃)</u>	<u>DOC (mg/l)</u>	<u>HC5 at 50th % confidence limit (µg/l) using Log normal distribution</u>
Small River	Low	6.9	260	12.0	43.6
Medium River (1)	Medium	8.1	165	3.2	8.1
Medium River (2)	Medium	7.6	159	8.0	19.0
Large River (1)	Medium	7.8	217	2.8	10.8
Large River (2)	Medium/High	8.2	273	3.7	8.7
Lake (1)	High	7.7	48.3	2.5	7.1
Lake (2)	Medium	6.7	27.8	3.8	12.1

Based on the remaining uncertainty, consideration of the amount, type and nature of available chronic data on aquatic species an Assessment Factor was chosen for the aquatic effects data set on nickel in its present status.

Summary: A semi-probabilistic approach was used to characterize the risk of nickel to aquatic organisms at the regional scale. Bioavailability-normalized PNECs were compared with distributions of PECs that were based on measured dissolved nickel data obtained from monitoring programs for the selected ecoregions identified in Table 2.

The most sensitive aquatic environment identified was represented by the Medium River (1) Scenario (low DOC/high pH/medium hardness implying high sensitivity). However, data on the distribution of nickel and the relevant abiotic factors (pH, hardness, and DOC) was insufficient in the Lake (1) scenario to perform the semi-probabilistic approach. The relative bioavailability of this system is high (Table 2), which would indicate a sensitive environment. In generic terms, therefore, sensitive aquatic environments to nickel exposure at the regional scale occur in systems with combinations of high pH and low DOC.

Sediment

The classical Equilibrium Partitioning - K_p approach to derive the PNEC sediment failed to deliver reliable values. A comprehensive sediment testing program was therefore initiated in support of the EU Risk Assessment of Nickel, and included testing for six species of benthic invertebrates in a range of sediment types.

The chronic data generated by this program in combination with additional data collected from open literature formed the basis for the PNEC sediment derivation using a Species Sensitivity Distribution (SSD). However, the results of the laboratory experiments were confounded by the diffusion of nickel from the spiked sediments into the overlying water. In fact, it was shown that the concentration of nickel in the overlying water in the

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semi-static test system generally correlated better with the observed effect concentrations on the sediment organisms than the nickel concentrations measured in the bulk sediment. Therefore, extensive calculations were necessary to extrapolate from overlying water nickel concentrations to sediment concentrations using the equilibrium partitioning approach. The very cautious assumptions that were necessarily taken in this extrapolation implied a high degree of scientific uncertainty. As a consequence, a high assessment factor was deemed appropriate when calculating the PNEC from the estimated HC5(50%) (55 mg Ni/kg based on 5% sediment organic carbon) based on the above mentioned approach. The scientific uncertainty of the described approach yielded a PNEC_{sed} of 18.3 mg Ni/kg, which is close to or below nickel background concentrations in many sediments of EU countries.

Based on the results of the draft Sediment Effects Assessment and the impact of this PNEC_{sed} on risk characterization for the sediment compartment it was determined that all local sites would be estimated to be at risk, and that risk would be concluded at the regional scale as well. Because of this and because the PNEC_{sed} was also shown to be below a generic natural background concentration of 29 mg Ni/kg for EU countries, it was concluded that the current sediment data set should not be used to derive a PNEC sediment and that additional research was warranted for generation of scientifically justified nickel sediment toxicity test data in order to derive a reliable PNEC for the sediment compartment.

To this end, a subsequent sediment testing program has been initiated, with the goal of performing tests in a way that limits the release of dissolved Ni from sediments to the overlying water similar to those of relevant natural systems. The results of this research will be reported post-SIAM as soon as it has been completed and the results analysed.

Marine

Effect data sets: The marine chronic ecotoxicity database is represented by 15 species of marine organisms from 14 families, and includes a wide range of taxonomic groups, including unicellular algae, macroalgae, crustaceans, molluscs, echinoderms, and fish.

EC₁₀ values for four species of **marine algae** are reported, ranging from 97 µg Ni/L for growth of giant kelp (*Macrocystis pyrifera*) to 17891 µg Ni/L for growth of the dinoflagellate, *Dunaliella tertiolecta*.

EC₁₀ values are reported for nine species of **marine invertebrates**, ranging from 22.5 µg Ni/L for reproduction of the polychaete, *Neanthes arenaceodentata*, to 335 µg Ni/L for development of the echinoderm, *Strongylocentrotus purpuratus*.

EC₁₀ values are reported for two species of **marine fish**, ranging from 3599 µg Ni/L for growth of the topsmelt, *Atherinops affinis*, to 20,760 µg Ni/L for growth of the sheepshead minnow, *Cyprinodon variegatus*.

In summary, the chronic EC₁₀ data used in the derivation of the HC5 (50%) for the marine compartment ranged from 22.5 µg Ni/L for *Neanthes arenaceodentata* to 20,760 µg Ni/L for *Cyprinodon variegatus*.

Bioavailability: No incorporation of the potential modifying effect of abiotic factors was included in this analysis. Most of the factors known to affect Ni bioavailability and toxicity in freshwater, e.g., Ca²⁺, Mg²⁺, and H⁺, are relatively constant in marine waters, and therefore the utility of bioavailability correction is limited. Dissolved organic carbon (DOC) can vary considerably in coastal marine waters, and has been shown to be an important factor controlling the toxicity of nickel in the freshwater environment. Therefore, DOC may also be important in the marine environment. However, the range of DOC concentrations present in the natural seawaters tested as part of this program (0.22 to 2.7 mg/L) was probably too narrow with the obtained precision and accuracy of the EC_x results to accurately quantify any variation of effect concentrations attributable to DOC.

HC5 and PNEC derivation: A range of statistical options were explored for determining the HC5(50%) from the marine ecotoxicity data using the SSD approach. Alternatives to the preferred approach of using the lognormal distribution were required because this distribution was rejected based on Goodness of Fit tests. The alternative approaches included

- 1) alternative non-rejected parametric frequency distributions (all data points)
- 2) log-normal distribution using a reduced data base (with exclusion of fish and dinoflagellate data based on a mechanistically based hypothesis) ; and,
- 3) a non-parametric approach called “flexible kernel density estimation” (all data points).

It was concluded that each of the above approaches had advantages and disadvantages (pros and cons) and that

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no approach could be said to be scientifically and indisputably superior. A weight-of-evidence approach was used to evaluate the options, and it was agreed to take the mean from the most cautious approach of option 1 (i.e. the arithmetic mean HC5 (50%) value of 19.9 µg/L for all statistically valid parametric distributions) and the outcome of option 3 (i.e. the HC5 (50%) of 14.5 µg/L of the Kernel Density Estimation approach with optimal band width). Therefore an HC5 (50%) value of 17.2 µg/L is taken forward for the PNEC_{marine} determination.

Based on the amount, type and nature of chronic data on marine organisms and remaining uncertainty an Assessment Factor was chosen.

STP

An assessment of effects of nickel exposure on microbial activity in STPs will be completed under the same regulatory framework as the Sediment Effects Assessment. A PNEC_{microorganism} will be derived, and local scale risk characterization for the EU will be completed and afterwards reported post-SIAM.

Soil

As for the aquatic compartment, bioavailability models were used to normalize ecotoxicity data to sets of standard physicochemical conditions. For the soil compartment, relationships between cation exchange capacity (CEC¹) and chronic nickel toxicity were used to normalize the ecotoxicity data. Appropriate use of normalization of chronic toxicity to soil organisms necessitates that the CEC boundaries of the experimentally derived relationships are defined relative to the environmental conditions considered. Hence data from studies that passed the reliability and relevance criteria in general, but that were conducted on soils that fell outside of this CEC range were not maintained for PNEC derivation. Data from studies that did not report CEC or additional information enabling an estimation of CEC were rejected. Data that were not maintained for PNEC derivation were, however, listed in separate tables. Definition of the relevant environmental conditions and the exclusion of otherwise reliable ecotoxicity data relative to these conditions may need to be adapted for other regions.

Effect data sets: Extensive chronic soil toxicity data sets exist for soil microbial processes, plants, and invertebrates. More than 250 individual NOEC/EC₁₀ values were screened for quality and relevancy, which resulted in a data set of 173 individual high quality data that covered 42 different species. The selected data set covers 8 different families, different trophic levels and feeding patterns for invertebrates, and microbial activities. Chronic toxicity data for individual species were generated in 16 different soils, enabling a toxicity comparison between soils and the establishment of toxicity soil-type models. This data set is, to date, the largest data set on a metal for soil.

Data for 12 **microbial processes** were available, with NOEC/EC₁₀ values range from 28 mg Ni kg⁻¹ for nitrification to 2,491 mg kg⁻¹ for respiration. Additional data were available for enzyme activity measured in soil, with NOEC/EC₁₀ values ranging from 7.9 mg Ni/kg⁻¹ for dehydrogenase to 7,084 mg Ni kg⁻¹ for arylsulfatase activity. Data also exist for the growth of 13 individual microbial species, with EC₁₀ values ranging from 13 mg Ni kg⁻¹ for *Aspergillus clavatus* to 530 mg Ni kg⁻¹ for *Trichoderma viride*.

NOEC/EC₁₀ values were available for 11 **plant species**, ranging from 10 mg kg⁻¹ for *Spinacea oleracea* to 1,127 mg Ni kg⁻¹ for *Hordeum vulgare*.

Chronic data were available for 6 different species of **soil invertebrates**, including both soft- and hard-bodied invertebrates. NOEC/EC₁₀ values ranged from 36 mg Ni kg⁻¹ for reproduction by the springtail *Folsomia candida* to 1,140 mg Ni kg⁻¹ for reproduction by the earthworm *Eisenia fetida*.

Bioavailability correction: As clear toxicity differences between various soils were observed, bioavailability correction models (7 in total) were established for 2 plant and 2 invertebrate species, and for 3 microbial processes. The toxicity data from the tested soils showed that among the parameters tested, i.e. CEC, pH, organic material (OM), Clay and Ni_{background}, the CEC alone consistently explained a large fraction of variability for the 7 species and endpoints tested in the 16 soils ($r^2 = 0.60$ to 0.92). The CEC range is from 1.8 to 52.8 cmol kg⁻¹, which covers most soils. Accordingly, the intra-species variability in chronic toxicity to nickel may to a large extent be due to differences in soil chemistry. Hence, to reduce soil-type related impact on the determination of an HC5 (and subsequently the PNEC) for a given soil, all data in the nickel soil

¹ Cation exchange capacity (CEC) is a quantitative measure of a soil to sorb cations, and is a function of soil organic matter, clay content, and pH. CEC can be measured at the ambient pH of a soil (which is called **effective CEC, or eCEC**) or at a buffered pH. eCEC was used in the development of the bioavailability models, and is used interchangeably with CEC in the SIAP and SIAR documents.

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ecotoxicity database were normalized to a set of standard soil properties, using the established CEC based models. Although models were established for 7 species, more species were present in the toxicity database. Therefore extrapolation of the normalization model from species with CEC based chronic toxicity models was also performed to species without such a model (cross-species extrapolation, as for the aquatic compartment): for all plants, except *L. esculentum* which has its own model, a *H. vulgare* model was used; an *E. fetida* model was used for all soft-bodied and a *F. candida* for all hard-bodied invertebrates. For all nitrifying organisms a nitrification model was used, maize induced respiration was used for all respiration measures and Substance Induced Respiration was used for all microbial biomass measures.

Research has demonstrated that chronic toxicity decreases over time, and that the relationship is directly related to pH (i.e., ageing is more pronounced at higher soil pH). The relationship between time (equilibration time, tested for up to 15 months) and chronic toxicity has been demonstrated in 3 soils for the same 7 species/processes for which the soil-type bioavailability models were established. A pH-dependent “ageing factor” has therefore been developed and applied to the toxicity data (cf. also the Zinc SIAR). The purpose of the ageing factor is to place data from laboratory experiments, in which soluble nickel was spiked into test soils, into a field-based context, where the majority of soil-associated nickel has been shown to be in the solid phase. Therefore, the pH-dependent ageing factor is applied prior to CEC normalization.

Ecoregion approach: As for the aquatic system it was concluded that statistical approaches based on “reasonable worst case” abiotic factor combinations were not relevant. An Ecoregion approach has instead been developed based on 6 reference soil scenarios that represent typical soil conditions. These include agricultural and natural soils that exhibit wide ranges of textures, pH, and CEC. The Ecoregion approach was developed for conditions typically found in EU soils and its applicability for use in other jurisdictions should be evaluated on a case by case basis (Table 3).

HC5 and PNEC derivation: For PNEC derivation, data for the most sensitive endpoint for a given species were aggregated to derive a species mean ecotoxicity value. Species mean values were used to establish a species sensitivity distribution (SSD), from which an HC₅ was derived. The Predicted No Effects Concentration (PNEC) was derived as a function of the HC₅ and an assessment factor (PNEC = HC₅/Assessment Factor).

For each soil Ecoregion scenario, the HC₅ was determined by full cross-species normalization approach resulting in HC₅ values ranging from 8.6 mg Ni/kg in acidic sandy soils to 194.3 mg Ni/kg for alkaline clay soils (Table 3)

Based on the amount, the type and nature of chronic data on soil organisms, remaining uncertainty an Assessment Factor was chosen for the soil nickel effects data set in its present status.

Table 3. Physico-chemical characteristics for six typical soils. Soil pH and CEC were used to normalize soil ecotoxicity data for ageing and bioavailability. HC₅ values represent the 5th percentile of the Species Sensitivity Distribution based on BLM-normalized data assuming log-normal distributions.

Type	Description	pH	OM %	Clay%	CEC cmol/kg	HC5 mg Ni/kg
Acid sandy soil	Agricultural soil from arable land	4.8	2.8	7	2.4	8.6
Loamy soil	Agricultural soil from arable land	7.5	2.2	26	20	100.0
Peaty soil	Agricultural soil from grassland	4.7	40	24	35	188.7
Acid sandy soil	Natural soil from forested land	3.0	9	7	6	25.2
Clay soil	Natural soil from wooded land	7.4	4.5	46	36	194.3

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Different types	Composite of soils representing agricultural and forested land	6.3	0.6	8.9	10.4	47.5

Summary: A broad range of representative soil types and relevant abiotic parameters were assessed based on extensive soil databases that supported the bioavailability normalization approach described above. Some scenarios were shown to be sensitive independent of the ecoregion they belonged to. In most cases the sensitivity shown was explained by high ambient concentrations, which include contributions of natural background.

Secondary Poisoning

Marine, freshwater, and terrestrial habitats were evaluated, and both mammalian and bird food chains were addressed for each of these habitats.

A tiered approach was developed and applied for both the aquatic and the terrestrial food chain. The default approach suggested by the European Union's Technical Guidance Document was always used as the first tier. If potential risk was concluded from this tier, then in subsequent assessment tiers, refinements on absorption of dietary nickel and the dietary composition of the predators were considered.

Tier 1: default assessment

- PNECoral values were derived from reference NOAELs (from long-term studies) without species-specific modification;
- bioavailability of dietborne nickel was assumed to be 100%;
- diets were composed of one food source with a single nickel concentration.

Tier 2: correction for species specific info on PNECoral

- Species-specific PNECoral values were developed for relevant consumer organisms.

Tier 3: correction for bioavailability of the dietborne fraction

- Bioavailability of dietborne nickel was incorporated into the assessment. Relative absorption factors (RAFs) were calculated from the literature for different relevant dietary components in the mammalian food chain, including a soil RAF and a comprehensive RAF used for other dietary components.

Tier 4: correction for diet composition

Use a more realistic dietary composition instead of assuming that the predator consumes only one food source containing nickel.

PECoral

In general, the Tier 1 PECoral values were obtained by applying a relevant Bioaccumulation Factor (BAF) to the PEC in the media of interest (water or soil) for obtaining a tissue concentration in relevant prey organisms chosen according to "the reasonable worst case" principle.

For the **marine mammalian and bird foodchains**, it was assumed that the cockle *Cerastoderma edule*, which accumulates Ni more than other marine organisms, would be a potential food item for the harbor seal and oystercatcher. At other locations, it was assumed that *C. edule* would not be a relevant food item and that harbor seals and oyster catchers would feed on prey items (e.g., fish) that do not bioaccumulate Ni to the same level. Nickel concentrations in prey items (i.e., the PEC) were estimated from dissolved Ni concentrations in surface water using a BAF of 1631 L/kg for locations where *C. edule* is relevant or 270 L/kg for other food items (realistic worst case BAF for fish and other bivalves is 270).

For the **freshwater mammalian and bird foodchains**, the BAF of 270 L/kg was used.

For the **terrestrial food chains**, earthworm nickel concentrations (PECoral) were estimated from the Ni concentration in the earthworm's tissue and the Ni content of the soil in the earthworm's digestive tract. A BAF of 0.30 was used to estimate the Ni in the tissue of the earthworm, and it

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was also assumed that the soil in the earthworm gut amounted to 10% of their body weight.

For the first two tiers of the **terrestrial mammalian foodchain**, it was assumed that shrews will feed exclusively on earthworms. For the third tier it is assumed that shrews will feed on 30% earthworms and 70% other invertebrates, as represented by isopods. A BAF of 0.066 was used to estimate the Ni concentration in isopods.

For Tiers 3 and 4 of the mammalian food chains, bioavailability was taken into account by applying a Relative Absorption Factor (RAF) of 0.025. This RAF value was derived from studies on humans that showed nickel sulfate absorption of 27% when administered with water compared with 0.7% when administered with food ($0.7/27 = 0.025$, or 2.5%). The terrestrial food chains assume that soil in the earthworm amounted to 10% of their body weight. A separate RAF was calculated for soil-associated nickel. This RAF was based on a rat study in which the relative absorption of soil-associated nickel compared with absorption of nickel sulfate in water ranged from 2.1 to 3.9%, depending on soil type. To be cautious, the highest value of 3.9% was used. Based on a study comparing Ni concentrations between earthworms with and without soil in their guts, it was estimated for earthworms with soil in their guts that 24% of the Ni concentration is bioaccumulated by the earthworm, and that 76% is adsorbed to soil in the earthworm's gut. Thus, the overall weighted relative absorption factor for bioaccumulated and soil adsorbed Ni in earthworms can be calculated as

Weighted RAF for mammals consuming Earthworms =

((fraction associated with worm tissue) x $RAF_{\text{water/food}}$) + (fraction adsorbed to soil) x

$RAF_{\text{water/soil}}$) =

$0.24 \times (2.5\%) + 0.76 \times (3.9\%) = 3.6\%$

This weighted RAF was used for exposure scenarios involving earthworm-consuming mammals.

Assimilation efficiencies of Ni will likely vary according to food type, soil composition, consumer organism, and other factors. This variability is accounted for to some extent by the 10-fold assessment factor used in the derivation of the PNEC_{oral}, which is intended to account for interspecies variability and lab-to-field extrapolation. The interspecies variation could include differences between humans (upon which the tissue-specific RAF of 0.025 was based) or rats (upon which the soil-specific RAF of 0.039 was based) and other mammals with respect to the efficiency with which Ni from food and soil is absorbed. This approach taken as a whole can be considered to be cautious because the back-calculated critical soil concentration is 60 mg Ni/kg, a value that is within the range of natural background concentrations for some regions of Europe (e.g., Greece and Spain).

Summary:

Aquatic: The freshwater foodchains in the Secondary Poisoning Assessment were generally shown to be less sensitive compared to direct nickel toxicity to aquatic organisms.

Terrestrial: The most sensitive endpoint among terrestrial food chains for the Secondary Poisoning Assessment was based on a PNEC_{oral} for shrews, which led to a critical soil concentration of 60 mg Ni/kg.

EXPOSURE

Production and Use (Western Europe)

Ni chloride: is mainly used in the plating sector (71%) and catalyst production (29%). A small but unidentified portion is also used in chemicals manufacturing.

Ni dinitrate: is mainly used for the production of catalysts (50-75%) and the manufacturing of Ni-Cd batteries (10-50%) – together 92.5% of total EU production. An estimated additional 5-10% is used for other applications; including chemical pretreatment of products.

Ni hydroxycarbonate: Approximately 70% of is used for plating, 20% for catalyst production, 5% for pigment production, and lesser amounts in electronic components.

Ni sulphate is mainly used in the plating sector (89%) and catalyst production (11%). A small, but unidentified portion is also used in chemicals manufacturing.

Ni metal: The major uses of primary and secondary nickel metal in the EU for 2000 was the manufacture of stainless steel (71%), non-ferrous alloys (14%), alloy steels (5%), foundry steels (4%), and plating (4%). Other end uses, including Ni-based batteries, catalysts, and chemicals, accounted for less than 3% of total nickel use.

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Occupational exposure

Occupational exposure to the five nickel compounds occurs primarily by inhalation of aerosols containing nickel sulfate and by dermal contact. Direct oral exposure (ingestion) is considered to be negligible; however, indirect oral exposure in connection with the inhalational exposures may give a contribution to the internal systemic dose.

Typical exposure levels of inhalable metallic nickel range from 0.004 mg Ni/m³ for refinery to 0.3 mg Ni/m³ when metallic nickel is used as a feedstock in nickel battery production. Worst-case levels are substantially higher, ranging from 1.1 mg Ni/m³ to 5 mg Ni/m³.

Typical exposure levels of inhalable nickel sulfate range from 0.004 mg Ni/m³ for production of catalysts and of nickel compounds/salts to 0.07 mg Ni/m³ for nickel sulfate production, other leaching processes and purification of impure nickel sulfate. Worst-case levels are substantially higher, ranging from 0.15 mg Ni/m³ to 7 mg Ni/m³.

Typical exposure levels of inhalable nickel chloride range from 0.002 mg Ni/m³ for production of catalysts to 0.35 mg Ni/m³ for nickel chloride production from metallic nickel. Worst-case exposure levels range from 0.3 mg Ni/m³ to 8.3 mg Ni/m³.

Typical exposure levels of inhalable nickel dinitrate range from 0.002 mg Ni/m³ for production of catalysts to 0.27 mg Ni/m³ for other uses of nickel: chemicals production. Worst-case exposure levels range from 0.05 mg Ni/m³ to 7 mg Ni/m³.

Typical exposure levels of inhalable nickel carbonate range from 0.002 mg Ni/m³ for use in synthesis of other nickel containing chemicals to 0.1 mg Ni/m³ for production from nickel salts. Worst-case exposure levels range from 0.9 mg Ni/m³ to 7 mg Ni/m³.

Typical dermal exposure levels of metallic nickel are estimated to be 0.04 mg Ni/day (0.048 µg Ni/cm²) for contact with coins and tools. Worst-case dermal exposure levels estimated to be 0.12 mg Ni/day (0.143 µg Ni/cm²) for contact with coins.

Typical dermal exposure levels of nickel sulfate range from 0.027 mg Ni/day (0.046 µg Ni/cm²) for nickel plating to 0.8 mg Ni/day (0.4 µg Ni/cm²) for nickel refining and production of nickel compounds/salts. Worst-case dermal exposure levels range from 0.37 mg Ni/day (0.44 µg Ni/cm²) to 1.8 mg Ni/day (0.9 µg Ni/cm²).

Typical dermal exposure levels of nickel chloride range from 0.028 mg Ni/day (0.033 µg Ni/cm²) for nickel plating to 0.8 mg Ni/day (0.4 µg Ni/cm²) for other scenarios. Worst-case dermal exposure levels range from 0.37 mg Ni/day (0.44 µg Ni/cm²) to 1.8 mg Ni/day (0.9 µg Ni/cm²).

Typical dermal exposure levels of nickel dinitrate range from 0.04 mg Ni/day (0.048 µg Ni/cm²) for use in chemical pre-treatment of metals to 0.8 mg Ni/day (0.4 µg Ni/cm²) for other scenarios. Worst-case dermal exposure levels of range from 0.4 mg Ni/day (0.48 µg Ni/cm²) to 1.4 mg Ni/day (0.7 µg Ni/cm²).

Typical dermal exposure levels of nickel carbonate have been estimated to 0.4 mg Ni/day (0.2 µg Ni/cm²) and worst-case dermal exposure levels to 0.8 mg Ni/day (0.4 µg Ni/cm²).

The report recognises that exposure to nickel occurs in welding. The welding process is characterised by the presence of a number of substances potentially hazardous to health, present both as part of the welding materials (rod, core etc.) and as components of the surfaces to be welded. The hazards associated with the process are primarily associated with the fumes generated, and the composition of these fumes depends on the components of the welding process, as well as on the welding method used and need to be considered as a process.

Consumer exposure

Consumer exposure to nickel metal occurs by dermal exposure to nickel-ion releasing products and by oral exposure to the soluble nickel ion.

Consumers are exposed to nickel metal via dermal contact with a range of nickel-containing objects.

One type of exposure to certain nickel-containing objects occurs when contact is directly with undamaged skin, and where the contact is prolonged. Examples of this are jewellery, watches and a

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number of other objects. In this case the assessment is made in terms of the measured nickel release rate in $\mu\text{g}/\text{cm}^2/\text{week}$.

A second type of dermal exposure is equally direct, but where the exposure time is less prolonged. Examples are coins, tools and other nickel-releasing surfaces. This second type of consumer exposure is similar in all respects to the occupational exposure to the same range of objects, although the frequency of consumer exposure would normally be expected to be less than for occupational exposure.

Insertion of piercing posts in connection with ear piercing or piercing in other parts of the body involves two different types of exposure. Initial insertion of the post involves direct contact with a wound during the period of epithelisation. Following epithelisation, the contact is a contact similar to the "direct and prolonged" contact described above. This form of consumer exposure is already regulated in the EU.

Consumer exposure also includes exposure to nickel in food from nickel-plated and nickel-alloy food-contact materials and kitchen utensils. Whilst the release is related to metallic nickel, the effects are due to nickel dissolved in the food or water.

The nickel release to food from stainless steel surfaces is considered to be negligible in comparison with the amounts of nickel naturally present in food. No information was available on the release of nickel from other nickel-releasing surfaces, such as nickel-iron or nickel-silver alloys, or nickel-plated surfaces, to food. Nickel can be released to drinking water from pipes and taps, and from nickel surfaces in kettles and other water-heating appliances.

The maximum release after descaling of a kettle is calculated to lead to a short-term daily intake of 1.0 mg nickel per day. An average consumer could have a daily intake of 0.24 mg Ni, with a lower range of 0.026 mg Nickel from this source.

The estimated release of nickel into drinking water from taps or piping with nickel surfaces exposed to stagnant water has been calculated as 0.003 mg/kg bw/day.

Consumer exposure to medical uses of nickel (iatrogenic implants, orthodontic materials, release from syringes etc.) is regulated in the EU

The only known consumer exposure to nickel sulfate or nickel chloride is as a component of multivitamin/mineral food supplements. The dose per tablet is often 5 μg Ni for adults (ca. 0.08 $\mu\text{g}/\text{kg}$ for a 60 kg adult), but tablets with up to 100 μg Ni for adults (ca. 1.7 $\mu\text{g}/\text{kg}$ for a 60 kg adult) have been reported. Tablets for children may contain 1 μg Ni (ca. 0.08 $\mu\text{g}/\text{kg}$ for a 12 kg toddler). The recommended dose for many of these mineral supplements is 1 tablet per day.

There is no known consumer exposure to nickel dinitrate or nickel carbonate.

Indirect human exposure

The Indirect Human Exposure assessment describes the indirect exposure of the general population to nickel for the geographical local scales of the nickel producing/using sectors and for the EU regional scale. Indirect exposures include exposure to nickel via drinking water, inhalation of air, ingestion of soil and dust, and through the diet. Indirect exposures are first described as external exposures to humans. Subsequently, these values are converted to aggregate internal doses. The external doses were used for assessing local effects in relation to inhalation (respiratory effects), and internal doses were used for assessing systemic effects. A Combined Exposure scenario was also included where the indirect exposures and the workplace and consumer exposures were aggregated.

External Exposures

For the regional scale, dietary intake was found to be the most important exposure pathway. Over 95 % of the external Ni exposure under normal conditions originates from dietary intake. A diet consisting of foods with very high natural nickel content (e.g., breads, cereals, certain fruits) corresponding to the 99th percentile of the dietary exposure was also evaluated. The indirect exposure at the local scales can be significantly influenced by the air contribution (up to 23 % of the typical external exposure, e.g., refining sector).

Absorbed doses

In order to aggregate exposures by the different pathways, the external exposure values can be first converted to absorbed doses, accounting for the different absorption rates from the different intake media. At the

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regional level, food is still the dominant contributor to the absorbed dose. For some industrial sectors, air becomes the most significant source of absorbed nickel.

Environmental exposure

Nickel is a naturally occurring element with a ubiquitous distribution in the environment. It is found in high concentrations in nickel ores. Economically workable deposits of nickel for nickel metal production are ores which can be classified as either sulphidic or laterite (oxides or silicates). Approximately two thirds of the world's known nickel resources for production of nickel metal are in the form of nickel bearing laterites, and the remaining third as sulphides. The principle sulphidic ores contain the mineral pentlandite $[\text{Fe,Ni}_9\text{S}_8]$ which is almost always found associated with chalcopyrite $[\text{CuFeS}_2]$ and large amounts of pyrrhotite $[\text{Fe}_{1-x}\text{S}]$. Occasionally, sulphidic nickel ores can be found in combination with arsenic minerals, such as niccolite $[\text{NiAs}]$ and gersdorffite $[\text{NiAsS}]$. Natural sources of airborne nickel include soil dust, sea salt, volcanoes, forest fires, and vegetation exudates.

The main sources of Ni emissions at a continental and regional scale are (% specific to western Europe presented in parentheses below):

- to agricultural soil: application to agricultural soil of phosphate fertiliser (52%), manure (39%), sewage sludge accounts (9%);
- to air: oil combustion (70%) -i.e. industrial combustion processes; power production, refineries, other activities-. Industry (17%) -i.e. metal production and processing, basic organic chemicals production, production of cement, lime, glass, mineral substances or ceramic products- and traffic (10%) are less important sources
- to surface water (direct emissions): waste management (70%) -i.e. in particular waste water treatment plants- and industry (24%) -i.e. metal production and processing; basic inorganic and organic chemicals production.

Important industrial sectors discharging nickel to an off-site waste water treatment plant are the following: metal production and processing (53% of facilities), basic organic chemicals production (16%), installations for surface treatment -i.e. plating- (10%) and waste treatment installations (15%).

Industrial surface water emitters are Ni metal producers (9% of total industrial emissions), multiple steel product manufacturers (5%), Ni chemicals producers (3%) and Ni plating sites (3%).

Industry sectors emitting to air are Ni metal production (12%), stainless steel production (15%), multiple steel product manufacturers (3%) and other steel production (2%).

These data were mainly based on extrapolated emission data from local sites.

Modeled Ni concentrations for the plating sector showed the highest site-specific concentrations for the aquatic and sediment compartments, and also exhibited the greatest variability.

Median PEC_{total} concentrations ranged from 3.9 µg Ni/L (chemical manufacturing sector) to 5.2 µg Ni/L (powder metallurgy sector) for the aquatic compartment, and from 33.5 mg Ni/kg (battery manufacturing sector) to 85.0 mg Ni/kg (powder metallurgy sector) for the sediment compartment. Median PEC_{total} values for soil ranged from 5.5 mg Ni/kg (steel sector) to 17.6 mg Ni/kg (chemical manufacturing sector).

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The five substances are candidates for further work. The chemicals possess properties indicating hazards for human health depending on the individual substances, acute oral and inhalation toxicity, skin and severe eye irritation, skin and respiratory sensitisation, chronic inhalation toxicity, genotoxicity, carcinogenicity by inhalation and reproductive toxicity. Other member countries are invited to perform an exposure assessment and if necessary a risk assessment.

Environment: Nickel and the 4 nickel substances considered are candidates for further work. The ionic (bioavailable) form has properties indicating a hazard for the environment (chronic toxicity). Member countries are invited to conduct an exposure assessment for the environment (including

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bioavailability assessment) and if necessary an environmental risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	109-59-1
Chemical Name	2-(1-methylethoxy)ethanol
Structural Formula	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{CH}-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH} \end{array} $

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

2-(1-methylethoxy)ethanol is a colourless liquid with a melting point of < -50 °C and a boiling point of 142.7 °C. Measured vapour pressure and water solubility are 600 Pa at 25 °C and > 100 g/L at 20 °C respectively. The measured octanol-water partition coefficient (Log K_{ow}) is 0.04.

Human Health

There is no standard toxicokinetic study available. However, 2-(1-methylethoxy)ethanol is considered to be easily absorbed into the body and to be widely distributed to tissues, because results from repeated-dose studies and inhalation studies suggested absorbed substance caused systemic toxicological effects.

There is one intraperitoneal administration study using rats and dogs. In rat, 2-(1-methylethoxy)ethanol is mainly metabolized to isopropoxyacetic acid (30%), N-isopropoxyacetyl glycine (46%) and ethylene glycol (13%), and 88% of dose by intraperitoneal administration is excreted within 24 hours mainly via the urine. Similar metabolic profiles were obtained in dog.

The oral LD₅₀ value was greater than 2000 mg/kg bw for male and female rats. The substance caused reddish urine and decrease in fecal volume and body weight.

2-(1-methylethoxy)ethanol was irritating to the skin. Primary irritation index 4.8 was shown in the Draize method performed in rabbits, but no data are available on reversibility of the observed effects.

No reliable experimental data are available for eye irritation in animals. No experimental data are available for respiratory tract irritation in animals. No studies are available on sensitization of 2-(1-methylethoxy)ethanol.

The repeated dose toxicity of 2-(1-methylethoxy)ethanol has been investigated in four studies. In a repeated dose oral toxicity study in rats following OECD TG 407, the substance was administered via gavage to 5 or 10 animals/sex/dose at 0, 30, 125 and 500 mg/kg bw/day, for 28 days. No death was observed in either sex. Treatment related effects observed as critical findings were occult blood and bilirubin in urinalysis, anemia like changes in hematology, increase of erythroid cells and decrease of myeloid cells in bone marrow myelogram, increased weight of spleen, and

histopathological findings in spleen and bone marrow. These findings were recognized in male and female groups at 500 mg/kg bw/day, and changes in hematology, increased weight of spleen (females) and histopathological findings in spleen were also found at 125 mg/kg bw/day. The findings in bone marrow myelogram were observed in both sex groups at 30 mg/kg bw/day. Based on effects in bone marrow myelogram, the LOAEL for repeated dose oral toxicity was considered to be 30 mg/kg bw/day in this study.

In a reproductive and developmental toxicity screening test in rats following OECD TG 421, the substance was administered via gavage to 13 animals/sex/dose at 0, 8, 30 and 125 mg/kg bw/day, for 41-48 days. No death was observed in either sex. Hematuria, organ weight and pathological change in spleen were observed as systemic toxicity in parental animals at 125 mg/kg bw/day. Hematuria was also observed in one female at 30 mg/kg bw/day. Although this effect was not statistically significant, it was considered to be dose responsive. The NOAELs of this study were considered to be 30 mg/kg bw/day in males and 8 mg/kg bw/day in females.

The overall NOAEL for repeated dose oral toxicity was considered to be 8 mg/kg bw/day.

A repeated dose inhalation toxicity study in rats was conducted in accordance with OECD TG 412. The substance was administered via inhalation (whole body) to 10 animals/sex/concentration at 0, 142, 441 and 891 ppm (0, 0.61, 1.90, and 3.83 mg/L) for the first study, and to 5 animals/sex/concentration at 0, 10, 30, 100 ppm (0, 0.04, 0.13, 0.43 mg/L) in the additional second study, for 4 weeks, 6h/day, 5day/week. No treatment related death was observed in either sex. At the end of the exposure period, hemolytic anemia was observed in rats exposed to 100 ppm and higher. Decreased plasma bilirubin values were observed in rats exposed to 891 ppm, and decreased urinary pH values occurred in rats exposed to 441 and higher, and increase in spleen weight recognized in rats at 441 ppm and higher. Extramedullary hematopoiesis and brown pigment accumulation in the spleen were observed in rats at 142 ppm and higher. Based on hemolytic anemia at the end of the exposure period, the NOAEC for repeated dose inhalation toxicity was considered to be 30 ppm.

In repeated dose inhalation toxicity studies, the substance was administered via inhalation whole body to 40 rats/sex/dose, 2 rabbits/sex/dose, 30 guinea pigs/sex/dose and 2 dogs/sex/dose at 0, 25, 50, and 200 ppm (0, 0.1075, 0.215, and 0.86 mg/L), for 26 weeks, 6h/day, 5 day/week. No toxicological significant findings were observed in rabbits, guinea pigs and dogs. In rats, no treatment related death was observed for either sex. Treatment related effects, decrease in hemoglobin concentration and packed cell volume, and increase in mean cell volume were observed in the male and female rats in the 200 ppm group. The osmotic fragility of the erythrocytes of rats was significantly changed at 25, 50 and 200 ppm. Increase in the spleen weight was observed in male and female rats in the 200 ppm group. In histopathological examination, the amount of brown pigment in kupffer cells of the liver was observed in female rats in the 200 ppm group. Excessive amounts of hemosiderin in the red and white pulp of the spleen were observed in male and female rats in the 50 ppm and 200 ppm groups. Extramedullary hematopoiesis was observed in the spleen of rats in the 200 ppm group. Small amounts of lipid in the liver parenchyma were observed of male rats in the 200 ppm group. Based on hemolytic effect, LOAEC for repeated dose inhalation toxicity was considered to be 25 ppm in rats.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium* and *Escherichia coli* [OECD TG 471], 2-(1-methylethoxy)ethanol was negative both with and without metabolic activation. An *in vitro* chromosomal aberration test using the cell line from Chinese hamster lung (CHL/IU) was negative with and without metabolic activation. Since two *in vitro* studies were negative in genotoxicity, *in vivo* studies are not required. Based on these results, 2-(1-methylethoxy)ethanol is considered to be non genotoxic *in vitro*.

No data are available for the carcinogenicity of 2-(1-methylethoxy)ethanol.

The reproductive toxicity of the 2-(1-methylethoxy)ethanol has been well investigated in a reproductive and developmental toxicity screening test in rats OECD TG 421. In this study, 2-(1-methylethoxy)ethanol was administered via gavage to 13 animals/sex/dose at 0, 8, 30 and 125 mg/kg bw/day, for 41-48 days. No death was observed in either sex. No adverse effects on reproductive parameters were observed up to 125 mg/kg bw/day. No abnormalities were observed in delivery and lactation conditions in dams in each group. No adverse effects on development were observed up to 125 mg/kg bw/day. Hematuria was observed at 30 mg/kg bw/day and higher and the NOAEL for general toxicity was considered to be 8 mg/kg bw/day. Based on these observations, the NOAEL for reproductive/developmental toxicity was considered to be 125 mg/kg bw/day in both sexes. Based on these results, 2-(1-methylethoxy)ethanol is considered not to be a reproductive/developmental toxicant.

Environment

2-(1-methylethoxy)ethanol is stable in water as hydrolysis test according to OECD Guideline 111 showed no hydrolysis at pH 4, pH 7 and pH 9 at 50 °C for 5 days. 2-(1-methylethoxy)ethanol is not readily biodegradable (Biodegradability by BOD: 8%) under aerobic conditions after 4 weeks cultivation period according to OECD Guideline 301C. Bioaccumulation potential of 2-(1-methylethoxy)ethanol seems to be low based on a measured Log K_{ow} of 0.04, which is supported by a calculated BCF value of 3.16 with BCFWIN. In the atmosphere, indirect photo-oxidation of 2-(1-methylethoxy)ethanol by reaction with hydroxyl radicals is estimated to result in a half-life of 0.458 days.

2-(1-methylethoxy)ethanol has an estimated Henry's law constant of 9.2×10^{-7} atm.m³/mole at 25 °C, which suggests that volatilization from the water phase is expected to be negligible. Level III fugacity model shows that if 2-(1-methylethoxy)ethanol is released simultaneously to air, soil and water, this chemical is mainly distributed in the soil compartment (51.4 %) and water compartment (47.0 %) with minor amount in air compartment (1.5 %) and negligible amount in sediment compartment (0.09%).

The following acute toxicity test results have been determined for aquatic species:

Fish	<i>Oryzias latipes</i> (OECD TG-203):	96h-LC ₅₀ > 100 mg/L (nominal)
Invertebrate	<i>Daphnia magna</i> (OECD TG-202):	48h-EC ₅₀ > 970 mg/L (measured)
Algae	<i>Pseudokirchneriella subcapitata</i> (OECD TG-201):	72h-ErC ₅₀ > 1,000 mg/L (growth rate / nominal)
Algae	<i>Pseudokirchneriella subcapitata</i> (OECD TG-201);	72h- EbC ₅₀ > 1,000 mg/L (area under curve method / nominal)

The following chronic toxicity test results have been determined:

Invertebrate	<i>Daphnia magna</i> (OECD TG-211):	21d-NOEC (reproduction) = 98 mg/L (measured)
Algae	<i>Pseudokirchneriella sub capitata</i> (OECD TG-201):	72h-NOECr = 1,000 mg/L (growth rate / nominal)
Algae	<i>Pseudokirchneriella subcapitata</i> (OECD TG-201):	72h-NOECb = 1,000 mg/L (Area under curve method / nominal)

Exposure

In Japan, 2-(1-methylethoxy)ethanol was commercially produced and/or imported with an annual volume of 917 tonnes in the fiscal year 2007. According to the SPIN database, the total use of 2-(1-methylethoxy)ethanol in the Nordic countries was less than 10 tonnes in 2006. Worldwide

production volume is not available.

2-(1-methylethoxy)ethanol is produced by reaction of ethylene oxide with *iso*-propanol. All processes for the production of 2-(1-methylethoxy)ethanol are treated in a closed system in the sponsor country. 2-(1-methylethoxy)ethanol is used as a solvent for industrial painting processes, and is sold only for industrial users in the sponsor country.

Exposure to the environment may occur during the production and industrial use of 2-(1-methylethoxy)ethanol. Although limited amounts of 2-(1-methylethoxy)ethanol may be released to the water compartment with waste-water stream from the production and application sites, the waste-water is treated in the waste-water treatment plant. As all processes of the production and formulation are conducted in a closed system in the sponsor country, no significant emissions into the environment is foreseen.

Major occupational exposure routes are inhalation of vapour and dermal route. Workers wear personal protective equipment.

2-(1-Methylethoxy)ethanol is not used in general consumer products in the sponsor country. Therefore, no consumer exposure is foreseen.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is of low priority for further work. The chemical possesses properties indicating a hazard to human health (skin irritation, repeated dose toxicity (haemolytic effects and bone marrow toxicity)). Based on data presented by the Sponsor country, adequate risk management measures are being applied. Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment: This chemical is currently of low priority for further work because of its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1185-55-3
Chemical Name	Trimethoxy(methyl)silane (MTMS)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties****Reduced Testing rationale**

MTMS undergoes rapid hydrolysis in the presence of water; the half life at pD 7 and 25°C is 2.2 hours. Based on the chemical structure of MTMS, this hydrolysis is expected to produce 3 moles of methanol and 1 mole of methylsilanetriol. Silanetriols (at concentrations greater than 500 mg/L) can condense to form highly cross-linked, high molecular weight polymers. Because MTMS is hydrolytically unstable, water solubility, partition coefficient and biodegradation were not measured; modeled values are provided for water solubility and partition coefficient. In aqueous solutions, exposures to MTMS are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products methanol, methylsilanetriol, and condensed silanetriol materials (high molecular weight polymers). Data from the hydrolysis product methanol were presented at SIAM 19. The biodegradation data for methanol are provided; neither methylsilanetriol nor condensed silanetriol materials are expected to be readily biodegradable. A complete data set for the essential endpoints regarding human health is available for MTMS.

The EPISuite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training data set) ; therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

MTMS is a liquid with a melting point of <-77 °C, a boiling point of 102 °C at 1013 hPa and a measured vapour pressure of 106.8 hPa at 20 °C. The calculated octanol-water partition coefficient (log K_{ow}) is -0.67, and the water solubility is 1×10^6 mg/L at 25 °C. The water solubility and log K_{ow} values may not be applicable because the chemical is hydrolytically unstable.

Human Health

No data are available on the toxicokinetics, metabolism or distribution of MTMS. However, under physiological conditions MTMS was hydrolyzed in water, PBS, and PBS plus 10% rat serum with half-lives of 24, 6.7, and 8.6 minutes, respectively producing methanol and silanetriol.

The 6-hr LC_{50} of MTMS as a vapor in rats is > 42 mg/L in a study conducted in accordance with OECD TG 403. Following inhalation exposure, clinical signs included discolored urine, fecal staining, head and muzzle soiling; necropsy showed urinary bladder calculi and kidney foci in both sexes, an enlarged kidney in one male and abscessed prostate glands in two males. The oral LD_{50} of

MTMS in rats is greater than 9500 mg/kg bw in a study conducted in accordance with OECD TG 401. Following oral (gavage) administration, clinical signs included depression, laboured respiration, ataxia, and excessive urination; there were no findings at necropsy. No data are available regarding the acute dermal toxicity of MTMS.

Slight erythema but no edema was observed at the 24 hour observation point when applied to intact skin; no signs of irritation were observed at the 72-hour observation point. Slight conjunctival irritation in 5 animals and moderate conjunctival irritation in one animal was observed but had completely subsided in all six animals by the third day. There was no corneal damage. MTMS was slightly irritating to the rabbit skin and eyes.

No experimental data are available for skin sensitization in animals.

The repeated dose toxicity of the MTMS has been investigated in two studies. In a repeated dose inhalation toxicity study in rats following OECD TG 413, MTMS was administered via inhalation (whole body) to 10 rats/sex/concentration at ca. 0.14, 0.56, 2.2 and 8.9 mg/L, for 6 hours/day, 5 days/week for 90 days. One 2.2 mg/L/day group male one 8.9 mg/L/day group male died during the study. Increased incidence of abdominal and urogenital soiling was observed in the 2.2 and 8.9 mg/L/day groups. There was an increase in female adrenal weights at 2.2 and 8.9 mg/L/day and an increase in female kidney weights at 8.9 mg/L/day. Findings at necropsy included calculi in the urinary bladder at 2.2 and 8.9 mg/L/day; calculi in urinary bladder of males and females exposed to 8.9 mg/L/day persisted through the 28-day recovery period. Kidney dilation was observed for 8.9 mg/L/day group animals. Histopathological findings were observed in the kidney of male animals exposed to 8.9 mg/L/day, the urinary bladder in males and females at 2.2 and 8.9 mg/L/day, and the prostate in all groups with a slight increase in severity at 8.9 mg/L/day. Based on the increased incidence of grossly observed urinary bladder calculi along with the kidney dilation at the 2.2 mg/L/day exposure level, the No Observable Adverse Effect Level (NOAEL) was 0.56 mg/L (100 ppm) and the LOAEL was 2.2 mg/L/day (400 ppm).

In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), the substance was administered via gavage to 10 rats/sex/dose at 0 (corn oil), 50, 250 and 1000 mg/kg bw/day. Males were treated during pre-mating and mating periods. Males and toxicity group females were sacrificed after they had been treated for 28 days. Clinical signs included transient inactivity or salivation following dosing. Statistically significant decreases in body weight gain and food consumption were noted for 1000 mg/kg bw/day group males. Increased liver weight was observed at 250 and 1000 mg/kg bw/day. Liver weights were increased at 250 mg/kg bw/day; males showed significant decrease in thymus weight. Histopathological examination showed changes in the thyroid gland (males and females) and liver (females). Hematological examination indicated an increased prothrombin time (males). At 1000 mg/kg bw/day, increased liver weight, increased platelet concentration, and histopathological changes in the liver, thyroid, adrenal (females only), duodenum and jejunum was observed. Males also had decreased thymus weight, acanthocytosis, increased red blood cell concentration, increased prothrombin time and increased serum alanine amino-transferase activity. Females had an increased incidence of adrenal gland apoptosis and lymphocytic infiltration. The NOAEL for systemic toxicity was 50 mg/kg bw/day with a LOAEL of 250 mg/kg bw/day.

MTMS did not induce gene mutations in *Salmonella typhimurium*/*Escherichia coli* WP2 uvrA *in vitro* (OECD TG 471); however, in TK-locus of mouse lymphoma L5178Y cells (OECD TG 476), it increased the mutation frequency in the presence of metabolic activation. Two *in vitro* chromosomal aberration tests using CHO cells (OECD 473) MTMS induced chromosomal aberrations in the presence of metabolic activation; however, in an *in vivo* micronucleus assay (OECD TG 474) no statistically significant increase in the incidence of micronucleated PCE's over the control value was observed. Based on these results, MTMS showed positive response when tested *in vitro*; however, it

did not cause chromosomal aberrations at the limit dose (2000 mg/kg bw) when tested *in vivo*.

No data are available for the carcinogenicity of MTMS.

The reproductive toxicity of the MTMS has been investigated in a in a reproductive and developmental toxicity screening test in rats [OECD TG 422]. In this study, MTMS was administered via gavage to 10 rats/sex/dose at 0 (corn oil), 50, 250, and 1000 mg/kg bw/day, for at least 28 days (males) and up to PND 4 (females). No adverse effects on reproductive parameters were observed up to the highest dose tested. No adverse effects on development were observed up to the highest dose tested. Based on no adverse effects the NOAEL for reproductive toxicity was considered to be 1000 mg/kg bw/day. Based on no adverse effects the NOAEL for developmental toxicity was considered to be 1000 mg/kg bw/day.

MTMS may present hazard for human health (repeated-dose (kidney and bladder) and genetic toxicity *in vitro*). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The hydrolysis half-life for MTMS is 2.2 hours at 25 °C and pH 7. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 4.1 days. The biodegradation of MTMS was not determined; based on the rapid hydrolysis of this material, any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only biodegradable materials in the test system will be methanol, silanetriol, and condensed silanetriol materials (high molecular weight polymers). Methanol is readily biodegradable (75 – 82 % and 95% removal in standard ready tests after 5 and 20 days respectively). Neither methylsilanetriol nor condensed silanetriol materials are expected to be readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that MTMS will distribute mainly to the water (46.5%) and soil (41.2%) compartments with minor distribution to the air compartment (12.2%) and negligible amount in the sediment compartment. However, MTMS is unlikely to be found in the environment, as this material is hydrolytically unstable. Henry's Law constant of $8.67 \times 10^{-5} \text{ atm}\cdot\text{m}^3/\text{mole}$ ($8.8 \text{ Pa}\cdot\text{m}^3/\text{mole}$) suggests that volatilization from the water phase for MTMS is not expected to be high.

MTMS reacts to form methanol and silanetriol through hydrolysis. The BCF for MTMS and silanetriol cannot be accurately predicted, but are expected to be low. Methanol has a low estimated bioaccumulation potential ($\text{BCF} = 3.2$). Furthermore, due to these properties, current estimation models are not capable of calculating physicochemical or environmental fate values with a known degree of accuracy. No information on the environmental fate of methyl silanetriol was found. However, based on studies on related monomeric silanols, it is expected that the adsorption of methyl silanetriol onto surfaces and condensation to disiloxanes in dilute aqueous solution may be important properties of this chemical. Methyl silanetriol is expected to partition primarily to water, soil and sediment due to its high water solubility and potential to bind to mineral surfaces. In water and air, methyl silanetriol may degrade photolytically. Slow biodegradation in water and soil might also occur.

Due to the rapid hydrolysis of MTMS, aquatic organisms are likely exposed to the parent material and its hydrolysis products, methanol, silanetriol, and condensed silanetriol materials.

The following acute and chronic toxicity test results have been determined for aquatic species:

Fish [<i>Oncorhynchus mykiss</i>]	96 h $\text{LC}_{50} > 110 \text{ mg/L}$ (flow-through; measured)
Invertebrate [<i>Daphnia magna</i>]	48 h $\text{EC}_{50} > 122 \text{ mg/L}$ (flow-through; measured)
Algae [<i>Pseudokirchneriella subcapitata</i>]	72 h $\text{ErC}_{50} > 120 \text{ mg/L}$ (growth rate method)

(static; nominal)

72 h EbC₅₀ > 120 mg/L (area under growth curve method)

72 h NOEC = 120 mg/L

MTMS does not present hazard for the environment based on its low hazard profile. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

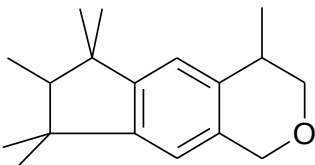
Exposure

MTMS is commercially produced with an annual production volume of approximately 1769 tonnes in 2005 in the United States of America. Worldwide production volume was estimated to be approximately 3140 tonnes/year in 2005. MTMS is used in formulations at <5-100% as a coupling agent in thermoplastics and thermosetting resins, crosslinker in silicone sealants, polymeric filler treatment, water repellent component, adhesives, as a key ingredient in silicone hardcoats for plastics or manufacturing intermediate.

No monitoring data for effluents, surface water in occupational settings are available from the production and processing sites in the United States. During manufacturing, occupational exposure through dermal and inhalation routes is possible, although worker exposures due to non-accidental releases are expected to be low, and are expected to occur only during packaging and sampling. These exposures are minimized by use of personal protective equipment (PPE) and engineering controls. PPE includes impermeable chemical resistant gloves, goggles, fire resistant clothing, safety shoes, hard hat, and respirators. Engineering controls include ventilation devices and related equipment, closed sampling loops, and vacuum systems. At the industrial customer level, MTMS is used in open and/or closed systems; however, engineering controls and PPE are recommended to minimize exposures.

Consumer exposure may occur through oral, dermal or inhalation routes. At the consumer level, MTMS is used in silicone sealants at concentrations less than 10%. Dermal and inhalation exposures are possible during application. Once cured, silicone sealants are expected to contain essentially no MTMS, because it is reacted during use and loses its chemical identity. Therefore, environmental exposure is also expected to be low.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1222-05-5
Chemical Name	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta- γ -2-benzopyran (HHCB)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

HHCB is a viscous liquid with a melting point between -10 and 0°C and a boiling point of 325 °C. The vapour pressure is 0.0727 Pa at 25 °C. HHCB has a measured water solubility of 1.75 mg/l at 25°C. The log Kow as determined by the slow stirring method was 5.3.

Human Health

There are no toxicokinetic data available of HHCB after oral or inhalation exposure. After intravenous administration numerous HHCB metabolites were found in rat and pig urine samples. In an *in vitro* absorption study using 1% HHCB in 96 % alcohol with human epidermal membranes 5.2% of the applied dose was absorbed over 24 hours.

HHCB was also found in human milk samples from women in several European countries, which were not intentionally exposed, at levels up to 1316 µg/kg fat and in adipose tissue at levels ranging from 12 – 189 µg/kg fat.

The oral LD₅₀ for rats, as well as the dermal LD₅₀ for rabbits were > 3000 mg/kg bw. The dermal LD₅₀ for (female) rats was > 6500 mg/kg bw. Data for acute inhalation toxicity were not available.

HHCB was not corrosive, not irritating and not sensitizing to the skin, as determined from irritation and sensitisation studies in animals and humans. No data on respiratory tract irritation were available. In relevant studies, HHCB was considered to be a minimal eye irritant in rabbits. There were some indications from animal studies (rabbits and guinea pigs) that HHCB could be a photo-irritant. Human and *in vitro* studies showed no photo-irritating effects.

In a 90-day oral study in accordance with OECD Guideline 408 with 15 animals/sex/dose (concentrations via diet were 5, 15, 50 or 150 mg/kg bw/day), there were no mortalities or adverse clinical signs. Body weight and food consumption of treated groups were similar to those observed in the control group. No changes in ophthalmologic evaluation were observed and no significant histopathological findings at any dose were observed. Haematology and blood chemistry differences from controls were all small, often not proportional to dose. These findings were not accompanied by any adverse histopathology or other related findings, led to the conclusion that they were not adverse effects. A NOAEL of 150 mg/kg bw/day, the highest dose tested, for HHCB in rats was concluded.

HHCB was a non-genotoxic substance as evidenced by a wide array of *in vitro* tests and in an *in vivo* mouse micronucleus test. *In vitro*, HHCB was negative in gene mutation tests with bacteria with and without metabolic activation, in a chromosomal aberration assay with CHO-K1 cells with and without metabolic activation, in SCE and micronucleus tests with human cells with and without metabolic activation, and in an UDS test with primary rat hepatocytes. HHCB also did not induce significant chromosome aberrations in the *in vivo* micronucleus test.

There were no carcinogenicity test data available.

No standard multiple generation studies were available. In the 13-week oral repeated dose toxicity study, administration of doses of 0, 5, 15, 50 and 150 mg/kg bw/day via the diet had no effects on the reproductive organs of male or female rats. Furthermore, no effect on reproduction performance was found in a peri/postnatal study.

In an oral peri/postnatal toxicity study groups of 28 pregnant female rats were exposed once daily by gavage to doses of 0, 2, 6 and 20 mg/kg bw/day from day 14 of pregnancy through weaning on day 21 post partum (exposure of only the F₁-generation to HHCB *in utero* during the perinatal phase or through any transfer in the milk of the lactating dams). No toxicity in dams or their F1 and F2 offspring was seen at up to the highest dose. A NOAEL of 20 mg HHCB /kg bw/day (the highest dose tested) was established.

In an oral developmental study HHCB was administered by gavage in corn oil to groups of 25 female rats at doses of 50, 150 and 500 mg/kg bw/day on day 7 through 17 of pregnancy. Signs of maternal toxicity were observed at 150 mg/kg bw/day and higher. There was an increased incidence of skeletal malformations and decreased ossification in foetuses at the highest dose of 500 mg/kg bw/day. The NOAEL for maternal toxicity was 50 mg/kg bw/day and for developmental toxicity the NOAEL was 150 mg/kg bw/day. From the peri/postnatal toxicity study described above a NOAEL of 20 mg/kg bw/day (the highest dose tested) was established. HHCB had a very weak estrogenic potency *in vitro*, but such effects were not seen *in vivo* in a uterotrophic assay in non-ovariectomized mice but otherwise similar to OECD TG 440 up to 40 mg/kg bw (300 ppm in the diet of mice for 2 weeks).

HHCB does not present a concern for reproductive/developmental toxicity based on the information available.

HHCB does not present a hazard for human health due to its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

HHCB is considered hydrolytically stable, because the molecule does not contain any functional groups that would react with water. Under atmospheric conditions direct photolysis by sunlight and gas phase reaction with OH radicals are considered to be the major degradation routes for HHCB. Based on the measured rate constant of $2.6 \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ sec}^{-1}$ and assuming a daylight period of 12h and OH radical concentration of $1.5 \times 10^6 \text{ OH-radicals/cm}^3$, the atmospheric half-life is 3.7 hours. The half-life for degradation by UV radiation in lake water was circa 109 hours in a laboratory set-up comparable to mid-summer clear sky sunlight conditions at 50°N. HHCB was not readily biodegradable in an OECD TG 301B test. In a primary biodegradation process HHCB was rapidly transformed to a series of more polar metabolites, with HHCB-lactone and hydroxycarboxylic acid as likely intermediates. In a river water die-away study with 10 mg activated sludge to simulate surface water conditions at the point of discharge, the disappearance of ¹⁴C-labeled parent material and the formation of metabolites was determined. The overall half life was 100 hours and the biological degradation (primary) was over 60% in 28 days. In a sludge die-away study a half-life of 10 to 15 hours was observed, with 70% present as metabolite after 28 days. Mesocosm studies on spiked soil and sediment indicate that HHCB disappeared almost completely within

one year. Residues in soil, expressed as the sum of HHCB and AHTN (CAS. 1506-02-1), in fields with regular sludge application were well below 1% of the estimated applied amount within a few years after the last sludge application.

A level III fugacity model with equal and continuous distribution to air, water and soil compartment suggest that HHCB will distribute in air <<1%, water, 2%, soil, 34% and sediment 64%. The measured Henry's Law Constant is 36.9 Pa.m³/mol at 25°C. The calculated log K_{oc}, based on log K_{ow} is 4.39 and is within the range of the measured log K_{oc} values (3.6 to 4.9 in various matrices). The measured bioconcentration factor of HHCB determined according to OECD TG 305E in bluegill sunfish was 1584 and in zebra fish 624. The half-life for elimination was less than 2 days.

Acute aquatic toxicity data are available:

Taxon	Test species	Endpoint	Result mg/L	Guideline	M/N**
Fish	<i>Lepomis macrochirus</i> Bluegill sunfish	96h-LC ₅₀ (mortality)	1.36	OECD TG 204	M
Invert	<i>Daphnia magna</i>	72h-EC ₅₀ * (immobility)	0.88	OECD TG 202- part 2	M
Algae	<i>Pseudokirchneriella subcapitata</i>	72h-EC ₅₀ (growth rate biomass)	0.854 0.723	OECD TG 201	M
Invert	<i>Acartia tonsa</i> [marine]	48h-LC ₅₀ (mortality)	0.47	draft ISO/DIS 14669	N
Invert	<i>Nitocra spinipes</i> [marine]	48h-LC ₅₀ (mortality)	1.9	draft ISO/DIS 14669	N

* Derived from OECD TG 202-part 2 test (see below)

**N: nominal; M: measured

The following chronic toxicity test results have been determined for aquatic species:

Taxon	Test species	Endpoint	Result mg/L	Guideline	M/N*
Alga	<i>Pseudokirchneriella subcapitata</i>	72h-NOEC (growth rate)	0.201	OECD TG 201	M
Invert	<i>Daphnia magna</i>	21d-NOEC (reproduction)	0.111	OECD TG 202-part 2	M
Invert	<i>Acartia tonsa</i> [marine]	6d-EC10 (larval development ratio)	0.044	OECD draft TG (life cycle test) (2004)	M
Fish	<i>Lepomis macrochirus</i> Bluegill sunfish	21d-NOEC (respiration, equilibrium)	0.093	OECD TG 204	M
Fish	<i>Pimephales promelas</i> Fathead minnow	32d-NOEC (survival, growth, development)	0.068	OECD TG 210	M

*N: nominal; M: measured

Toxicity tests were carried out with three species of sediment organisms according to or in line with OECD TG 218. The 28-day NOEC for the midge larvae *Chironomus riparius* was 200 mg/kg dwt (development), for the amphipod *Hyalella azteca* 7.1 mg/kg dwt (growth) and for the aquatic oligochaete worm *Lumbriculus variegatus* 16.2 mg/kg dwt (growth) at an organic carbon content of 2%. Toxicity tests were also carried out with soil organisms. The 8-week NOEC (reproduction) for the earthworm *Eisenia foetida* according to OECD TG 207 and the 4-week NOEC (reproduction) for springtail *Folsomia Candida* were both 45 mg/kg according to ISO/CD 11267.

HHCB may present a hazard for the environment (acute aquatic toxicity values <1 mg/L and not readily biodegradable). Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

The entire production of HHCB is at one plant in Europe, with a production volume in 2000 between 1000 and 5000 ton/y. Use volumes are according to RIFM (Research Institute of Fragrance Materials) and IFRA (International Fragrance Association) based on regional surveys carried out between 1993 and 2006. For the countries belonging to EU-15 plus the two associated countries Norway and Switzerland, the use volumes declined from 2400 ton per year in 1992, 1427 ton per year in 2000 to 1307 ton per year in 2004.

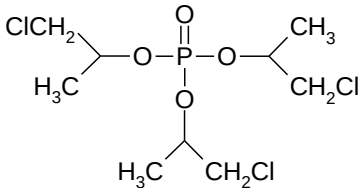
HHCB is used as an ingredient in fragrance oils (fragrance oils is also referred to in literature as fragrance compounds, fragrances, fragrance composition, perfume oil or perfume compositions). HHCB is the largest volume product of the fragrance materials known collectively as polycyclic musks. Fragrance oils are complex mixtures, prepared by blending (compounding) many fragrance ingredients in varying concentrations. Most of these ingredients are liquids, in which HHCB is dissolved. Applications of the fragrance oils are mainly in consumer products such as perfumes, cosmetics, soaps, shampoos, detergents, fabric conditioners, household cleaning products and air fresheners. Blending of the fragrance oil with other ingredients to make the final consumer product is often referred to as a formulation.

Environmental release of HHCB may occur during production, during compounding, during formulation and during/after use by consumers. It is assumed that the total use volume is discharged to the sewer.

Occupational exposure is possible during production, during compounding, during formulation and during cleaning by professional cleaners. Dermal and inhalation occupational exposure to pure HHCB and dermal exposure to mixtures containing HHCB are relevant. Compounding fragrance oils and formulating consumer products involve a high level of automation, intensive ventilation and a high working accuracy required to prevent any cross contamination. Professional cleaners may be exposed to HHCB while using cleaning products and dermal exposure may occur each time hands are submersed in the diluted cleaning solution.

Consumer exposure may occur following dermal and inhalation exposure of which the dermal exposure is the highest.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	13674-84-5
Chemical Name	TRIS(2-CHLORO-1-METHYLETHYL) PHOSPHATE (TCPP)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties**

TCPP is a liquid at room temperature, has a melting point of less than -20°C and a boiling point of 288°C . TCPP has a relative density of 1.288 at 20°C , a vapour pressure (measured) of 1.4×10^{-3} Pa at 25°C and water solubility of 1080 mg/l at 20°C . The log k_{ow} is 2.68. It is of low volatility (vapour pressure 1.4×10^{-3} Pa at 25°C).

Human Health

The metabolic fate of ^{14}C labelled TCPP was examined in rats following oral administration. Absorption was extensive (about 80%) and rapid (blood T_{max} 0.5-2 hours). Distribution of radioactivity to tissues was rapid and widespread, but actual tissue levels of radioactivity were low and approximately 97-99% of dose was excreted within 7-8 days. Excreted material was <2% parent compound, indicating extensive metabolism. Most radioactivity appeared in the urine but about 20% appeared in the faeces, some of which reflected biliary excretion/enterohepatic recirculation. Metabolites identified in urine and faeces, in order of abundance, were o,o-[Bis(1-chloro-2-propyl)]-o-(2-propionic acid)phosphate, bis(1-chloro-2-propyl)monophosphoric acid and 1-chloro-2-propanol. An *in vitro* dermal study with TCPP using human skin membranes determined that the total absorption was 23%. A second study, mimicking handling of flexible PUR foam containing TCPP, determined that approximately 40% was absorbed by skin. Toxicokinetic data for the inhalational route of exposure were not available.

The acute oral LD_{50} (rat) ranged between 632 mg/kg bw and 4200 mg/kg b, with the majority of values less than 2000 mg/kg bw. Clinical signs of systemic toxicity noted in all studies included ataxia, hunched posture, lethargy, laboured respiration, increased salivation, partially closed eyelids, body tremors, clonic/tonic convulsions, pilo-erection, ptosis, loss of righting reflex, and red-brown staining around the mouth. The dermal LD_{50} (rat) following occluded contact for 24 hours, is greater than 2000 mg/kg bw. The 4 hour LC_{50} (rat) is greater than 4.6 mg/L. Clinical signs following inhalation exposure included mild lethargy, matted fur, acute bodyweight depression and convulsions. There was no evidence of inhibited plasma acetylcholinesterase or brain neurotoxic esterase enzyme levels in a delayed neurotoxicity study in hens. The findings on microscopic examination in that study were comparable between negative controls and TCPP treated hens.

Skin and eye irritation studies demonstrated that TCPP did not induce more than slight irritation. TCPP is not corrosive. Data on respiratory irritation were not available, but a few signs seen in several acute inhalation studies suggested that TCPP may be a mild respiratory tract irritant.

No evidence of skin sensitisation was found in a guinea pig maximisation test with TCPP and in a local lymph node assay in mice. TCPP is considered to be a non-sensitiser. Repeat dose toxicity data are available. In a thirteen week dietary study, broadly compliant with OECD Guideline 408, in which groups of 20 male and 20 female rats were fed diets containing 0, 800, 2500, 7500 or 20000 ppm TCPP, corresponding to mean substance intake values of 0, 52, 160, 481 or 1349 mg/kg bw/day, respectively, for males and 0, 62, 171, 570 or 1745 mg/kg bw/day, respectively, for females. A LOAEL of 800 ppm (52 mg/kg bw/day), the lowest tested

concentration, was derived for males based on an increase in absolute and relative liver weights, accompanied by mild thyroid follicular cell hyperplasia. A NOAEL of 2500 ppm (171 mg/kg bw/day) was derived for females based on increased absolute and relative liver weights. Other treatment related findings included a significant increase in absolute and relative liver weights in females at 570 and 1745 mg/kg bw/day, a reduction in mean body weight and periportal hepatocyte swelling in animals at the highest doses, 1349 mg/kg bw/day in males and 1745 mg/kg bw/day in females, and a significant increase in kidney weight in males at 481 and 1349 mg/kg bw/day.

In a 28-day oral gavage study in rats, broadly compliant with OECD Guideline 407, the liver was identified as the target organ. Increased absolute and relative liver weights were observed in males and females at the highest dose (1000 mg/kg bw/day), accompanied by hepatocyte hypertrophy in all high-dose males. A significant decrease in ALAT activity was also observed in high-dose males and females. Based on liver weight changes, accompanied by hepatocyte hypertrophy and changes in ALAT in high dose animals, a NOAEL of 100 mg/kg bw/day (mid dose) was derived.

In vitro, TCPP is not a bacterial mutagen and did not induce gene conversion in fungi. It did not cause DNA damage in hamster lung cells. The results of a mouse lymphoma cell assay indicated that TCPP was mutagenic in the presence of metabolic activation. A clear increase in the proportion of small colony mutants was also observed, suggesting that TCPP is a clastogen in the presence of metabolic activation in mammalian cells. TCPP did not induce unscheduled DNA synthesis in two assays but the result was considered equivocal in one other assay. TCPP induced transformed foci in BALB/3T3 cells. *In vivo*, TCPP tested negative in a mouse micronucleus test. A Comet assay indicated that TCPP did not induce DNA damage in rat liver. It is concluded that TCPP is non-genotoxic *in vivo*.

Carcinogenicity data were not available for TCPP. TCPP is structurally similar to two other chlorinated alkyl phosphate esters, TDCP and TCEP, both of which might be considered non-genotoxic carcinogens. It is considered that there is some information from the structures, physical-chemical properties, toxicokinetics and mutagenic profiles of TCEP, TDCP and TCPP to support a qualitative read-across for carcinogenicity. However, based on the available data, there are differences in the metabolism, target organs, the severity of the effects observed and the potency of the three substances, which indicate that a direct quantitative read-across for carcinogenicity from either TDCP or TCEP to TCPP may not be appropriate.

An oral two-generation reproduction toxicity study in rats was carried out in accordance with OECD Guideline 416. Animals administered 0, 1500, 5000 or 15000 mg/kg TCPP in the diet, corresponding to overall intake values of 0, 85, 293 or 925 mg/kg bw/day, respectively, for males and 0, 99, 330 or 988 mg/kg bw/day, respectively, for females. There were no treatment-related effects in pre-coital time, mating index, female fecundicity index, male and female fertility parameters, duration of gestation and post-implantation loss. An increase in oestrus cycle length and a decrease in uterus weight were observed in all dosed females of F0 generation and high dose females in F1 generation. The mean number of oestrus cycles was also increased in high dose animals of both generations. Effects were noted on ovarian weights in high dose females of F0. Absolute pituitary weights were decreased in high dose females in F0 and all dosed females in F1. It is noted that organ weight changes occurred in the absence of any histopathological changes, and it is accepted that uterine weight can fluctuate during oestrus cycle. Therefore the effects observed may possibly be due to normal variation in cycling females. In the same study, the number of live pups per litter was reduced on PND 1 at the high dose for pups born from the F0 generation and at the mid and high doses for pups born from the F1 generation. These effects correlate with a decrease in maternal body weight observed during the gestation period in these dose groups. There was a treatment related effect on the number of runts (defined as a pup with a weight less than the mean pup weight of the control group minus 2 standard deviations) observed in all TCPP-treated groups of the F0 generation on PND 1 and persisted to PND 21 in the mid- and high-dose groups. Increased numbers of runts in all dose groups of the F0 generation on PND 1 could indicate systemic toxicity to the pups *in utero*, although it is noted that no similar significant increase in the number of runts was observed in the F1 generation or in the preliminary study at PND 1. A LOAEL of 99 mg/kg bw/day was derived for developmental toxicity based on the increased number of runts seen in the F0 generation, which may be relatively precautionary as the effect on runts was not observed in both generations. A LOAEL of 99 mg/kg bw/day was derived for parental toxicity in females. This was based on a decrease in uterus weight in all dosed F0 females and decreased body weight and food consumption seen in mid- (330 mg/kg bw/day) and high-dose (988 mg/kg bw/day) females in both generations. For males, a NOAEL of 85 mg/kg bw/day was derived for parental toxicity, based on decreased body weights, food consumption and organ weight changes observed at mid- (293 mg/kg bw/day) and high-dose (925 mg/kg bw/day) males.

Environment

TCPP has a low adsorption capacity (K_{oc} is 174, by read across of the $\log K_{oc} - \log K_{ow}$ relationship from the structurally-related substance TDCP, for which a reliable adsorption study has been conducted). TCPP has a

low potential to bioaccumulate in fish (measured BCF is 0.8-4.6).

Fugacity modelling shows that if released to air, most TCPP would be precipitated to soil (>90%) and some would pass to water (9%). If released to water, most (>99%) would remain in water. If applied to soil, most would remain in soil (>90%) though some would migrate to water (9%). There is little movement of TCPP between soil and water, because transfer via the air compartment is very slow.

TCPP is not readily biodegradable, showing 0-14% degradation over 28 days in two studies. It did, however, pass the criteria for inherent biodegradability under the conditions of a SCAS test and also those of a non-standard test method (in which, after a long acclimation period mineralisation occurred). Evidence of partial degradation was also seen in several other studies. While phosphate esters are known to be chemically susceptible to hydrolysis, TCPP is expected to have a half-life of at least one year under environmental conditions, based on a standard preliminary hydrolysis test. It is expected to degrade in the atmosphere by reaction with hydroxyl radicals and a half-life of 8.6 hours has been estimated (rate constant = $44.763 \times 10^{-12} \text{ cm}^3/\text{molecule} \cdot \text{sec}$).

Valid measured toxicity data are available for three aquatic taxonomic groups. The lowest effect values in short-term tests are a 96-h LC_{50} of 51 mg/l for Fathead minnow (*Pimephales promelas*), a 48-hour EC_{50} of 131 mg/l for the invertebrate *Daphnia magna*, and a 72-hour E_1C_{50} and E_bC_{50} of 82 mg/l and 33 mg/l respectively for the alga *Pseudokirchneriella subcapitata*.

Two chronic test results are also available: the 21-day NOEC for *D. magna* reproduction is 32 mg/l. The 72-hour ErC_{10} and 72-hour NOEC for growth rate for *P. subcapitata* are 42 mg/l (95% confidence interval 36-50 mg/l) and 13 mg/l respectively. A $\text{PNEC}_{\text{aquatic}}$ of 0.64 mg/l has been derived by dividing the NOEC for *D. magna* by an assessment factor of 50. There are no data for sediment-dwelling organisms. An IC_{50} of 784 mg/l was obtained for wastewater treatment plant micro-organisms (activated sludge).

Data are also available for terrestrial organisms. A 14-day LC_{50} of 97 mg/kg and a 56-day NOEC of 53 mg/kg soil dry weight were determined in tests with the earthworm *Eisenia foetida*. A lowest NOEC of 17 mg/kg soil dry weight was determined for lettuce (*Lactuca sativa*) in a 21-day post emergence test with three plant species that also included wheat (*Triticum aestivum*) and mustard (*Sinapis alba*). A 28-day NOEC of ≥ 128 mg/kg wet weight (no inhibition at the highest concentration tested) was determined for inhibition of nitrogen transformation by soil micro-organisms for the structurally related substance TDCP (CAS 13674-87-8). Due to the structural similarity of TDCP to TCPP, their similar physico-chemical properties and their lack of toxicity to WWTP micro-organisms, it is considered justifiable to read-across this NOEC from TDCP to TCPP.

Exposure

Total EU production of TCPP in the year 2008 was 46,000 tonnes, with production taking place in three sites in Germany and one site in the UK. A total of 12,500 tonnes of TCPP was exported from the EU in the year 2008. TCPP is used as an additive flame retardant mostly (~98%) in polyurethane or PUR. It is physically combined with the material being treated rather than chemically combined. The amount of flame retardant used in any given application depends on a number of factors such as the flame retardancy required for a given product, the effectiveness of the flame retardant and synergist within a given polymer system, the physical characteristics of the end product and the use to which the end product will be put. TCPP may be exported in its raw format, may be used in the manufacture of polyurethane (PUR) foam for use in the furniture and automotive industries or may be used in the manufacture of rigid foam for use in building applications. Additionally, a number of company-specific, low-tonnage minor uses have been identified. These are not described due to commercial sensitivity.

Occupational exposure to TCPP may occur during its manufacture, during the manufacture and cutting of flexible PUR foams, during the production of foam granules and rebonded PUR foam, and the manufacture and use of spray foam, rigid PUR foam and one-component foams. Inhalation of vapours and skin contact are the predominant routes of exposure. Oral exposure is not considered to be a significant route of exposure. Exposure of workers to TDCP via the inhalation route does not present a concern due to the presence of adequate controls, such as local exhaust ventilation. Dermal exposure during manufacture of TCPP and the manufacture of flexible PUR foams may present some concerns. It is considered that the exposure could be controlled by improved occupational hygiene practices e.g. wearing of personal protective equipment (e.g. gloves) and changing of contaminated gloves. Dermal exposures for other scenarios are controlled through the use of personal protective equipment.

The foam is only used in ways in which it is enclosed and therefore it is concluded that exposure to consumers is negligible.

TCPP concentrations in a wide range of environmental media and domestic/industrial locations have been reported. Emissions to the environment can occur to the atmosphere (by evaporation) and waste water. Sources of release include sites undertaking TCPP production; formulation of polyol (a PUR component) into 'systems'; manufacture of flexible and rigid foams; foam recycling ('rebonding' and 'loose-crumb'); manufacture of 'one-component' canned foams; and processing sites associated with the minor uses. Emissions to the environment could also occur from finished articles during their use and at disposal, via both evaporation and generation of small particles, due to weathering and wear. Leaching from landfill sites is considered possible, based on the physicochemical properties of TCPP. In the EU risk assessment, landfill leachate monitoring data from England and Wales are used to calculate the regional input into the environment.

RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (acute oral toxicity and repeated dose toxicity [including effects on uterine weight]). However, based on the data presented by the Sponsor country the exposure situation at the workplace is controlled and adequate risk management measures are in place. Individual countries may wish to carry out their own exposure assessments, relevant for their own scenarios followed by a risk assessment.

Environment

The chemical is of low priority for further work because of its low hazard profile.

Note: TCPP is one of four closely-related chlorinated phosphate ester flame retardants, all of which have undergone risk assessment in the EU. The other substances are: TDCP, CAS no. 13674-87-8; V6, CAS no. 38051-10-4; TCEP, CAS no. 115-96-8. The identified uses of TCPP do not lead to a concern for the environment in the EU. The human health risk assessment is still being conducted.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	13674-87-8
Chemical Name	TRIS[2-CHLORO-1-(CHLOROMETHYL)ETHYL] PHOSPHATE (TDCP)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties**

TDCP is a liquid at room temperature, with a melting point of less than -20°C and a boiling point of approximately 326°C. TDCP has a relative density of 1.513 at 20°C, a vapour pressure (measured) of 5.6×10^{-6} Pa at 25°C and water solubility value of 18.1 mg/l at 20°C. The log k_{ow} is 3.69 at 20 °C. It is of low volatility (vapour pressure 5.6×10^{-6} Pa at 25°C).

Human Health

Dermal absorption was determined to be 15% at a dose of 0.003 mg/cm³, 11% at a dose of 0.01 mg/cm³ and 6% at a dose of 0.12 mg/cm³ using an *in vitro* percutaneous absorption study with human skin membranes. TDCP is metabolised by oxidative and conjugating pathways, mainly to the metabolite bis(1,3-dichloro-2-propyl) phosphate (BDP).

TDCP has a low acute toxicity, with an oral LD₅₀ (rat) greater than 2000 mg/kg bw. The dermal LD₅₀ (rat) following occluded contact for 24 hours, was greater than 2000 mg/kg bw. For inhalational exposure, the 4 hour LC₅₀ (rat) was greater than 5.22 mg/l.

Skin and eye irritation studies in rabbits indicate that neat TDCP induced only mild, transient signs of irritation. TDCP was not corrosive. Data on respiratory irritation were not available.

No evidence of skin sensitisation was found in a guinea pig maximisation test with TDCP. Data on the respiratory sensitisation potential of TDCP were not available.

Repeat dose toxicity data are available. In a non-guideline 2-year oral carcinogenicity study, in which rats were fed diets containing 0, 5, 20 or 80 mg/kg bw/day TDCP for 24 months. The effects of TDCP administered up to 80 mg/kg bw/day included significantly greater mortality in high dose males and a clear decrease in body weights in high dose males and females throughout the study, with body weights at termination >20 % lower than controls. A significant reduction in red blood cell parameters was noted for high-dose animals. Absolute and relative kidney, liver and thyroid weights were also increased in mid- (20 mg/kg bw/day) and high-dose animals. Other histopathological effects seen in the animals at 24 months included germinal epithelial atrophy, oligospermia in the testes and epididymes, and seminal vesicle atrophy with associated decreased secretory product. A LOAEL of 5 mg/kg bw/day, the lowest dose tested, was derived based on an increase in the incidence of hyperplasia of the renal convoluted tubule epithelium in males and effects in the testes of males in all treatment groups. In a 90-day neurotoxicity study, hens administered TDCP via gastric intubation did not exhibit induced mortality or delayed neurotoxicity.

TDCP was mutagenic in the Ames mutation assay and in mouse lymphoma L5178Y cells in the presence of metabolic activation. Chromosomal aberration tests conducted in mouse lymphoma cells, in the presence of metabolic activation were positive, however no increase in chromosomal aberrations or polyploidy was observed in CHO cells. *In vivo*, TDCP was not clastogenic in a mouse erythrocyte micronucleus test nor in two mouse bone marrow chromosome aberration tests. Negative results with TDCP were indicated in an unscheduled DNA

synthesis study in rats. It is concluded that TDCP is non-genotoxic *in vivo*.

Data from the 2-year dietary carcinogenicity study in rats indicated a significant increased incidence of renal cortical adenomas in males and females at mid- (20 mg/kg bw/day) and high-dose (80 mg/kg bw/day), benign testicular interstitial cell tumours in males at mid- and high-dose, hepatocellular adenomas in males and females at the high-dose, adrenal cortical adenomas females at the high-dose. There was also a dose-related increase in hepatocellular carcinomas in both sexes, although the increases did not achieve statistical significance at any dose. TDCP is non-genotoxic *in vivo* and might be considered a threshold carcinogen. A LOAEL of 5 mg/kg bw/day, the lowest dose tested, was derived based on the observed hyperplasia of the convoluted tubule epithelium in the kidneys. Hyperplasia was observed from the lowest dose tested and is often considered as a preneoplastic lesion.

A study conducted to investigate the mortality experience of workers in a TDCP manufacturing plant from 1956 to 1980 concluded that there was no evidence linking cancer with exposure to TDCP, although the study population was small and the TDCP exposures were extremely low. An adjunct morbidity study was conducted at the same TDCP manufacturing plant in 1981. No increased risk of adverse respiratory effects or abnormal clinical findings was observed in workers exposed to TDCP compared to non-exposed workers. However, the study involved very few exposed workers and exposures were extremely low.

In a non-guideline fertility study, male rabbits were administered TDCP by oral gavage with 2, 20 or 200 mg/kg bw/day for twelve weeks prior to mating. Although the study was not conducted to current guidelines, the treatment period is considered sufficient to cover the spermatogenic cycle of the rabbit. Mating, fertility, pregnancy parameters and sperm analysis were unaffected by treatment and there were no histopathological changes observed in the male reproductive tract. Some effects were noted in the male reproductive tract in the 2 year carcinogenicity study, described above. However, as these effects were not observed at 12 months, it is possible that they were secondary to the natural ageing process of the rats rather than a specific effect on the male reproductive system. It is considered that there is no concern for male fertility. There were no data available on the effects of TDCP on female fertility.

A non-guideline but well conducted developmental study is available, in which mated female rats were orally administered TDCP during gestation at doses of 25, 100 or 400mg/kg bw/day on gestation days 6-15. A significantly increased rate of resorptions and retarded skeletal development, accompanied by significant maternal toxicity were observed at the high dose (400 mg/kg bw/day). TDCP did not increase foetal malformations. A NOAEL of 100 mg/kg bw/day for developmental toxicity was derived, based on increased resorptions and decreased foetal viability at 400 mg/kg bw/day. A NOAEL of 100 mg/kg bw/day for maternal toxicity was derived based on significantly decreased body weight gain and clinical signs of toxicity observed at 400 mg/kg bw/day (the highest dose tested).

Environment

TDCP is moderately adsorbing (K_{oc} is 1780, by a reliable, guideline-compliant study in soils, sediment and sludge). TDCP has a low potential to bioaccumulate in fish (measured BCF 0.3-89 in various test systems).

Fugacity modelling shows that if released to air, most TDCP would be precipitated to soil (>98%). If released to water, most would remain in water (>92%) but some would adsorb to sediment (7%). If applied to soil, it would remain in soil (>98%). There is relatively little movement of TDCP between soil and water, because transfer via the air compartment is very slow.

TDCP is not readily biodegradable, showing 0-4% degradation over 28 days in two studies. Very little degradation (<6%) occurred in soil in a 17-week study using four soil types (there was no inhibition of the soil micro-organisms at a loading rate of 1 mg/kg). No definitive conclusion can be reached regarding inherently biodegradability on the basis of the existing data set. Phosphate esters are known to be chemically susceptible to hydrolysis, and TDCP is expected to have a half-life of approximately 120 days at pH 9 at 20 °C. Under neutral and acidic conditions, a half-life of at least one year would be expected, based on a standard preliminary hydrolysis test. It is expected to degrade in the atmosphere by reaction with hydroxyl radicals and a half-life of 21.3 hours has been estimated (rate constant = 18.0819×10^{-12} cm³/molecule.sec).

Valid measured toxicity data are available for three aquatic taxonomic groups. The lowest effect values in short-term tests are a 96-h LC₅₀ of 1.1 mg/l for Rainbow trout (*Oncorhynchus mykiss*), a 48-hour EC₅₀ of 3.8 mg/l for the invertebrate *Daphnia magna*, and a 72-hour E_rC₅₀ and E_bC₅₀ of 4.5 mg/l and 2.8 mg/l respectively for the alga *Pseudokirchneriella subcapitata*.

Two chronic test results are also available: the 21-day NOEC for *D. magna* reproduction is 0.5 mg/l. The 72 hour

E_rC_{10} and 72-hour NOEC for growth rate for *P. subcapitata* are 2.3 mg/l (95% confidence interval 1.9-2.8 mg/l), and 1.2 mg/l respectively. A $PNEC_{aquatic}$ of 0.01 mg/l has been derived, by dividing the *Daphnia* NOEC by an assessment factor of 50.

In 28-day tests with three species of sediment-dwelling invertebrates, the midge, *Chironomus riparius*, the oligochaete, *Lumbriculus variegatus* and the amphipod, *Hyallela azteca*, it was found that *C. riparius* was most susceptible to the effects of TDCP. A NOEC of 8.8 mg/kg dwt was obtained for this species in sediment containing 5.3% total organic carbon. The NOEC was based on the geometric mean exposure concentrations over the first 3 days of the test.

A NOEC of 1,000 mg/l was obtained for wastewater treatment plant micro-organisms (activated sludge).

Data are also available for terrestrial organisms. A 14-day LC_{50} of 130 mg/kg, and a 56-day NOEC for reproduction of 9.6 mg/kg soil dry weight were determined in tests with the earthworm *Eisenia foetida*. A lowest NOEC of 19.3 mg/kg soil dry weight was determined for mustard (*Sinapis alba*) in a 21-day post emergence test with three plant species that also included wheat (*Triticum aestivum*) and red clover (*Trifolium pratense*). A 28-day NOEC of ≥ 128 mg/kg wet weight (no inhibition at the highest concentration tested) was determined for inhibition by TDCP of nitrogen transformation by soil micro-organisms. The soil contained 1% organic matter. The study gave an unexpected result with increased micro-organism activity at the highest concentrations of TDCP. This could be due to possible beneficial effects of TDCP on micro-organisms mineralising nitrogenous organic compounds and/or the nitrifying micro-organisms, possibly caused by the test substance providing a source of phosphorus.

Exposure

Total EU production in 2008 was less than 10,000 tonnes, with production taking place in Germany and the UK. Both producers exported TDCP from the EU in the year 2008. The EU is a net exporter of finished goods containing TDCP.

TDCP is used as an additive flame retardant mostly (>80%) in flexible polyurethane foams. It is physically combined with the material being treated rather than chemically combined. The amount of flame retardant used in any given application depends on a number of factors such as the flame retardancy required for a given product, the effectiveness of the flame retardant and synergist within a given polymer system, the physical characteristics of the end product and the use to which the end product will be put. TDCP may be exported in its raw format or may be used in the manufacture of polyurethane (PUR) foam for use in the furniture and automotive industries. Additionally, a small number of company-specific, low-tonnage minor uses have been identified. These are not described due to commercial sensitivity.

Occupational exposure to TDCP may occur during its manufacture, during the manufacture and cutting of PUR foam and during the production of rebonded and loose crumb foam. Inhalation of vapours and skin contact are the predominant routes of exposure. Oral exposure is not considered to be a significant route of exposure. Workers exposed to TDCP via the inhalation route did not present a concern due to the presence of adequate controls such as local exhaust ventilation. However, dermal exposure during manufacture of TDCP and the manufacture of flexible PUR foams may present some concerns. It is considered that the exposure could be controlled by improved occupational hygiene practices e.g. wearing of personal protective equipment (e.g. gloves) and changing of contaminated gloves. Dermal exposures for other scenarios were controlled through the use of personal protective equipment. The foam is only used in ways in which it is enclosed and therefore it is concluded that exposure to consumers is negligible.

Emissions to the environment can occur to the atmosphere (by evaporation) and waste water. Sources of release include sites undertaking TDCP production; manufacture of flexible foams; foam recycling ('rebonding' and 'loose-crumb'), and processing sites associated with the minor uses. Emissions to the environment could also occur from finished articles during their use and at disposal, via both evaporation and generation of small particles, due to weathering and wear. Leaching from landfill sites is considered possible, based on the physicochemical properties of TDCP. However, landfill leachate monitoring data collected in England and Wales did not detect any TDCP and this route of input to the environment was considered to be negligible for the EU risk assessment.

**RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION
AND NATURE OF FURTHER WORK RECOMMENDED****Human Health**

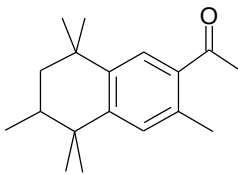
The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (repeated dose toxicity and carcinogenicity). There is an information gap for female fertility hazard. Member countries are invited to consider female fertility hazards as part of their risk assessment. However, based on data presented by the Sponsor country, the exposure in the workplace is controlled and adequate risk management measures are in place. Individual countries may wish to carry out their own exposure assessments, relevant for their own scenarios followed by a risk assessment.

Environment

The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (chronic aquatic toxicity to *Daphnia* and *Chironomus riparius* and a lack of rapid degradation). Based on the EU risk assessment, the major uses of TDCP do not lead to a concern, but for three confidential minor applications risk management is recommended. Member countries may decide to perform further exposure assessment and if indicated a risk assessment.

Note: TDCP is one of four closely-related chlorinated phosphate ester flame retardants, all of which have undergone risk assessment in the EU. The other substances are: TCPP, CAS no. 13674-84-5; V6, CAS no. 38051-10-4; TCEP, CAS no. 115-96-8. The human health risk assessment is still being conducted.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1506-02-1 or 21145-77-7
Chemical Name	1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (AHTN)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

AHTN is a white crystalline solid with a melting point of $> 54^{\circ}\text{C}$ and a boiling point of 326°C . The vapour pressure is 0.0682 Pa at 25°C . AHTN has a measured water solubility of 1.22 mg/l at 25°C and a pH of 7. The log Kow as determined by the slow stirring method was 5.4.

Human Health

The available data show oral absorption but do not allow establishment of an exact absorption percentage. Based on urine, cage washing and tissue levels from a 2-week oral study in rats, oral absorption of at least 50% can be concluded. The metabolic profile in urine, faeces and liver samples revealed the formation of numerous and complex metabolites. Only metabolised AHTN was detected in the urine and liver; extensive levels were seen in the faeces. There are no data available on the toxicokinetics of AHTN after inhalation exposure. Besides other available studies the main study, an in vitro dermal absorption study using human epidermal membranes (with a 1% solution in ethanol), indicated that 4.1% of the applied dose is absorbed over 24-hr. Intravenous administration of AHTN to rats and the pig resulted in rapid distribution. Excretion in the rat is primarily via the faeces as was seen in the dermal study but in the pig the principle route of excretion is via urine, similar to what was seen in the human study. Only metabolised AHTN was present in the urinary radioactivity in these studies. AHTN is found in human milk in several studies, ranging from undetectable levels up till 565 μg AHTN/kg milk fat.

The oral LD_{50} for rats ranged from 825 – 1377 mg/kg bw and the dermal LD_{50} for female rats is 7940 mg/kg bw. Data for acute inhalation toxicity are not available. Upon acute oral exposure, clinical signs included lethargy, piloerection and signs of emaciation.

AHTN is not corrosive and not irritating to the skin, as determined from irritation studies in animals and humans. In relevant studies, AHTN can be considered to be a minimal eye irritant in rabbits. No data on respiratory tract irritation are available.

AHTN is not a skin sensitizer as determined from animal and human studies. Because AHTN absorbs in the UV region, studies to detect a possible photoirritation or photosensitisation hazard have been conducted, in both animals and humans. In the photoirritation studies in animals,

minimal dermal irritation was observed after irradiation with UV light. Photoirritating effects were not found in human studies. Also, the 3T3 NRU Phototoxicity Test *in vitro* was negative. In animal studies investigating photosensitising effects, mostly positive results were reported, whereas only negative results were reported in human studies on photosensitisation. The positive results may be due to sensitising effects from photodegradation products arising from the interaction of AHTN and UV light, evidenced from a study in guinea pigs where two of the four photodegradation products of AHTN reacted positive. Therefore AHTN can be a photosensitiser in animals but this effect was not seen in humans.

In a 28-day oral gavage study according to OECD Guideline 407 with 5 animals/sex/dose, rats were exposed to 0, 1, 3 or 10 mg/kg bw/day AHTN in *Oleum maydis germinis* (total dose volume

10 ml/kg bw). No effects were seen at doses up to and including 10 mg/kg bw/day (the highest dose tested). In a 90-day oral study according to OECD Guideline 408 with 15 animals/sex/dose, rats received by dietary admixture nominal doses of 0, 1.5, 5, 15 and 50 mg AHTN/kg bw/day. Clear mild haematological effects were seen at the highest dose administered, 50 mg/kg bw/day. These effects may be associated with observations of dark discolouration of the liver and mesenteric lymph nodes seen in most high dose animals but not in animals at lower doses. Observations in animals maintained on a treatment-free regime for 28 days following the 90-day treatment period indicate that all effects are reversible. Although the differences from controls were small and generally within historical ranges seen for rats in this laboratory, the overall pattern is such that it cannot be excluded that these effects are of adverse nature. At the lower doses, some statistically significant differences from controls in blood biochemistry and haematology were found, but these differences were small and within the values for historical controls. Some of these, however, showed a dose-response relationship at 15 and 50 mg/kg bw/day. The green colouration of the lachrymal gland was clearly dose-related but not associated with any histopathology at any dose in any animal. The most likely explanation for this observation is accumulation of a pigment resulting from reaction of a photo-oxidation product of AHTN with proteins, and this finding, albeit undesirable, is not considered an adverse effect. Therefore the systemic NOAEL is 5 mg/kg bw/day, based on the marginal effects observed at 15 mg/kg bw/day.

Repeated dose toxicity studies after inhalation exposures are not available for AHTN.

From none of the three conducted sub-chronic dermal studies of AHTN in rats, primarily designed to screen for possible neurotoxicity as observed for a structural closely related substance, it is possible to establish a NOAEL, due to several shortcomings.

In a sub-acute study with *i.p.* administration, AHTN did not show peroxisome proliferating and cytochrome P450 inducing properties.

AHTN has been tested in a wide array of *in vitro* tests and in an *in vivo* mouse micronucleus test. *In vitro*, AHTN was negative in gene mutation tests with bacteria with and without metabolic activation, in an SOS chromotest with bacteria with and without metabolic activation, in SCE and micronucleus tests with human cells with and without metabolic activation and in an UDS test with primary rat hepatocytes. Equivocal results were obtained for AHTN in one *in vitro* chromosome aberration test in CHO cells. However, AHTN did not induce chromosome aberrations in the *in vivo* micronucleus test. Hence, it can be concluded that AHTN is a non-genotoxic substance.

There are no carcinogenicity test data available. AHTN is demonstrated to be not genotoxic. There are no indications from repeated dose toxicity studies, which could be used to judge the carcinogenic potential. It has been shown that AHTN has no liver tumour initiating and promoting activity in rats exposed to human-relevant doses.

No standard multi-generation studies are available. However, no effect on reproductive organs was found in the 13-week oral (dietary) repeated dose toxicity study with rats, after administration of doses of up to 50 mg/kg bw/day to female and male rats. In a peri/postnatal study no effect on reproduction performance was found.

In an oral peri/postnatal toxicity study, rats were exposed once daily by gavage to doses of 0, 2, 6, or 20 mg/kg bw/day from day 14 of pregnancy through to weaning on day 21 post partum. Exposure of the F1-generation to AHTN was only in utero during the perinatal phase or through transfer in the milk of the lactating dams. No toxicity was seen at dose levels of 2, 6 or 20 mg/kg bw/day in the dams or their F1 and F2 offspring. A NOAEL of 20 mg/kg bw/day can be established, the highest dose tested.

In an oral developmental study, AHTN in corn oil was administered by gavage to groups of 25 female rats on days 7 through 17 of presumed gestation at dosages of 0, 5, 15 and 50 mg/kg bw/day. Maternal toxicity occurred at 50 mg/kg bw/day, the highest dose tested. Therefore, the NOAEL for maternal toxicity can be established at 15 mg/kg bw/day. Developmental toxicity was not seen up to the highest dose administered (50 mg/kg bw/day), the developmental NOAEL is therefore 50 mg/kg bw/day (the highest dose tested).

AHTN has a very weak estrogenic potency *in vitro* but no such effect is seen *in vivo* in an uterotrophic assay in non-ovariectomized mice but otherwise similar to OECD TG 440 at dosages of 2 and 6.5 mg/kg bw/day (10 and 50 ppm in the diet of mice for 2 weeks).

AHTN does not present a concern for reproductive/developmental toxicity based on the information available.

AHTN does not present a hazard for human health due to its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

AHTN is considered hydrolytically stable, because the molecule does not contain any functional groups that would react with water. Under atmospheric conditions direct photolysis by sunlight and gas phase reaction with OH radicals are considered to be the major degradation routes for AHTN. Based on the estimated rate constant of $1.7 \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ sec}^{-1}$ and assuming a daylight period of 12h and OH radical concentration of $1.5 \times 10^6 \text{ OH-radicals/cm}^3$, the calculated atmospheric half-life is 7.3 hours. The half-life for degradation by UV radiation in lake water was determined at 4 hours in a laboratory set-up comparable to mid-summer clear sky sunlight conditions at 50°N. In standard tests for ready or inherent biodegradation AHTN did not biodegrade. In a primary biodegradation process AHTN is rapidly transformed to a series of more polar metabolites. In a river water die-away study with 10 mg activated sludge to simulate surface water conditions at the point of discharge, the disappearance of ^{14}C -labeled parent material and the formation of metabolites was determined. The overall half-life was 9 days and the biological degradation (primary) was over 40% in 28 days. In a sludge die-away study a half-life of 12 to 24 hours was observed, with 59% present as metabolite after 28 days. In a Continuous Activated Sludge test with realistic sewage treatment plant operation conditions, half of the total removal of AHTN from the water phase (87.5%) was caused by biotransformation (42.5%) and half was caused by sorption (44.3%), whereas volatilization played a minor role (3.3%). Residues in soil, expressed as the sum of AHTN and HHCb (CAS nr. 1222-05-5), in fields with regular sludge application were well below 1% of the estimated applied amount within a few years after the last sludge application.

A level III fugacity model with equal and continuous distribution to air, water and soil compartment suggest that AHTN will distribute in air 0.1%, water, 2.2%, soil, 33.3% and sediment 64.4%. The measured Henry's Law Constant is $37.1 \text{ Pa m}^3/\text{mol}$ at 25 °C. The calculated log Koc, based on log Kow is 4.47 and is

within the range of the measured log K_{oc} values (3.0 to 4.8 in various matrices). The measured bioconcentration factor of AHTN determined according to OECD TG 305E is 597 in bluegill sunfish and 600 in zebrafish. The half-life for elimination was less than 2 days.

Acute aquatic toxicity data are available:

Taxon	Test species	Endpoint	Result mg/L	Guideline	M/N**
Fish	<i>Lepomis macrochirus</i> Bluegill sunfish	96h-LC ₅₀ (survival)	1.49	OECD TG 204	M
Invert	<i>Daphnia magna</i>	72h-EC ₅₀ * (mobility)	> 0.80	OECD TG 202-part 2	M
Alga	<i>Pseudokirchneriella subcapitata</i>	72h-EC ₅₀ (growth rate Biomass)	> 0.835 0.63	OECD TG 201	M
Invert	<i>Acartia tonsa</i> [marine]	48h-LC ₅₀ (survival)	0.71	draft ISO/DIS 14669	N
Invert	<i>Nitocra spinipes</i> [marine]	48h-LC ₅₀ (survival)	0.61	draft ISO/DIS 14669	N

* Derived from OECD 202-part 2 test (see below).

**N: nominal; M: measured.

The following chronic toxicity test results have been determined for aquatic species:

Taxon	Test species	Endpoint	Result mg/L	Guideline	M/N*
Alga	<i>Pseudokirchneriella subcapitata</i>	72h-NOEC (growth rate)	0.405	OECD TG 201	M
Invert	<i>Daphnia magna</i>	21d-NOEC (reproduction)	0.196	OECD TG 202-part 2	M
Invert	<i>Acartia tonsa</i> [marine]	6d-EC10 (larval development ratio)	0.028	OECD draft TG (life cycle test) (2004)	M
Fish	<i>Lepomis macrochirus</i> Bluegill sunfish	21d-NOEC (growth)	0.089	OECD TG 204	M
Fish	<i>Brachydanio rerio</i> Zebrafish	34d-NOEC (growth, development)	0.035	OECD TG 210	M
Fish	<i>Pimephales promelas</i> Fathead minnow	36d-NOEC (growth, development)	0.035	OECD TG 210	M

*N: nominal; M: measured.

Toxicity tests were carried out with three species of sediment organisms according or similar to OECD TG 218. The 28-day NOEC for the midge larvae *Chironomus riparius* was 101 mg/kg dwt (development), for the amphipoda *Hyalella azteca* 18.2 mg/kg dwt (growth) and for the aquatic oligochaete worm *Lumbriculus variegatus* 7.1 mg/kg dwt (growth) at an organic carbon content of 2%. Toxicity tests were also carried out with soil organisms. The 8-week NOEC (reproduction) for earthworm *Eisenia foetida* according to OECD TG 207 was 105 mg/kg and the 4-week NOEC (reproduction) for the springtail *Folsomia candida* 45 mg/kg according to ISO/CD 11267.

AHTN may present a hazard for the environment (acute aquatic toxicity values below < 1 mg/L and not readily biodegradable). Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

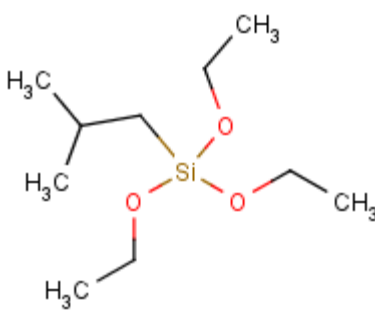
AHTN is produced on one site in Europe, with a production volume in the year 2000 between 1000 and 5000 ton/y. Circa 62% of the production volume is exported outside Europe. Use volumes are according to RIFM (Research Institute of Fragrance Materials) and IFRA (International Fragrance Association) based on regional surveys carried out between 1993 and 2006. For the countries belonging to EU-15 plus the two associated countries Norway and Switzerland, the use volumes declined from 885 ton per year in 1992, 358 ton per year in 2000 (used for the quantification of the industrial releases in the SIAR) to 247 ton per year in 2004. Environmental release of AHTN may occur during production, during compounding, during formulation and during/after use by consumers. It is assumed that the total use volume is discharged to the sewer.

AHTN is used as an ingredient in fragrance oils (fragrance oils is also referred to in literature as fragrance compounds, fragrances, fragrance composition, perfume oil or perfume compositions). AHTN is the second largest volume product of the fragrance materials known collectively as polycyclic musks. Fragrance oils are complex mixtures, prepared by blending (compounding) many fragrance ingredients in varying concentrations. Most of these ingredients are liquids, in which AHTN is dissolved. Applications of the fragrance oils are mainly in consumer products such as perfumes, cosmetics, soaps, shampoos, detergents, fabric conditioners, household cleaning products and air fresheners. Blending of the fragrance oil with other ingredients to make the final consumer product is often referred to as a formulation.

Occupational exposure is possible during production, during compounding, during formulation and during cleaning by professional cleaners. As AHTN has a very low vapour pressure, exposure to vapour is considered negligible. Dermal and inhalation occupational exposure to pure AHTN and dermal exposure to mixtures containing AHTN are relevant. Compounding fragrance oils and formulating consumer products involve a high level of automation, intensive ventilation and a high working accuracy required to prevent any cross contamination. Professional cleaners may be exposed to AHTN while using cleaning products and dermal exposure may occur each time hands are submersed in the diluted cleaning solution.

Consumer exposure may occur following dermal and inhalation exposure of which the dermal exposure is the most relevant.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	17980-47-1
Chemical Name	Isobutyl triethoxysilane (IBTEO)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties**

The IBTEO is a liquid with a melting point of $<-72^{\circ}\text{C}$, a boiling point of 186.6°C at 1013 hPa. The measured vapor pressure is 6.1 hPa at 20°C . The measured water solubility of IBTEO is 86 mg/L; the log Kow is 2.033 at 20°C . The water solubility and log Kow values may not be accurate because the chemical is hydrolytically unstable.

The EPISuite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

Human Health

Toxicokinetics, metabolism and distribution data are not available for IBTEO.

The 4-hour inhalation LC_{50} in male and female rats for a respirable aerosol of IBTEO was $> 5.88 \text{ mg/L}$ (following guideline similar to OECD 403). Signs of respiratory irritation were noted during exposure. Transient effects on body weight, food and water consumption were noted following exposure. Discoloration of the lungs of two male rats was noted; however there were no microscopic findings. The dermal LD_{50} in male and female rats was $> 2000 \text{ mg/kg bw}$ following OECD TG 402. There were no clinical signs of toxicity associated with a 24 hour dermal exposure to IBTEO. The oral (gavage) LD_{50} in male and female rats was $> 5000 \text{ mg/kg bw}$ (following OECD TG 401); transient clinical signs included piloerection, hunched posture and waddling.

IBTEO was moderately irritant to rabbit skin and slightly irritating to the rabbit eyes (OECD TG 404 and 405). IBTEO was not a skin sensitizer in Guinea Pig Maximization Tests.

Daily six-hour exposure to IBTEO by nose only inhalation, at mean achieved atmosphere concentrations of up to 2.54 mg/L for 90 days in the rat produced no toxicologically significant effects in the parameters measured (following OECD TG 413). The No Observed Effect Level (NOEC) was 2.54 mg/L/d (the highest concentration tested). Groups of 5 rats/sex were administered IBTEO by oral (gavage) at $1000 \text{ mg/kg bw/day}$

for 28 days. Relative to body weight, liver and kidney weights in female rats receiving IBTEO were statistically higher than in the female controls. However, no macroscopic or microscopic abnormalities were observed in these organs. In all other respects, including general health, food consumption and both macroscopic and microscopic pathology, rats treated with IBTEO were comparable to controls. The NOAEL was 1000 mg/kg bw/day.

IBTEO was negative for mutagenicity with and without metabolic activation in *Salmonella typhimurium* (Guideline 84/449/EEC B.14) and in Chinese hamster ovary cells (OECD TG 476). IBTEO did not induce chromosomal aberrations in Chinese hamster lung cells (V79) (OECD TG 473) *in vitro* and did not increase micronuclei *in vivo* in mouse micronucleus test (OECD TG 474). IBTEO is considered to be non genotoxic *in vitro* and *in vivo*.

No data were available for carcinogenicity.

In an OECD TG 415 "One-generation reproduction toxicity study" no adverse effects on reproduction were observed up to the highest dose tested. The NOAEL for reproductive toxicity was 1000 mg/kg bw/day. In an OECD TG 414 "Teratogenicity" study no adverse effects on development were observed up to the highest dose tested. The NOAEL for maternal toxicity was 250 mg/kg bw/d; the NOAEL for developmental toxicity was 1000 mg/kg bw/day. It is therefore considered that IBTEO is not likely to have potential for reproductive or developmental toxicity.

IBTEO may present hazard for human health (skin and eye irritation). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

IBTEO is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions. Due to limitations on the analytical procedure, the hydrolysis rate at 20°C could not be determined, but the half life was extrapolated to be approximately 6 - 9 hours in an unbuffered solution (at pH 6.15). In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.48 days. The hydrolysis products of IBTEO attained 75% degradation within 28 days and as such can be considered as readily biodegradable when tested in an OECD TG 301 D "Ready Biodegradability: Closed Bottle Test". The observation that 75% percent of the material is degraded after 28 days suggests that most of the degradation was associated with ethanol. In aerobic conditions using adapted wastewater from domestic sewage, degradation was 74% after 5 days rising to 95% by day 15 and in similar conditions in synthetic seawater, ethanol was 45% degraded after 5 days rising to 75% by day 20.

Level III Fugacity modeling, using loading rates of 1000 kg/h each for Air, Soil, and Water, shows the following percent distribution when IBTEO is released simultaneously to all three compartments: Air = 12.2%; Soil = 7.84%; Water = 79.6%; Sediment = 0.32%. There is uncertainty associated with these results as the water solubility and log Kow values may not be accurate because the chemical is hydrolytically unstable. However, IBTEO is unlikely to be found in the environment, as this material is hydrolytically unstable. Henry's Law constant of 4.75×10^{-4} atm-m³/mole at 25 deg C (48.11 Pa m³/mole) suggests that volatilization of IBTEO from the water phase is expected to be moderate.

IBTEO reacts to form ethanol and isobutylsilanetriol through hydrolysis. The BCF for IBTEO and isobutylsilanetriol cannot be predicted accurately, but are expected to be low. Ethanol is not likely to bioaccumulate (calculated BCF=3.16). Furthermore, due to these properties, current estimation models are not capable of calculating physicochemical or environmental fate values with a known degree of accuracy. No information on the environmental fate of isobutylsilanetriol was found. However, based on studies on related monomeric silanols, it is expected that the adsorption of isobutylsilanetriol onto surfaces and condensation to disiloxanes in dilute aqueous solution may be important properties of this chemical. Isobutylsilanetriol is expected to partition primarily to water, soil and sediment due to its high water solubility and potential to bind to mineral surfaces. In water and air, isobutylsilanetriol may degrade photolytically. Slow biodegradation in water and soil might also occur.

Due to the rapid hydrolysis of IBTEO in ecotoxicity studies, aquatic organisms are exposed to the parent material and its hydrolysis products, ethanol, isobutyl silanetriol, and condensed silanetriol materials (polyisobutyl siloxane). Silanetriols (at concentrations greater than 500 mg/L) can condense to form highly cross-linked, high molecular weight polymers.

The following acute toxicity test results have been determined for aquatic species:

Fish [rainbow trout: *Salmo gairdneri*]: 96 h LC₅₀ = 85 mg/L (semistatic, nominal)

Invertebrate [*Daphnia magna*]: 48 h EC₅₀ > 49.1 mg/L (static, nominal)

Algae [*Scenedesmus subspicatus*]: 72 h ErC₅₀ > 36 mg/L (growth rate) (nominal)

Algae [*Scenedesmus subspicatus*]: 72 h EbC₅₀ > 36 mg/L (biomass) (nominal)

72 h NOEC = 36 mg/L

IBTEO may present hazard to the environment (acute aquatic toxicity values between 1 and 100 mg/L)). Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

In the Sponsor Country, production volume in 2005 was approximately 454 - 4536 tonnes. IBTEO is not imported in the Sponsor Country. Europe and Asia (Japan) did not report production of IBTEO in 2005.

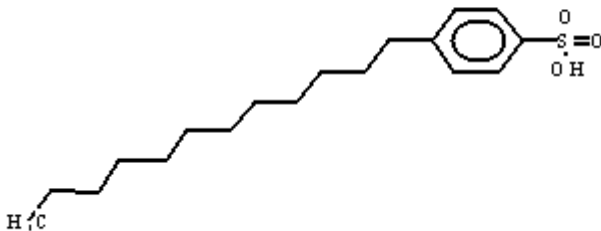
IBTEO is used as a water repellent for mineral building materials, especially for substrates with low porosity (e.g., concrete, brick masonry, ceramic tiles). In addition it is applied as a water repellent under top coats. The product is applied to saturation by low pressure spray, brush or roller. Once the material contacts the substrate it hydrolyzes, and forms ethanol and is expected to form silanetriols. The silanetriols react chemically with the siliceous interface in pores and capillaries of the mineral surface and forms chemical bound water-repellent interfacial compounds.

Worker exposure is not expected as IBTEO is produced in closed systems. Engineering controls are used to minimize potential exposures to the substance include scrubbers and vents. The chemical will be transported in moisture resistant, sealed, plastic lined or coated metal containers and stored in well-ventilated areas; such that workers involved in transport and storage are unlikely to be exposed to significant amounts of the product. At the industrial consumer level, workers potentially exposed to the product will include those involved in application. Workers involved in application will likely be using the liquid at low pressure (e.g., spray) or without pressure (roller or brush), almost exclusively in outdoor areas. Applicators are advised to wear protective equipment such as eye protection; face shields, chemical resistance gloves, and to always have adequate ventilation. After the completion of application, potential exposure to the product is not expected to exist as the substance hydrolyzes and bonds chemically to the application surface. Once cured the chemical is not expected to leach from the substrate to which it was applied.

There are no consumer uses of IBTEO. Public exposure to the product is anticipated to be limited. People in areas adjacent to the site being treated may have potential for exposure, especially under adverse (windy) weather conditions. Following good work practices public exposure would be negligible, and of a short term nature. Mass release during usage is expected to be low.

Leaching or run-off from any treated surface is not expected to carry the chemical into either natural waters or soil in any measurable amounts. Significant evaporation of the material is unlikely given the high level of adsorption to silica based substrates and the non-volatile nature of the isobutyl silanol. Therefore, exposure to the environment is expected to be low.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	27176-87-0
Chemical Name	Dodecylbenzenesulfonic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

The Linear Alkylbenzene Sulfonate(LAS) category was assessed at SIAM 20. Data from the C12-LAS substances dodecylbenzene sulfonate and sodium dodecylbenzene sulfonate have been included in the assessment of Dodecylbenzenesulfonic acid for acute oral toxicity, skin and eye irritation, ready biodegradation, aquatic toxicity to fish and invertebrates endpoints.

Physical and chemical properties

Dodecylbenzenesulfonic acid (DBS) is a liquid organic substance (light yellow to brown). It has a melting point of 10°C and a boiling point of 460°C (calculated). An estimated pKa of 0.7 indicates that this acid is fully dissociated in the environmental pH range 4 to 9. Sodium dodecylbenzenesulfonate (CAS No. 25155-30-0) is a very close analogue of the dissociated acid because it readily dissociates in water and release the dodecylbenzene sulfonic anion in solution. Experimental aqueous solubility and log K_{OW} for this salt have been determined to be 300 mg/L and 1.96. A very low (modelled) vapour pressure of 3×10⁻¹³ Pa designates an acid with a negligible volatility.

Human Health

There is limited toxicokinetic information on DBS, which indicates uptake from the gastrointestinal tract was around 30% in a 5-week dietary administration study in rats. The main route of excretion was via the urine.

Low levels of Sodium dodecylbenzene sulfonate-derived residues were detected in all tissues analyzed on day 35 of the experiment. 8 male Wistar rats were given a single i.p. dose of 384.7 µg [¹⁴C]DBS in a 0.6% physiological NaCl solution. Within 10 days after dosing, rats excreted 94.5% of the dose applied, 84.7% in the first 24h.

The acute oral LD50 in male/female rats is 650 mg/kg bw. No significant gross abnormalities were seen at autopsy. There is no available acute dermal and inhalation toxicity data for dodecylbenzenesulfonic acid.

Linear alkyl benzene sulfonate(LAS) was slightly irritating to the skin. Guinea-pig skin after 7 days exposure to LAS appeared shrunken, with thin layers of dermis and epidermis of guinea pigs in the histologic sections

compared to controls. A solution of 5% linear alkyl benzene sulfonate sodium salts, was slightly irritating to the eye of rabbit.

In a repeated dose oral toxicity study in rats [OECD TG 422], dodecylbenzenesulfonic acid was administered via gavage to male rats at 0, 100, 200, and 400 mg/kg bw/day, for from 2 weeks before mating to the end of the mating period (at least 28 days) and to female rats at 0, 100, 200, and 400 mg/kg bw/day, for from 2 weeks before mating to day 4 of lactation including the mating and gestation periods. One treatment-related death was observed in male rats in the high dose group. Oral administration of dodecylbenzenesulfonic acid to rats resulted in soft feces, and squamous cell hyperplasia of stomach in both sexes at 400mg/kg bw/day, and liquid feces and soiled perineal region, a decrease in body weight and food consumption in males at 400 mg/kg bw/day. In histopathological examination, squamous cell hyperplasia of stomach was observed in both sexes at 200 mg/kg bw/day and forestomach erosion/ulcer was observed in males at 400mg/kg bw/day. Based on these effects the NOAEL value was 100 mg/kg bw/day for male and female rats and the LOAEL value was 200 mg/kg bw/day for male and female rats. From these results, the target organ for oral dosing of dodecylbenzenesulfonic acid was considered to be the stomach.

In a bacterial reverse mutation assay [OECD TG 471], dodecylbenzenesulfonic acid was negative both with and without metabolic activation. An *in vitro* test chromosome aberration test [OECD TG 473] using Chinese hamster lung cells (CHL) was negative with and without metabolic activation. There was no data of *in vivo* test with dodecylbenzenesulfonic acid.

No data are available for the carcinogenicity of dodecylbenzenesulfonic acid.

In reproductive and developmental toxicity study performed according to the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], test conditions and dose were same as repeated dose toxicity. No treatment-related changes were observed in the copulation, fertility and pregnancy indices, gestation length, the number of corpora lutea and implantation, delivery index. Also no treatment - related changes were observed in all parameters of offsprings during the parturition and lactation periods. Based on these effects, the NOAEL for fertility and developmental toxicity was 400mg/kg bw/day, the highest dose tested.

Environment

For indirect photolysis in the atmosphere, the half-life of dodecylbenzenesulfonic acid is estimated to be 7.8hr (OH rate constant $16.36 \times 10^{-12} \text{ cm}^3/\text{molecule-sec}$) with the AOPWIN model. Less than 10% hydrolysis was observed after 5 days at pH 4.0, 7.0 and 9.0 at $50 \pm 5^\circ \text{C}$ [OECD TG 111].

C12-LAS is readily biodegradable (more than 60% by mineralization within 28 days) [OECD TG 301 F].

Level III Fugacity modeling using EQC for a Type2 chemical, with equal releases to air, soil, and water shows the following percent distribution: air = 0.5%; soil = 65%; water = 32%; sediment = 2.5%. If released exclusively to water, the acid will primarily partition to water (93%) and sediment (7%). If released only to soil, it will remain in this compartment (100%). Results from calculations of environmental fate have to be considered with caution because the environmental partitioning of this substance is not exclusively function of its hydrophobicity, hence of its fugacity. For example, recent research shows that linear alkylbenzene sulfonates tend to partition to positively charged substrates in soils and sediments. A K_d value of 3210 L/kg has been determined for a C12 LAS in activated sludge with an organic carbon content of 26%. A K_{OC} value of 9076 has been obtained for a C12 LAS with the OECD TG 106 method. The estimated BCF of dodecylbenzenesulfonic acid is 70.79 with the BCFWIN model and experimental BCF values in fish, invertebrates and alga of sodium dodecylbenzenesulfonate ranged from 36 to 119. It suggests that dodecylbenzenesulfonic acid has a low potential for bioaccumulation.

Ecotoxicity data are available for dodecylbenzene sulfonic acid, C12 LAS and its salt with several comprehensive reviews having been completed.

The toxicity results from studies with aquatic organisms are as follows :

1) Acute toxicity :

Fish (*Salmo gairdnei*) / Dodecylbenzenesulfonic acid Na salts : 96 hr-LC₅₀ is 3.20-5.60 mg/L (nominal).

Invertebrates (*Daphnia magna*) / LAS : 48 hr-LC₅₀ is 3.5±1.0 mg/L(nominal).

Green algae (*Selenastrum capricornutum*) / Dodecylbenzenesulfonic acid: 72 hr-EC50(growth rate) is 65.4mg/L (measured) and 72 hr-EC50(yield) is 21.0 mg/L(measured). 72 hr-NOEC(growth rate and yield) is 7.9mg/L(measured)

Microorganism (activated sludge) / Na-12C LAS: 3hr-EC₅₀ is 500-723 mg/L(nominal).

2) Chronic toxicity :

Fish (*Pimephales promelas*) / C_{11.8} LAS : 1yr-NOEC is 0.90 mg/L(measured).

Invertebrates (*Daphnia magna*) /Sodium dodecylbenzene sulfonate : 21days-NOEC is 1.65 mg/L(nominal).

3) Soil dwelling organism

Lumbricus terrestris /LAS : 14days-LC₅₀ is 1.33mg/g(nominal).

Eisenia foetida / LAS : 14days-LC₅₀ > 1mg/g. (nominal).

Exposure

In the Republic of Korea estimated production amounts of dodecylbenzenesulfonic acid were approx. 89,460, 99,542, and 100,464 tons in 2005, 2006 and 2007, respectively. The estimated used amounts of the substance were approx. 7,410, 7,713, and 7,756 tons in 2005, 2006, and 2007, respectively. In Nordic countries estimated production amounts of this chemical were approx. 8,723, 12,522 and 10,400 tons in 2004, 2005 and 2006, respectively.

Dodecylbenzenesulfonic acid is used in production of detergents and in manufacturing of catalyser and as additives. Most of dodecylbenzenesulfonic acid that is used in industrial and consumer products as surfactant and ingredient in detergents will be disposed of by the sewerage system. Exposure to the environment may occur mainly via effluents of STP's and application of sewage sludge in agriculture.

In the Republic of Korea, dodecylbenzenesulfonic acid is produced by reacting SO₃ and LAB(linearalkylbenzene) in a continuous closed reactor. After this reaction is finished, atmosphere contaminants such as SO₂ and dust are emitted to atmosphere but the concentrations of the SO₂ and dust were below 10% level of environmental emission standard. All organic waste solvents occurred are burned by waste consignment treatment. Wastewater is treated chemically and biologically, and then it is discharged to wastewater treatment plant.

As for human exposure, in the sponsor country, this substance is produced in a continuous closed system and the manufacturing processes have been designed to maximize production yield and minimize potential releases. Good manufacturing design practices (e.g., enclosed production in agglomeration processes, exhaust ventilation and dust collection) and personal protective equipment in place at facilities that manufacture products are anticipated to mitigate worker exposure to this substance.

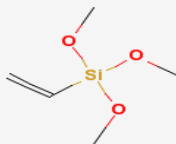
Dodecylbenzenesulfonic acid is the most common synthetic anion surfactant and it is usually used as an ingredient of detergents. Consumer can be exposure to dodecylbenzenesulfonic acid using detergents.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work because of its low hazard profile.

Environment: The chemical is currently of low priority for further work . The chemical possess properties indicating a hazard for the environment (acute aquatic toxicity to fish and invertebrates between 1 and 100 mg/L). However, the chemical does not warrant further work due to its ready biodegradation and limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2768-02-7
Chemical Name	Vinyl trimethoxysilane (VTMS)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties****Reduced Testing Rationale**

VTMS is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions. At pH 7 and 50°C, the half-life is < 2.4 hours. This hydrolysis is expected to produce 3 moles of methanol and 1 mole of ethenyl silanetriol. Silanetriols (at concentrations greater than 500 mg/L) can condense to form highly cross-linked, high molecular weight polymers. In aqueous solutions, exposures to VTMS are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products methanol, ethenylsilanetriol, and condensed silanetriol materials (high molecular weight polymers). Because VTMS is hydrolytically unstable, water solubility and partition coefficient were not measured; however, modeled values are provided for water solubility and partition coefficient.

The EPISuite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

VTMS is a liquid with a melting point of -97 °C, a boiling point of 123 °C at 1013 hPa. The measured vapour pressure is 15.93 hPa at 25°C. The estimated water solubility of VTMS is 5.043×10^5 mg/L; the estimated log Kow is -0.032. The water solubility and log Kow values may not be applicable because the chemical is hydrolytically unstable.

Human Health

Toxicokinetics, metabolism and distribution data are not available for VTMS.

The acute toxicity of VTMS has been studied by the inhalation, dermal and oral routes in rats. The combined 4 hour inhalation LC₅₀ in rats for VTMS was ca. 16.8 mg/L. The study was conducted in a manner consistent with OECD TG 403. Clinical signs included perinasal, periocular, perioral and

urogenital wetness, perioral and perinasal encrustation, unkempt fur, hypoactivity, blepharospasm, lacrimation, respiratory difficulties, ataxia, prostration, tremors, distended stomachs, and negative righting and pinch reflexes. Body weight gains for all exposure groups were depressed during post-exposure week 1. There were no findings at necropsy in surviving animals. The dermal LD₅₀ for VTMS for male rats was 4.00 mL/kg bw (ca. 3880 mg/kg bw) and for female rats was 3.36 mL/kg bw (3259 mg/kg bw). The study was conducted in a manner consistent with OECD TG 402. Discomfort, sluggishness, unsteady gait, and prostration were observed. Most deaths occurred at one to 5 days; surviving animals recovered by day 3. There were no findings at necropsy in surviving animals. Skin reactions included erythema, ecchymosis and desquamation. The oral LD₅₀ for VTMS for male rats was 7.34 mL/kg bw (ca. 7120 mg/kg bw) and for females was 7.46 mL/kg bw (7236 mg/kg bw). The study was conducted in a manner consistent with OECD TG 401. Sluggishness, red to brown discharge, lacrimation, piloerection, unkempt appearance, prostration, emaciation and unsteady gait were among the signs of toxicity observed. Deaths occurred at 2.5 hours to 4 days. Survivors recovered by day 5. Most survivors had no remarkable gross lesions; one female animal in the 8.0 mL/kg bw dose group was observed to have an enlarged kidney. The combined oral LD₅₀ of VTMS in rats was 8.20 mL/kg bw (ca. 7954 mg/kg bw). The study was conducted in a manner consistent with OECD TG 401. Signs of toxicity included lethargy, diuresis and diarrhea within 6 hours of administration followed by blood staining around mouth and nostrils at 24 hours. Deaths occurred up to 96 hours after administration. The oral LD₅₀ of VTMS in female rats > 300 mg/kg bw to 2000 mg/kg bw (OECD TG 423). Signs of toxicity included diarrhea, perianal soiling and reddish urine. Deaths occurred up to 3 days after administration of 2000 mg/kg bw. At necropsy, small thymi and spleens were noted in the animals that died at 2000 mg/kg bw. Histopathological examination showed atrophy of the cortex of the thymus and of the red and white pulp of the spleen.

Valid data regarding the skin irritation potential of VTMS are not available; VTMS is not irritating to the rabbit eyes (OECD TG 405). Under the conditions of the guinea pig maximization test (OECD TG 406), VTMS or VTMS (hydrolysate) did not elicit a delayed contact hypersensitivity response in guinea pigs. Under the conditions of the Buehler test (OECD TG 406), VTMS was determined to be a skin sensitizer.

The repeated-dose toxicity of VTMS has been studied by the inhalation and oral routes in rats. Groups of 20 rats/sex/concentration were exposed six hours per day, five days per week, for 14 weeks to vapor of VTMS at target concentrations of 0, 0.06, 0.6 or 2.4 mg/L³, respectively. Repeated inhalation exposure to 400 ppm VTMS resulted in effects primarily on the urinary bladder and kidney with the LOAEC of 0.6 mg/L and the NOAEC of 0.06 mg/L). In a combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], male and female rats were administered VTMS via gavage at 62.5, 250 and 1000 mg/kg bw/day for up to 42 days. Repeated oral exposure to VTMS resulted in effects primarily on the urinary bladder, intestine, kidney, and thymus in both sexes at all doses. The NOAEL was not established in this study. The LOAEL was 62.5 mg/kg bw/day (decreased urine osmolality and sodium, potassium and chloride concentrations (males) and slight decrease in body weight and body weight gain (females).

VTMS did not induce gene mutations in bacteria (Ames and bacterial reverse mutation assay) or mammalian cells (Sister chromatid exchange) *in vitro*. VTMS did not induce micronuclei in an *in vivo* test; however, it had a positive clastogenic effect *in vitro* in two chromosome aberration tests performed with metabolic activation only. VTMS is not considered to be genotoxic.

In the combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], there were no effects on reproductive performance of parental rats when VTMS was administered by oral gavage. The NOAEL was 1000 mg/kg bw/day for males, and 250 mg/kg bw/day for females (based on a reduced number of estrous cases). There were no effects on developmental parameters; the NOAEL for developmental effects was 1000 mg/kg bw. VTMS did not show any effects on the

reproductive organs in the 14-week repeated-dose toxicity study via inhalation. Exposure of pregnant rats to VTMS by inhalation during organogenesis resulted in a NOAEC of 0.15 mg/L for maternal toxicity. There was evidence of slightly delayed skeletal ossification in fetuses from the 1.8 mg/L group; the NOAEC for developmental effects was 0.60 mg/L. In the OECD TG 422 study, no effects were seen on the developmental parameters when VTMS was administered orally; the NOAEL for developmental toxicity was 1000 mg/kg bw/day.

VTMS may present hazard for human health (potential for skin sensitization, oral repeated-dose toxicity and developmental toxicity (only at the high concentration via inhalation)). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The hydrolysis half-life for VTMS is <2.4 hours at 50 °C and pH7. Estimated $t_{1/2}$ at 25°C using the Taft Equation and the measured hydrolysis rates are 8.2 seconds at pH 4, 16 minutes at pH 7 and 11 seconds at pH 9. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.372 days. An OECD TG 301F resulted in 51 % biodegradation after 28 days. VTMS is not readily biodegradable under aerobic conditions. Based on the rapid hydrolysis of this material, any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only biodegradable materials in the test system will be methanol, silanetriol, and condensed silanetriol materials (high molecular weight polymers). The hydrolysis product, methanol, is readily biodegradable; however, ethenylsilanetriol and the condensed silanetriol materials are not expected to be readily biodegradable. Level III Fugacity modeling, using loading rates of 1000 kg/h each for air, soil, and water, shows the following percent distribution of VTMS when it is released simultaneously to all three compartments: Air = 2.58%; Soil = 46.3%; Water = 51%; Sediment = 0.937%. However, VTMS is unlikely to be found in the environment, as this material is hydrolytically unstable. A Henry's law constant of 8.72×10^{-5} atm-m³/mole at 25°C (8.84 Pa-m³/mole) suggests that the volatilization of VTMS from the water phase is not expected to be high. VTMS reacts to form methanol and ethenylsilanetriol through hydrolysis. The BCF for VTMS and ethenylsilanetriol cannot be predicted accurately, but are expected to be low. Methanol has a low estimated bioaccumulation potential (BCF= 3.2). Furthermore, due to these properties, current estimation models are not capable of calculating physicochemical or environmental fate values with a known degree of accuracy. No information on the environmental fate of ethenylsilanetriol was found. However, based on studies on related monomeric silanols, it is expected that the adsorption of ethenylsilanetriol onto surfaces and condensation to disiloxanes in dilute aqueous solution may be important properties of this chemical. Ethenylsilanetriol is expected to partition primarily to water, soil and sediment due to its high water solubility and potential to bind to mineral surfaces. In water and air, ethenylsilanetriol may degrade photolytically. Slow biodegradation in water and soil might also occur.

Due to the rapid hydrolysis of VTMS, aquatic organisms are likely exposed to the parent material and its hydrolysis products, methanol, ethenyl silanetriol, and silanol oligomers.

The following acute toxicity test results have been determined for aquatic species:

- Fish [zebra fish :*Brachydanio rerio*]: 96h-LC₅₀ >100 mg/L (nominal)
- Invertebrate [*Daphnia magna*]: 48h-EC₅₀ = 168.7 mg/L (nominal)
- Algae [*Scenedesmus subspicatus*]: 72h-ErC₅₀ > 100 mg/L (growth rate method) (nominal)
- Algae [*Scenedesmus subspicatus*]: 72h-EbC₅₀ > 100 mg/L (area under growth curve method) (nominal);

72h-NOEC = 10 mg/L

VTMS may not present hazard for the environment based on its low hazard profile. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

In the Sponsor Country, production volume in 2005 was 953 tonnes. In that year, an additional 230 tonnes of VTMS were imported into the Sponsor Country. In 2009, a total use of 16.9 tons/year was registered in the Danish Product Register. In 2006, the total use in the Nordic countries (Denmark, Sweden, Finland and Norway) was 1253 tons, according to the SPIN database. The main use category was “manufacture of rubber and plastic products”. In Japan, the 2005 production volume was approximately 1000 tonnes and no VTMS was imported.

VTMS is a coupling agent used for plastics and wire and cable pipes. VTMS can be used as moisture scavenger in sealants; but there is no information that they are used as moisture scavengers in latex. VTMS can be used as a co-monomer in the preparation of latex dispersions with the purpose to promote adhesion of the latex dispersion on inorganic surfaces. The amount of VTMS used in industrial products is usually only 1-2 percent. The substance is reacted during use and little or no chemical is expected in final products. There are no consumer uses of VTMS.

In order to prevent the rapid hydrolysis and subsequent loss of this material in production, it is handled in closed systems [hard-piped]. Necessary engineering controls during production are recommended and include proper ventilation, containment, safety equipment and actual hardware designed to minimize exposure through splashing, or exposure to the air. VTMS is transported from the production site as the parent silane.

During industrial processing, the substance reacts completely and is no longer available for worker exposure. The substance hydrolyzes releasing methanol and silanetriols that can condense to form highly cross-linked, high molecular weight polymers. At the industrial customer level, the material may be used in open systems. Likely engineering controls during use include local ventilation (hoods) when the substance is being transferred or used in its application. Exposure due to non-accidental releases are expected to be low, and may include dermal and inhalation exposure during transfer and use.

Exposure to the environment is expected to be low.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	38051-10-4
Chemical Name	2,2-BIS(CHLOROMETHYL)TRIMETHYLENE BIS(BIS(2-CHLOROETHYL)PHOSPHATE) (V6)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties**

2,2-Bis(chloromethyl)trimethylene bis(bis(2-chloroethyl)phosphate (hereafter referred to as V6¹) is a liquid at room temperature, with a freezing point of less than -50.5 °C and a boiling point of 252°C. V6 has a relative density of 1.473 at 20°C and a water solubility value of 232 mg/l at 20 °C. All of the above values are measured. The value for vapour pressure was estimated at 2.75×10^{-6} Pa at 25 °C. The log k_{ow} is 2.83 at 20°C. It is of low volatility (estimated vapour pressure 2.75×10^{-6} Pa at 25°C).

Human Health

The distribution and kinetics of [¹⁴C]-V6 in male and female rats was investigated in accordance with OECD Guideline 417 and to GLP. Following oral administration of ¹⁴C labelled V6 in the rat, the bioavailability was ≥ 100% at the low dose (15 mg/kg bw) and approximately 50% at the high dose (600 mg/kg bw), which was judged to be an underestimate due to the methodology used. V6 was completely absorbed from the gastrointestinal tract and blood kinetics varied between males and females at 15 mg/kg bw. Elimination half-life was 99 – 113 hours, irrespective of dose, route or sex and excretion was via the biliary route (60 %), urine (20 %) and a small amount exhaled as ¹⁴CO₂. [¹⁴C]-V6 or its metabolites were distributed all over the body, but no target organs other than the organs of elimination were identified and major metabolites were found in the faeces. Limited information is provided for distribution and kinetics following intravenous administration, however it is of note that the elimination half lives for oral and i.v. routes are comparable, with differences observed in AUC and bioavailability are most likely due to differences in metabolism. An *in vitro* study conducted to GLP and to OECD Guideline 428, using human skin membranes as a model for dermal absorption, determined that the delivery of undiluted V6 and V6 in ethanol (0.2mg/cm²) was 0.51 % and 6 %, respectively.

V6 is not acutely toxic, with an LD₅₀ (rat) greater than 2000 mg/kg bw for both the oral and dermal routes of exposure. For inhalational exposure in a test carried out to OECD Guideline 403 (1981), the LC₅₀ (rat) was greater than 1.65 mg/l which was the highest attainable aerosol concentration. Serum cholinesterase was significantly decreased in rats of both sexes following oral administration; however this was determined not toxicologically relevant in accordance with the WHO/FAO joint meeting of experts in pesticides residues. Serum cholinesterase activity was unaffected following dermal administration and brain cholinesterase activity was unaffected following oral and dermal administration.

Skin and eye irritation studies indicate that V6 is neither irritant nor corrosive following a single exposure in the

¹ V6 is a trade name of 2,2-Bis(chloromethyl)trimethylene bis(bis(2-chloroethyl)phosphate containing up to 7.5% w/w of the impurity tris(2-chloroethyl) phosphate (TCEP). Purer forms of the substance are marketed under separate trade names (TL10 and V66).

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rabbit, and any mild effects were fully reversible. Data on respiratory irritation are not available.

V6 does not possess significant skin sensitisation potential in the guinea pig maximisation test carried out to OECD Guideline 406 (1992). Data on respiratory sensitisation are not available.

From a 28-day repeat dose toxicity study carried out in accordance with OECD Guideline 407 (1995), in which V6 was administered via oral gavage in rats, a NOAEL of 15 mg/kg bw/day was derived. This was based on an increase in relative and absolute liver weight and histopathological findings in the liver including hepatocellular hypertrophy and centrilobular hypertrophy in mid-dose (150 mg/kg bw/day) females and in high-dose (600 mg/kg bw/day) males and females. Other observations of note included significantly increased cholesterol levels and significant increases in absolute and relative thyroid weight in high dose males and females, and significantly increased prothrombin time in high-dose males. Data from a two-generation reproductive toxicity study (please refer to study detailed below) indicated similar findings; mid- (85.8 mg/kg bw/day) and high-dose (261.9 mg/kg bw/day) males and high-dose (302.3 mg/kg bw/day) females in the F0 generation had increased absolute and relative thyroid weight, accompanied by follicular hypertrophy and a reduction in colloid in males. High-dose males and females from both generations had increased absolute and relative liver weight, and in the F0 generation this was accompanied by hepatocyte hypertrophy. Based on this study, the NOAEL for parental toxicity in males is set at 29 mg/kg and for females at 97 mg/kg.

V6 did not induce gene mutation in bacterial assays with or without metabolic activation and did not induce an increase in the frequency of mutations in mouse lymphoma L5178Y cells, nor did it induce reproducible chromosomal aberration frequency in human lymphocytes in a test carried out to OECD Guideline 473 (1981). In an *in vivo* mouse micronucleus test conducted to OECD Guideline 474, V6 was not clastogenic. In conclusion, V6 is non-genotoxic *in vivo*.

Carcinogenicity data are not available for V6.

In an oral two-generation reproductive toxicity study conducted to OECD Guideline 416, V6 was administered to rats via the diet at doses of 29, 86 or 262 mg/kg bw/day for males and 33, 97 or 302 mg/kg bw/day for females. There were no effects on the male and female reproductive systems up to the highest doses tested and therefore the NOAEL derived for effects on fertility is approximately 262 and 302 mg/kg bw/day for males and females, respectively. Corpora lutea were not counted at scheduled sacrifice, which represented a deviation from the guideline. There was an increased number of runts on post-natal day one in mid- and high-dose groups of both generations, which may indicate toxicity to the offspring *in utero* and a decrease in pup weights in mid- and high-dose groups of both generations at certain time points. Other findings included decreased absolute spleen weight in high dose F0 pups and in all treated F1 pups, decreased relative spleen weight in high dose F1 pups, decreased absolute brain weight in all treated F1 pups, however relative weights were significantly increased. Absolute thymus weight of low and high dose F1 pups was also decreased, with no effect on the relative weights. A NOAEL of 29 mg/kg bw/day was derived for developmental toxicity based on the increased number of runts (defined as a pup with a weight less than the mean pup weight of the control group minus 2 standard deviations) and decreased pup weight at the mid- and high-doses. The low-dose of 29 mg/kg bw/day was considered the NOAEL for parental toxicity in males, based on thyroid weight changes and histopathology in mid- and high-dose groups for both generations and the mid-dose of 97 mg/kg bw/day was considered the NOAEL for parental toxicity in females based on liver and thyroid weight changes.

Environment

V6 has a moderately low adsorption coefficient (K_{oc} is 245, by read across of the $\log K_{oc} - \log K_{ow}$ relationship from the structurally-related substance TDCP, for which a reliable adsorption study has been conducted). V6 has a low potential to bioaccumulate in fish (estimated BCF = 50.8).

Fugacity modelling shows that if released to air, most V6 would be precipitated to soil (>93%) and some would pass to water (7%). If released to water, almost all will remain in water (>99%). If applied to soil, most would remain in soil (>93%) though some would migrate to water (7%). There is relatively little movement of V6 between soil and water, because transfer via the air compartment is very slow.

V6 is not readily biodegradable, showing 5% degradation over 28 days. Evidence of partial degradation was seen in a study of inherent biodegradability, though the test method did not allow for a period of adaptation. While phosphate esters are known to be chemically susceptible to hydrolysis, V6 is expected to have a half-life of at least one year under environmental conditions, based on a standard preliminary hydrolysis test. It is expected to degrade in the atmosphere by reaction with hydroxyl radicals and a half-life of 5.0 hours has been estimated (rate constant = $77.2926 \times 10^{-12} \text{ cm}^3/\text{molecule}\cdot\text{sec}$).

Valid measured toxicity data are available for three aquatic taxonomic groups. The lowest effect values in short-term tests are a 96-h LC₅₀ of 52 mg/l for Rainbow trout (*Oncorhynchus mykiss*), a 48-hour EC₅₀ of 42 mg/l for the invertebrate *Daphnia magna*, and a 72-hour ErC₅₀ and E_bC₅₀ of 35 mg/l and 21 mg/l respectively for the alga *Pseudokirchneriella subcapitata*.

Two chronic test results are also available: the 21-day NOEC for *D. magna* reproduction is ≥ 3.68 mg/l and the 72-hour NOEC for *P. subcapitata* is 10 mg/l. A PNEC_{aquatic} of 0.0736 mg/l has been derived by dividing the *D. magna* NOEC by an assessment factor of 50. There are no data for sediment-dwelling organisms.

A NOEC of 1,000 mg/l was obtained for wastewater treatment plant (WWTP) micro-organisms (activated sludge).

Data are also available for terrestrial organisms. A 14-day LC₅₀ of $> 1,000$ mg/kg soil dry weight was determined for the earthworm *Eisenia foetida* (no effects were observed). When corrected for organic carbon content in the test medium, a 'standardised' result of > 340 mg/kg soil dry weight can be derived for risk assessment purposes. Reliable long-term studies have been conducted for the structurally-related substances TCPP and TDCP, and read-across of the results to V6 may be justified.

Exposure

Less than 5,000 tonnes were produced within the EU in 2000, at a single location (UK). EU consumption of V6 is less than 2,500 tonnes per year, and the EU is a net exporter of finished goods containing V6.

V6 is used as an additive flame retardant mostly (over 95%) in flexible polyurethane foams. It is physically combined with the material being treated rather than chemically combined. The amount of flame retardant used in any given application depends on a number of factors such as the flame retardancy required for a given product, the effectiveness of the flame retardant and synergist within a given polymer system, the physical characteristics of the end product and the use to which the end product will be put. V6 may be exported in its raw format or may be used in the manufacture of polyurethane (PUR) foam for use mainly in the automotive industry, with some used in furniture. Additionally, a small number of company-specific, low-tonnage minor uses have been identified. These are not described due to commercial sensitivity.

Occupational exposure to V6 may occur during its manufacture, during the manufacture and cutting of PUR foam and during the production of rebonded and loose crumb foam. Inhalation of vapours and skin contact are the predominant routes of exposure. Oral exposure is not considered to be a significant route of exposure. Exposure of workers to V6 via the inhalation and dermal routes does not present concern due to the presence of adequate controls, such as local exhaust ventilation and use of personal protective equipment..

Consumers do not come into direct contact with PUR foams. The foam is only used in ways in which it is enclosed and therefore it is concluded that exposure to consumers is negligible.

Emissions to the environment can occur to the atmosphere (by evaporation) and waste water. Sources of release include sites undertaking V6 production; manufacture of flexible foams; foam recycling ('rebonding' and 'loose-crumb'); and processing sites associated with the minor uses. Emissions to the environment could also occur from finished articles during their use and at disposal, via both evaporation and generation of small particles, due to weathering and wear. Leaching from landfill sites is considered possible, based on the physicochemical properties of V6, although input to the environment via this route is considered to be negligible for the EU risk assessment.

**RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED****Human Health**

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (repeated dose toxicity and developmental toxicity). However, based on data presented by the Sponsor country, the exposure situation at the workplace is controlled and adequate risk management measures are in place. Individual countries may wish to carry out their own exposure assessments, relevant for their own scenarios followed by a risk assessment.

Environment

The chemical is of low priority for further work because of its low hazard profile.

Note: V6 is one of four closely-related chlorinated alkyl phosphate ester flame retardants, all of which have undergone risk assessment in the EU. The other substances are: TDCP, CAS no. 13674-87-8; TCPP, CAS no. 13674-84-5; TCEP, CAS no. 115-96-8. The identified uses of V6 do not lead to a concern for the environment in the EU. The human health risk assessment is still being conducted.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3896-11-5
Chemical Name	2- <i>tert</i> -Butyl-6-(5-chloro-2H-benzotriazol-2-yl)-4-methylphenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

The substance is a pale yellow solid with a melting point of 139 °C, a boiling point of ≥ 300 °C and a calculated vapour pressure of 7.6E-07 Pa at 25 °C (MPBWIN v1.43). The calculated octanol-water partition coefficient (log k_{ow}) is 5.55 (KOWWIN v1.67) and the water solubility is < 1.0 mg/L at 20 °C.

Human Health

No information on toxicokinetics or metabolism is available.

The inhalation LC_{50} was > 270 mg/m³ (the maximum attainable dust concentration) for 4-hr exposure in rats. There were no deaths during the study. Necropsy of all animals showed a slight amount of lung hyperemia. No other effects were noted. The oral [OECD TG 423] and dermal LD_{50} values in rats were > 2000 mg/kg bw. There were no deaths or clinical signs of systemic toxicity during the studies. No abnormalities were noted at necropsy in the oral study (necropsy was not performed in the dermal study).

The substance was not a skin or eye irritant. Some slight irritation, fully reversible within 72 hours, was observed in a skin irritation assay performed in rabbits. Mild conjunctivitis, fully reversible within 72 hours was observed in one animal out of six in an eye irritation assay performed in rabbits.

The substance was not skin sensitizing. A skin sensitization assay performed in guinea pigs and patch testing in humans were negative. The substance was not a photoallergen in guinea pigs.

The repeated dose toxicity of the substance has been investigated in four studies. In a repeated dose oral toxicity study in dogs the substance was administered via the diet to 5 animals/sex in the control and high dose groups and 4 animals/sex in the other dose groups at 0, 200, 1000 or 5000 ppm (equivalent to approximately 0, 6.2, 29.6 or 168 mg/kg bw/day for males and 0, 6.5, 32.2 or 153 mg/kg bw/day for females) for 13 weeks. One animal of each sex in the 0 and 5000 ppm groups were kept on the control diet for a further 4 weeks prior to sacrifice. All other animals were sacrificed at the end of the 13 week dosing period. No treatment-related deaths or clinical signs were observed in either sex. Treatment related effects (weight loss) were observed in females at 5000 ppm. Based on weight loss, the NOAEL for repeated dose oral toxicity is 1000 ppm (equivalent to 29.6 mg/kg bw/day for males and 32.2 mg/kg bw/day for females).

In a repeated dose oral toxicity study in rats [comparable to OECD TG 453] the substance was administered via the diet to 50 animals/sex/group at 0, 1000, 3000 or 10000 ppm (equivalent to approximately 0, 37.7, 113.2 or 382.6 mg/kg bw/day in males and 0, 50.4, 147.7 or 501.9 mg/kg bw/day in females) for 104 weeks. Based on a reduction in red cell parameters in males and females and bodyweight gain in males seen at 10000 ppm, the NOAEL for repeated dose toxicity is 3000 ppm (equivalent to 113.2 mg/kg bw/day for males and 147.7 mg/kg bw/day for females).

In a repeated dose oral toxicity study in mice [comparable to OECD TG 451] the substance was administered via the diet to 50 animals/sex/group at 0, 5, 50 or 500 mg/kg feed (equivalent to a mean daily intake of 0, 0.7, 6 and 62 mg/kg bw in males and 0, 0.7, 6 and 59 mg/kg bw in females) for 24 months. There were no treatment-related effects at any

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dose. The NOAEL for repeated dose toxicity is 500 mg/kg feed, equivalent to 62 mg/kg bw/day in males and 59 mg/kg bw/day in females.

In a combined repeated dose toxicity study with reproduction/developmental toxicity screening test in rats [OECD TG 422] the substance was administered via gavage to 12 animals/sex/group at 0 (vehicle), 62.5, 250 or 1000 mg/kg bw/day. Recovery group females (6 animals/group) were dosed at 0 (vehicle), 250 or 1000 mg/kg bw/day. Males were dosed for a total of 42 days, from 14 days before mating, and females were dosed from 14 days before mating throughout the mating and pregnancy period to day 6 of lactation (44-56 days). There were no treatment-related effects at any dose in test or recovery group animals. The NOAEL for repeated dose toxicity in adult animals is 1000 mg/kg bw/day.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium* and one strain of *Escherichia coli* [OECD TG 471], the substance was negative both with and without metabolic activation. An *in vitro* chromosomal aberration test in CHL cells [OECD TG 473] was negative with and without metabolic activation. *In vivo*, no evidence of a dominant lethal effect was observed in the offspring of male mice treated [comparable to OECD TG 478] with a single administration of the substance at 0, 1000 or 3000 mg/kg bw by gavage. The substance was not genotoxic in a bone marrow chromosome aberration test [comparable to OECD TG 475] or a micronucleus test [comparable to OECD TG 474] performed using Chinese hamsters dosed by gavage with the substance at 0, 500, 1000 or 2000 mg/kg bw/day on two consecutive days. Based on these results, the substance is considered to be non genotoxic *in vitro* and *in vivo*.

The carcinogenic potential of the substance has been investigated in two studies. In an oral study in rats [comparable to OECD TG 453] the substance was administered via the diet to 50 animals/sex/group at 0, 1000, 3000 or 10000 ppm (equivalent to approximately 0, 37.7, 113.2 or 382.6 mg/kg bw/day in males and 0, 50.4, 147.7 or 501.9 mg/kg bw/day in females) for 104 weeks. General toxicity effects are described in the repeat dose toxicity section above. There was no treatment related carcinogenic activity at any dose. In an oral study in mice [comparable to OECD TG 451] the substance was administered via diet to 50 animals/sex/group at non-toxic doses of 0, 5, 50 or 500 mg/kg feed (equivalent to a mean daily intake of 0, 0.7, 6 and 62 mg/kg bw in males and 0, 0.7, 6 and 59 mg/kg bw in females) for 24 months. There were no signs of general toxicity in this study and no treatment related carcinogenic activity at any dose. Based on these results the substance is considered to have no carcinogenic potential.

The reproductive toxicity of the substance has been investigated in the combined repeated dose toxicity study with reproduction/developmental toxicity screening test in rats [OECD TG 422] described above. No adverse effects on reproductive or developmental parameters were observed up to the highest dose tested. The NOAEL for reproductive/developmental toxicity in this combined study was considered to be 1000 mg/kg bw/day. The developmental toxicity of the substance has been investigated in prenatal developmental toxicity studies in rats and mice [comparable to OECD TG 414]. No evidence of developmental toxicity was observed in rats at doses up to 3000 mg/kg bw/day. In mice, there was a slight, but statistically significant, increase in the proportion of fetuses with incomplete ossification of sternebrae at a dose level of 3000 mg/kg bw/day, although the group mean foetal body weights were higher in the high dose group than controls. In rats and mice, no maternal toxicity was observed up to the highest dose tested, and no teratogenic effects were noted. The NOAELs for developmental toxicity from these studies in rats and mice are 3000 and 1000 mg/kg bw/day respectively. Based on these results, the overall NOAEL for reproductive /development toxicity of this substance is 1000 mg/kg bw/day.

Environment

The substance is not expected to be hydrolyzed under normal environmental conditions. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 8.6 hours (AOPWIN v1.92). An aerobic biodegradation study [OECD TG 301B] resulted in 2-10 % biodegradation and a second study [modified MITI Test (I), OECD TG 301C] resulted in 0 % biodegradation after 28 days. The substance is not readily biodegradable under aerobic conditions. A Mackay level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that the substance will distribute mainly to the soil (74.4 %) and sediment (19.5 %) compartments with minor distribution to the water compartment (6.1 %) and negligible amount in the air compartment. If released only to the air compartment, the substance will distribute mainly to the soil compartment (93.7 %) with minor distribution to the sediment compartment (4.8 %). If released to water, the substance will distribute mainly to the sediment (76.3 %) and water (23.7 %) compartments. If released to soil the substance stays in the soil compartment (99.9 %) with negligible amounts in other compartments. A calculated Henry's law constant of 1.19×10^{-8} Pa.m³/mole at 25 °C [HENRYWIN v3.20] suggests that volatilization of the substance from the water phase is not expected to be high. A log k_{oc} of 4.64 was estimated [KOCWIN v2.00] and

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indicates a high potential for accumulation in soil.

Although a log K_{ow} of 5.55 was estimated [KOWWIN v1.67], the substance is expected to have some ~~low~~ potential for bioaccumulation in the aquatic environment based on measured bioconcentration factors of 196-802 (0.05 mg/L) and 548-895 (0.005 mg/L) from a study [OECD TG 305C] where common carp (*Cyprinus carpio*) were exposed to the substance for 8-10 weeks at 25 °C.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Danio rerio</i>]	96 h LC ₅₀ > limit of water solubility.
Invertebrate [<i>Daphnia magna</i>]	24 h EC ₅₀ > limit of water solubility.
Algae [<i>Desmodesmus subspicatus</i>]	72 h E _b C ₅₀ > limit of water solubility (area under growth curve method).
Sewage sludge microorganisms	3 h IC ₅₀ > 100 mg/L (nominal)

The following chronic toxicity test results have been determined for aquatic species:

Algae [<i>Desmodesmus subspicatus</i>]	72 h NOE _b C > limit of water solubility

No information was identified concerning toxicity to soil or sediment-dwelling organisms.

Exposure

Annual domestic production and imported amounts in Japan was approximately 10 – 100 tonnes in 2003. Worldwide production volume is not available. The substance is used as a UV absorber for ink, paint, sealant, and plastics (mainly polyolefins and polyesters) used in, for example, building materials and automobile interior parts. It is also used as a UV filter for personal care formulations such as cosmetics and fragrance and is approved for use as an additive in food contact materials in the EU, Japan and US. The amount of the substance used in plastics is up to 0.5 %w/w. The substance may enter the environment at the production site and at chemical industries manufacturing the downstream products. Release to the environment from disposed products is limited due to its low water solubility. Release to the environment via wastewater is possible from its use in personal care products. Occupational exposure to the substance can occur mainly by inhalation and dermal routes at the production and user sites during operations. The atmospheric concentration was measured at one production site in Japan. A maximum concentration of 0.21 mg/m³ was recorded during removal of the product from the centrifuge however operators wear helmets, protective eye goggles and respirators during all operations in order to minimise their exposure to the substance. Consumer exposure to the substance can occur, mainly by the dermal route, through contact with a variety of finished products which contain the mixture. Some oral exposure may occur via migration into food from packaging.

RECOMMENDATIONS and RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

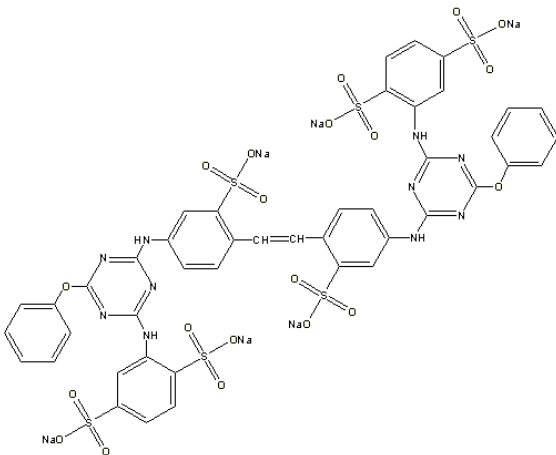
Human Health:

The chemical is currently of low priority for further work. The chemical is currently of low priority for further work because of its low hazard profile.

Environment:

The chemical is a candidate for further work. The chemical is a candidate for further work (not readily biodegradable, some potential for bioaccumulation). Further work recommended is a chronic toxicity study to sediment-dwelling organisms [OECD TG 218] as the sediment is the compartment most likely to be exposed.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	41267-43-0
Chemical Name	1,4-Benzenedisulfonic acid, 2,2'-[1,2-ethenediylbis[(3-sulfo-4,1-phenylene)imino(6-phenoxy-1,3,5-triazine-4,2-diyl)imino]]bis-, hexasodium salt Hereafter referred as "Fluorescent-271"
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

Fluorescent-271 is a pale yellow crystal with a water solubility of > 250 g/L at 20 °C. Both melting point and boiling point are > 300 °C. The estimated partition coefficient between octanol and water (Log K_{ow}) with KOWWIN is -1.27. The measured pressures is < 1.16×10⁻⁵ Pa at 80 °C, and the estimated value of vapour pressure with MPBPWIN is practically negligible.

As the EPISuite program developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for acid dyes, there is uncertainty associated with the calculated values and results should be used with caution.

Human Health

There is no available information on toxicokinetics.

In an acute toxicity study of Fluorescent 271 in rats, the oral LD₅₀ value was considered to be more than 2,000 mg/kg bw in females. No acute inhalation or dermal studies are available for Fluorescent 271.

There are no experimental data on irritation or sensitisation.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), rats were given Fluorescent 271 by gavage at 0, 20, 60, or 200 mg/kg bw/day. Males were dosed for a total of 43 days beginning 14 days before mating and females were dosed for 41-55 days beginning 14 days before mating to day 4 of lactation throughout the mating and pregnancy period. There were no deaths related to the treatment. No changes caused by the test substance were observed in general conditions, detailed clinical observations, sensory/reflex test, measurements of grip strength or motor activity. Body weights and food

consumption were decreased in both sexes receiving 200 mg/kg. Effects on the kidneys included pale coloring at 60 mg/kg or more, and enlargement and increase in kidney weights were observed at 200 mg/kg in both sexes. Histological evaluation revealed vacuolar degeneration of proximal tubules in both sexes in all treatment groups. With 200 mg/kg, anemia and changes in blood chemistry and urinalysis were considered to be effects related to the renal component in both sexes. At the end of the recovery period, clinical changes were more pronounced than at the end of the administration period. However, on histological evaluation, regeneration of renal tubules was apparent in the cortex. Therefore, it was concluded that the renal effects were corrected during the recovery period. A NOAEL value cannot be derived from the study. The LOAEL for repeated dose oral toxicity is considered to be 20 mg/kg bw/day for both sexes

The test substance did not induce gene mutations in a bacterial *in vitro* test, but significant positive result in chromosomal aberration test without metabolic activation was obtained at the highest concentration (5000ug/ml) after short-term (6 h) treatment. The concentration was much higher than the concentrations (625-1250ug/ml) causing cytotoxicity during long-term (24 h) treatment. The positive response in short-term treatment might be associated with cytotoxicity at the long-term treatment. Since an *in vitro* mutagenicity test is negative and an *in vitro* clastogenicity test is positive, further *in vivo* testing would help clarify the genotoxic property.

There is no available information on carcinogenicity.

In the above mentioned combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), histological evaluation revealed vacuolar degeneration of proximal tubules in both sexes in all treatment groups. The LOAEL of maternal toxicity was considered to be 20 mg/kg bw/day. Histopathological examinations of the testes, epididymides and ovaries revealed no toxicological changes. No treatment-related adverse effects on reproductive parameters, including estrous cycle, copulation index, fertility index, gestation length, numbers of corpora lutea and implantations, gestation index, implantation index, and delivery index were observed. Lowered body weights of pups were observed on day 0 of lactation in the 200 mg/kg bw/day group, but no treatment-related adverse effects on other offspring viability parameters, such as number of live pups on day 0 of lactation, birth index (number of live pups on day 0/number of implantation sites x 100), live birth index (number of live pups on day 0/number of pups born x 100), sex ratio of pups on day 0 of lactation, number of live pups on day 4 of lactation, viability of pups on day 4 of lactation, pups weight on day 4 of lactation, sex ratio of pups on day 4 of lactation, or external or visceral anomalies were detected. Based on these findings, the NOAEL for reproductive toxicity is considered to be 200 mg/kg bw/day (highest dose tested), and the NOAEL for developmental toxicity is considered to be 60 mg/kg bw/day because of lower body weight of pups on day 0 of lactation in the 200 mg/kg bw/day.

Environment

Sodium ions are dissociated from sulfonate groups of Fluorescent-271 in water. Anion part of Fluorescent-271 is stable in water as hydrolysis test according to OECD test-guideline 111 showed no hydrolysis at pH 4, pH 7 and pH 9 at 50 °C for 5 days. Fluorescent-271 is not readily biodegradable under aerobic conditions after 4 weeks cultivation period according to OECD Guideline 301C. Bioaccumulation potential of Fluorescent-271 seems to be low based on the low Log K_{ow} and the size of molecule. In the atmosphere, indirect photo-oxidation of Fluorescent-271 by reaction with hydroxyl radicals is estimated to result in a half-life of 0.87 hours with AOPWIN. However, the photo-degradation process in the air may not be an important process according to the very low vapour pressure of Fluorescent-271. As AOPWIN has not been validated for acid dyes, this result should be used with caution.

Level III fugacity model with EPISuite shows that if Fluorescent-271 is released simultaneously to air, soil and water, this chemical is mainly distributed in the water compartment (59.5 %) and soil compartment (40.3 %) with negligible amounts in air and sediment compartment. According to the high water solubility and low vapour pressure, the Henry's law constant of Fluorescent-271 is estimated to be very low, which means that volatilization of Fluorescent-271 from the water phase is expected to be negligible.

The following acute toxicity test results have been determined for aquatic species:

Fish	<i>Oryzias latipes</i> (OECD-TG-203):	96h-LC ₅₀ >	100 mg/L (measured)
Invertebrate	<i>Daphnia magna</i> (OECD-TG-202):	48h-EC ₅₀ >	97 mg/L (measured)

Algae	<i>Pseudokirchneriella subcapitata</i> (OECD-TG-201): 72h-ErC ₅₀ > 23 mg/L (growth rate / measured)
Algae	<i>Pseudokirchneriella subcapitata</i> (OECD-TG-201): 72h-EbC ₅₀ > 23 mg/L (area under growth curve method / nominal)

The following chronic toxicity test results have been determined:

Invertebrate	<i>Daphnia magna</i> (OECD-TG-211): 21d-NOEC (reproduction) = 17 mg/L (measured)
Algae	<i>Pseudokirchneriella subcapitata</i> (OECD-TG-201): 72h-NOErC = 8.6 mg/L (growth rate / measured)
Algae	<i>Pseudokirchneriella subcapitata</i> (OECD-TG-201): 72h-NOEbC = 8.6 mg/L (area under growth curve method / measured)

Exposure

Although Fluorescent-271 used to be manufactured in the sponsor country, currently only import is conducted. Annual volume of import into the sponsor country was 100 – 1000 tonnes in fiscal year 2007. Worldwide production volume is not available.

As Fluorescent-271 is not manufactured in the sponsor country, no detailed information of the production method is available. 4,4'-Dinitrostilbene-2,2'-disulfonic acid may be a starting substance for the production process, and this substance may be reacted with cyanuric chloride to produce Fluorescent-271. Fluorescent-271 is used as a whitening agent for paper manufacturing in the sponsor country. No other information on the use pattern is obtained.

As Fluorescent-271 has high water solubility and low vapour pressure, water compartment is the main target if Fluorescent-271 is released from industrial sites. No information is available to what extent the Fluorescent-271 can be released during paper manufacturing process. However, as all application processes are conducted in a closed system in the sponsor country, no significant emissions into the environment is foreseen. In general highest emissions for paper additives are expected during paper recycling. No data on emission during paper recycling for Fluorescent-271 are available.

From physical-chemical data of Fluorescent-271, main occupational exposure route is inhalation of dust, and dermal intake may be negligible. However, occupational exposure may not be significant as Fluorescent-271 is used in the closed system.

As Fluorescent-271 is used as a whitening agent in paper, consumers may be exposed by the residue of Fluorescent-271 on the surface of paper when they contact. However, no information is available on the residue of Fluorescent-271 on the paper, what extent Fluorescent-271 is bounded to the paper or to what extent Fluorescent-271 can be released.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses a hazard for human health (repeated dose toxicity on the kidney, in vitro clastogenicity). No information is available for occupational exposure in industries using the chemical nor for indirect human exposure by the residues in papers in the sponsor country. Member countries are invited to perform an exposure assessment for workers and consumers and if necessary a risk assessment. In vivo genotoxicity testing should be conducted as post-SIAM work to clarify the genotoxic potential.

Environment: This chemical is currently of low priority for further work because of its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	544-92-3
Chemical Name	Copper (I) cyanide
Structural Formula	$\text{Cu}^+ \quad \text{C}^{\ominus} \equiv \text{N}$

SUMMARY CONCLUSIONS OF THE SIAR**Physical and chemical properties**

Copper(I) cyanide is an inorganic substance, white to cream-colored powder. Copper (I) cyanide is sparsely soluble in water, depending on pH, salinity and concentrations of ligand species that may form complexes with copper(I). No reliable standard test data on aqueous solubility are available. However, solubility measurements from aquatic toxicity tests indicate that copper(I) cyanide may be soluble in surface water. It has a density of 2.9 g/cm³ and a melting point of 474°C. Upon introduction in water the salt will slowly dissociate and release copper and cyanide ions in solution. CN⁻ ions may transform to HCN depending on the pH of the water. The pK_a of HCN is 9.36. Copper(I) may be oxidised to copper(II) under oxidizing conditions in the environment. Vapor pressure and partition coefficient in n-octanol/water are not applicable for the salt of an inorganic substance. Copper(I) cyanide decomposes before boiling.

Human Health

There are no studies available for toxicokinetics, metabolism and distribution of copper cyanide.

In an acute oral toxicity study[OECD TG 423], 3 groups of 3 female rats received doses of 300 and 2000 mg/kg bw via oral application. The oral LD₅₀ value of copper (I) cyanide by single oral administration was range from 300 to 2,000 mg/kg bw for female rats. The substance caused subdued behaviour, soiled perineal region, soft feces and liquid feces were observed in all animals of the treatment groups.

No reliable skin/eye irritation and skin sensitization studies are available.

In a repeated dose oral toxicity study in rats [OECD TG 422], copper (I)cyanide was administered via gavage to male rats at 0, 4, 16, and 64 mg/kg bw/day, from 2 weeks before mating to the end of the mating period (at least 28 days) and to female rats at 0, 4, 16, and 64 mg/kg bw/day, from 2 weeks before mating to day 4 of lactation including the mating and gestation periods. No death was observed in either sex. A decrease in body weight and food consumption were observed in both sexes of the 64 mg/kg bw/day group. In hematology test, decrease of RBC count, hemoglobin and hematocrit, increase of mean corpuscular hemoglobin and reticulocyte were observed in female at 64mg/kg bw/day. Also, female rats at 64 mg/kg bw/day showed significant decrease in absolute weights of uterus and heart and an increase in absolute and relative weights of spleen and relative weight of lung and extramedullary hemopoiesis in liver and spleen, and increased hemopoiesis in femur/marrow and sternum/marrow. These findings were recovered or alleviated during the recovery period. The recovery animals were maintained undosed for 15 days for males and 16 days for females. There is no significant effects in 4 and 16 mg/kg bw/day. There is also no dose-related changes of neurobehavioral in all treatment groups and of urinalysis in any groups of males. From these results, target organs for oral dosing of copper cyanide were considered as spleen, femur/marrow and sternum/marrow. A treatment-related decrease in weight of salivary gland observed in males of the 16 and 64 mg/kg bw/day groups was not considered to be toxicological significance, since no treatment-related change was found in histopathological examination. Based on these effects, the NOAEL for repeated dose oral toxicity was 16 mg/kg bw/day for male and female rats and the LOAEL for repeated dose oral toxicity was 64 mg/kg bw/day for male and female rats. In a 90-day subchronic study, rats (20/sex/group) were administered by gavage at 0, 0.5, 5, 15 and 50 mg/kg/day copper cyanide in a 1.5% carboxymethylcellulose vehicle. As a result of this test, the NOAEL of 5mg/kg bw/day and LOAEL of 15mg/kg bw/day could be considered based on decreased body and organ weights in

both sexes and histopathological alterations in liver and kidney in females.

In a bacterial reverse mutation assay [OECD TG 471], copper (I) cyanide was negative both with and without metabolic activation. An *in vitro* test chromosome aberration test [OECD TG 473] using Chinese hamster lung cells (CHL) was negative with and without metabolic activation. There was no data of *in vivo* test with copper (I) cyanide.

No data are available for the carcinogenicity of copper (I) cyanide.

In reproductive and developmental toxicity study performed according to combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], copper (I) cyanide was administered via gavage to male rats at 0, 4, 16, and 64 mg/kg bw/day, for from 2 weeks before mating to the end of the mating period (at least 28 days) and to female rats at 0, 4, 16, and 64 mg/kg bw/day, for from 2 weeks before mating to day 4 of lactation including the mating and gestation periods. The NOAEL of copper (I) cyanide for fertility toxicity was 64 mg/kg bw/day for the parental animals. No treatment-related effects were observed on the reproductive organs and the fertility parameters (precoital time, mating index, fertility index and pregnancy index). For developmental toxicity, the NOAEL of 64 mg/kg bw/day for F1 pups was the highest dose tested. There were no treatment-related changes in all parameters (gestation length, the number of corpora lutea and implantation etc.) of offsprings during the parturition and lactation periods. And in developmental toxicity, fetuses were not examined for internal and skeletal malformations/anomalies

Environment

The concept of degradability and biodegradability is not applicable to metal-containing inorganic substances like Copper(I) cyanide. The hydrosis study is not applicable for copper(I) cyanide. The fugacity model is of limited use to inorganic substances therefore environmental fate model was not performed. No data were available for bioaccumulation of copper(I) cyanide. Cyanide is not expected to bioaccumulate due to rapid degradation. Copper is an essential micronutrient and will bioconcentrate at low environmental concentrations. However, bioconcentration decreases with increasing environmental concentration.

Acute aquatic toxicity tests of copper(I) cyanide were conducted according to [OECD TG 201, 202, 203] for fish, daphnia and algae. Analytical monitoring was performed using ICP-AES. The analytical measurements were made on copper which was back calculated to copper cyanide.

The acute toxicity results from studies with aquatic organisms are as follows:

Fish (<i>Oryzias latipes</i>) :	LC ₅₀ (96h) = 0.62 mg/L(measured)
Invertebrates (<i>Daphnia magna</i>) :	EC ₅₀ (48h) = 0.21 mg/L(measured)
Green algae (<i>Pseudokirchneriella subcapitata</i>) :	EC ₅₀ (72h) = 0.0891 mg/L(growth rate method) (measured)
	EC ₅₀ (72h) = 0.0409mg/L mg/L(yield method) (measured)
	NOEC(72h) = 0.018mg/L(growth rate method) (measured)

No data are available on terrestrial organisms.

Exposure

In the Sponsor Country, the estimated production volume of Copper(I) cyanide was aprox.4,516, 4,755, and 3,905 tons in 2005, 2006, and 2007, respectively. Aprox. 2,500 tons of produced Copper(I) cyanide in the Republic of Korea was exported abroad in 2007. Copper(I) cyanide is not imported in the Republic of Korea. In Nordic countries the estimated production volume of this chemical was 17, 10, and 0.8 tons in 2003, 2004, and 2005, respectively. In the Republic of Korea, Copper(I) cyanide is mainly used in electroplating of copper, partially in alkali-Cu plating and brass plating. In the Sponsor Country, Copper(I) cyanide is produced in a closed system. After production of Copper(I) cyanide, remaining raw materials are reused in the other process like reacting with HCl. Wastewater is treated in the facilities physically or chemically and then it is discharged to wastewater treatment plant. No data are available for monitoring in air and waste water. But the measured concentration of copper in treated waste water was approximately 0.7ppm.

Workers could be exposed potentially to dusts of Copper(I) cyanide in the packing process. To protect workers from exposure, the appropriate personal protective equipment such as dust masks, gloves, and protective clothing were provided and workplaces were managed by safe work practices. The measured concentration of dusts in the packaging process was 0.69mg/m³, which was below the occupational exposure limit of 10mg/m³. In the Copper(I) cyanide reaction process, the measured concentration of NaCl and HCl was 0.1594 and 0.0127mg/m³, which was

below the occupational exposure limit of 5mg/m³ and 7.5mg/m³, respectively.

In the Republic of Korea Copper(I) cyanide is used only industrially so that consumer exposure is not expected in the sponsor country.

**RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE
OF FURTHER WORK RECOMMENDED**

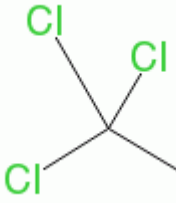
Human Health :

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (acute toxicity, and repeated dose toxicity). Based on the exposure data presented by the Sponsor country (production in a closed system and use only industrially), exposure to humans is anticipated to be low. Countries may desire to investigate any exposure scenario like uses as an insecticide/fungicide that were not presented by the Sponsor country.

Environment :

The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity in fish, daphnia and algae below 1 mg/L). Member countries are invited to perform an exposure assessment and if necessary a risk assessment. Consideration should be given to the assessment of other copper compounds in the OECD HPV chemical program.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	71-55-6
Chemical Name	1,1,1-Trichloroethane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

1,1,1-Trichloroethane is a clear/colourless liquid at room temperature with a melting point of -30.4°C, a boiling point of 74°C and a measured vapour pressure of 13,300 Pa at 20°C. The measured octanol-water partition coefficient (log K_{ow}) is 2.47, and the water solubility is 300 mg/L at 25°C.

Human Health

Experiments with animals and humans have demonstrated that the toxicokinetic behaviour of 1,1,1-trichloroethane has the same qualitative pattern in human, rats and mice, with some quantitative differences among the species. 1,1,1-Trichloroethane is rapidly absorbed by the lung, skin, and gastrointestinal tract, and distributed by the blood to tissues and organs throughout the body, including to developing fetuses, with preferential distribution to fatty tissues. The predominant pathway of elimination of 1,1,1-trichloroethane is exhalation of the unchanged compound. When exposure ceases, the compound is rapidly cleared from the body. In both animals and humans, a small amount (< 10%) of 1,1,1-trichloroethane is metabolized to trichloroethanol and trichloroacetic acid; these metabolites are excreted in the urine, and other minor metabolites (carbon dioxide and acetylene) are excreted in expired air.

The 3-hr inhalation LC_{50} for rats was 18,000 ppm (98.3 mg/L) and the 7-hr LC_{50} was 14,250 ppm (77.8 mg/L). The principal toxic effects were depression of the central nervous system. Marked changes were seen at necropsy in the liver (hepatocellular damage, liver necrosis, enzyme activity changes, and accumulation of fat in the liver). Other acute inhalation studies show similar results. The dermal LD_{50} [OECD TG 402] was > 2000 mg/kg bw in rats. Examination of the animals revealed an increased incidence of swollen livers. In an OECD TG 401 study, the oral LD_{50} was > 2000 mg/kg bw in rats. Clinical signs were indicative of effects on the autonomic nervous system, the central nervous system, motor-coordination, motor activity and on muscle tone. Macroscopic examination revealed swollen livers and microscopic examination revealed an increase in the incidence of hydropic degeneration of the hepatocytes and cloudy swelling of the renal tubular epithelium. Available human data indicate that the central nervous system is the most sensitive target for 1,1,1-trichloroethane toxicity. Exposure of 1,1,1-trichloroethane resulted in cardiac sensitization to adrenaline. Increases in concentration and duration of exposure were accompanied by a decrease in the amount of adrenaline needed to induce arrhythmia. 1,1,1-Trichloroethane is potentially toxic to the cardiovascular system by sensitizing the heart to adrenaline. Based on the effects noted in dogs and a limited number of humans, there is a potential for adverse cardiac effects following high exposures to 1,1,1-trichloroethane.

1,1,1-Trichloroethane is irritating to rabbit skin. 1,1,1-Trichloroethane is slightly irritating to the eyes of rabbits causing slight to moderate pain, slight conjunctival irritation but essentially no corneal damage. Any initial irritation disappeared within a few days. 1,1,1-Trichloroethane is irritating to human skin. The irritation increased from mild to chemical burns as exposure duration increases however, these effects are reversible. 1,1,1-Trichloroethane was mildly irritating to human eyes (most likely due to direct contact with the eye) when individuals were briefly exposed to high vapour concentrations. 1,1,1-Trichloroethane may have the potential for respiratory tract irritation.

No experimental data are available for skin sensitization in animals.

The repeated-dose toxicity of the 1,1,1-trichloroethane has been investigated in several inhalation and a few oral studies. In a repeated-dose inhalation toxicity study the substance was administered to male mice (160/concentration) via whole body exposures at 0, 1.37, or 5.46 mg/L/day, continuously for 14 weeks. No deaths were observed in either sex. This study identified a NOAEL of 1.37 mg/L/day and LOAEL of 5.46 mg/L/day for liver effects in mice with continuous exposure. In a repeated-dose oral toxicity study in mice, 1,1,1-trichloroethane was administered via microencapsulation to 10 animals/sex/dose at 0, 850, 1750, 3500, 7370, and 15,000 mg/kg bw/day (males) and 0, 1340, 2820, 5600, 11,125, and 23,000 mg/kg bw/day (females), for 7 days/week for 13 weeks. No deaths were observed in either sex. The males exhibited decreased epididymal sperm counts at the highest dose. The National Toxicology Program estimated the doses of 1750 mg/kg bw/day (males) and 2,820 mg/kg bw/day (females) to represent NOAELs. LOAELs were 3500 and 5600 mg/kg-bw/day in males and females, respectively based on reduced body weights. In a repeated dose oral toxicity study in rats, 1,1,1-trichloroethane was administered via microencapsulation to 10 animals/sex/dose at 0, 300, 600, 1200, 2400, and 4800 mg/kg bw/day (males) and 0, 300, 650, 1250, 2500, and 5,000 mg/kg-bw/day (females), for 7 days/week for 13 weeks. No death was observed in either sex. The final mean body weight and body weight gain of females at 1250 mg/kg bw/day were significantly less than those of the untreated controls. The final mean body weights and body weight gains of males at 2400 mg/kg bw/day (and higher) and the final mean body weight of females at 5000 mg/kg bw/day were significantly less than the vehicle controls. There was no decrease seen in final mean body weight or body weight gain for the 2500 mg/kg bw females compared to untreated or vehicle controls. The liver weights of female rats administered 5000 mg/kg bw/day were statistically significantly decreased. Male rats exposed to 1200 mg/kg bw/day or greater had a spectrum of non-neoplastic kidney lesions consistent with hyaline droplet nephropathy. At the highest dose, males also had lower sperm numbers in the epididymis. No treatment-related gross or microscopic lesions were observed in female rats. The NOAELs were estimated to be 2400 and 2500 mg/kg-bw/day in males and females, respectively. The LOAELs were 4800 and 5000 mg/kg-bw/day in males and females, respectively based on decreased liver weights in females and decreased epididymal sperm counts in males. Neurobehavioural effects have been observed in some epidemiological studies in humans.

In a subchronic neurotoxicity study, Fischer 344 rats were exposed to 200, 600, or 2000 ppm 1,1,1-trichloroethane via inhalation for 6 hour/day, 5 days/week, for 13 weeks. Rats were clinically examined regularly and were given a functional observational battery monthly (FOB, including forelimb and hindlimb grip performance testing). At the end of exposure, the rats were evaluated by FOB and by visual, auditory, somatosensory, and caudal nerve-evoked potentials. There were no post-exposure treatment-related findings in any parameters except for a slightly smaller forelimb grip performance in the 2000 ppm group. The toxic significance of this finding is unclear. There was also a lack of findings in any other clinical, evoked potential or morphologic parameter.

Available human and animal data indicate that the central nervous system is the most sensitive target for 1,1,1-trichloroethane toxicity. Clinical signs of toxicity associated with human exposure to large quantities of 1,1,1-trichloroethane include central nervous system depression, hypotension, cardiac arrhythmia, diarrhea and vomiting, mild hepatic effects, and dermal and ocular irritation. Lower-level exposure to 1,1,1-trichloroethane may result in more subtle neurological effects such as impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time.

In bacterial reverse mutation assays with multiple strains of *Salmonella typhimurium* /*E. coli*, 1,1,1-trichloroethane was negative both with and without metabolic activation in open systems but was positive when tested in closed systems. In an *in vitro* mouse lymphoma assay with L5178Y cells, 1,1,1-trichloroethane was negative with and without metabolic activation at one laboratory, and an equivocal (weakly positive) response was obtained at the second laboratory in the presence of metabolic activation only); 1,1,1-trichloroethane was not considered mutagenic in this test. In an *in vitro* chromosomal aberration test using CHO cells in the presence and absence of metabolic activation, 1,1,1-trichloroethane was positive without metabolic activation. In a sister chromatid exchange (SCE) assay with CHO cells, 1,1,1-trichloroethane was considered to be equivocal both with and without metabolic activation systems. In several *in vivo* micronucleus assays conducted in mice using oral, inhalation or intraperitoneal exposure, 1,1,1-trichloroethane was negative up to the maximum tolerated dose. In an oral multi-generation reproduction study modified to include screening for dominant lethal effects in mice, no effects on reproductive function or performance were observed. Overall, gene mutation studies conducted *in vitro* and micronucleus studies conducted *in vivo* showed no evidence of potential genotoxicity.

Exposure to 1,1,1-trichloroethane was not associated with treatment-related increases in tumour incidence in most studies in mice or rats exposed by inhalation or oral (gavage) routes of exposure, although high mortality and less than lifetime exposure in some studies limited the ability to make firm conclusions about

carcinogenicity. Most studies in humans did not find associations with cancers although some association has been found between 1,1,1-trichloroethane and multiple myelomas or cancers of the nervous system. The United States Environmental Protection Agency has concluded that the database is inconclusive as to the carcinogenicity of 1,1,1-trichloroethane in humans.

The reproductive toxicity of the 1,1,1-trichloroethane has been well investigated in several studies. In a two generation study in mice, 1,1,1-trichloroethane was administered via drinking water to 30 female and 10 male animals/dose at 0, 100, 300, or 1000 mg/kg bw/day, for 5 weeks prior to mating and throughout gestation and lactation of the F1a litters. At 2 weeks post-weaning of the F1a litters, the F0 adults were re-mated to produce F1b litters. At 2 weeks post-weaning of the F1b litters, the F0 adults were re-mated for teratology screening of F1c pups. The F1b litters were culled to 30 females and 10 males at weaning and placed on test solutions until age 14 weeks when they were mated to produce the F2a litters. At 2 weeks post-weaning of the F2a pups, the F1b adults were re-mated for teratology screening of F2b pups. Adult mortality among the treated and control F0 and F1b generations was sporadic. Among the naïve controls, there was 20% mortality in both sexes in the F0 generation. For the vehicle control, there was 10% and 3.3% mortality among the males and females, respectively, in the F0 generation. Mortality in the F0 generations was 0%, 10%, and 20% among males and 10%, 6.7%, and 13.3% among females exposed at 0.58, 1.75, and 5.83 mg/L, respectively. With the exception of 7.4% rate mortality in the females dosed at 0.58 mg/L, no mortality was observed in F1b generation. The reason for the sporadic incidences of increased mortality could not be discerned at necropsy. No adverse reproductive effects were observed up to the highest dose tested. There were no effects on reproductive function and there was no increase in the incidence of skeletal or visceral malformations in either generation, indicating the NOAEL for reproductive toxicity was 1000 mg/kg bw/day, the highest dose tested. Epididymal sperm counts were decreased at 4,800 mg/kg-bw/day in rats in 13-week dietary studies.

The developmental toxicity of 1,1,1-trichloroethane has also been investigated in several studies. In a standard one generation study in rats, 1,1,1-trichloroethane was administered via inhalation to 30 animals/sex/concentration at 0, 1000, 3000 or 6000 ppm (corresponding to 0, 5.4, 16.4 or 32.8 mg/L), for 6 hours/day on GD 6-15. No deaths were observed. Maternal effects were seen at 32.8 mg/L (hypoactivity, reductions in food consumption, body weight gain, body weight, and gravid uterine weight) and at the two lower doses (reduced body weight gain and reduced food consumption); the NOAEL for maternal toxicity was < 5.4 mg/L. Fetal body weight was significantly reduced only for female fetuses in the 32.8 mg/L group; decreases for male fetuses and all fetuses combined were not statistically significant. No increases in fetal malformations were observed. Effects suggesting slight developmental delay (poorly or unossified cervical centrum) were observed at the high dose. A NOAEL of 16.4 mg/L for mild fetotoxicity demonstrated by developmental delay and decreased body weights of female fetuses were identified in this study. In other inhalation studies, neurobehavioural effects were observed; across studies, effects occurred at 10.9 mg/L or higher. The developmental toxicity of 1,1,1-trichloroethane has been well investigated in oral studies in rats and mice; no toxicologically significant effects have been observed. In humans, epidemiological studies failed to find statistically-significant associations between 1,1,1-trichloroethane and adverse reproductive outcomes.

1,1,1-Trichloroethane may present a hazard for human health (mild skin, eye and respiratory irritation, cardiac sensitization, central nervous system effects, and liver effects (at higher concentrations)). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The measured hydrolysis half-life for this compound is 0.5 to 1 year at 25°C. In the atmosphere, before it reaches the stratosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 3.1 – 3.7 years, assuming a diurnally averaged OH radical concentration of $1.5 \times 10^6 / \text{cm}^{-3}$ or $5 \times 10^5 / \text{cm}^{-3}$, respectively). In the Sponsor country, 1,1,1-trichloroethane has been recognized as an ozone depleting substance. 1,1,1-Trichloroethane has an [ozone depletion potential](#) (ODP) of 0.11 (compared to an ODP of 1.0 for CFC-11; trichlorofluoromethane). An OECD 301 C Ready Biodegradability: Modified MITI Test resulted in 0% biodegradation after 14 days. 1,1,1-Trichloroethane is considered not readily biodegradable under aerobic conditions.

Level III fugacity model with equal and continuous distributions to air, water and soil compartments suggests that 1,1,1-trichloroethane will distribute mainly to the air (46%) and water (45%) compartments with minor distribution to the soil compartment (9%) and negligible amount in the sediments compartment. However, the emission to air only resulted in 99.8 % to air. A Henry

law's constant of 1.62×10^{-2} atm-m³/mole (16.4 hPa-m³/mole) at 25°C suggests that volatilization of 1,1,1-trichloroethane from the water phase is expected to be high.

1,1,1-Trichloroethane is not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor of 9 in *Lepomis macrochirus*; the half-life of 1,1,1-trichloroethane in the tissues (bioelimination) was less than 24 hours after reaching an equilibrium.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Pimephales promelas</i>]:	96 h LC ₅₀ = 52.8 mg/L (measured)
Invertebrate [<i>Daphnia magna</i>]:	48 h LC ₅₀ = 60 mg/L (measured)
Algae [<i>Chlamydomonas reinhardtii</i>]	72 h EC ₅₀ = 0.536 mg/L (measured; biomass)

The following subchronic toxicity test results have been determined for aquatic species:

<i>Cyprinus carpio</i>	14-d, LOEC = 30 mg/L (measured)
	14-d, NOEC = 7.7 mg/L (measured)
<i>Daphnia magna</i>	17-d, LOEC = 2.4 mg/L (measured)
	17-d, NOEC = 1.3 mg/L (measured)

1,1,1-Trichloroethane possesses properties that may present a hazard to the environment (acute toxicity to aquatic organisms < 1 mg/L [algae]). Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

1,1,1-Trichloroethane sales and use are governed under conditions outlined in the Montreal Protocol.

1,1,1-Trichloroethane is commercially produced with an annual production volume of 78,439 tonnes in the United States (2007). 1,1,1-trichloroethane is produced in closed systems. 1,1,1-Trichloroethane is used in the U.S. as feedstock for the production of hydrofluorocarbons and hydrochlorofluorocarbons. Greater than 98% of production used for feedstock use. In addition, developing countries also use 1,1,1-trichloroethane as a solvent in cleaning and adhesive applications; the provisions of the Montreal protocol establish that these uses must be phased out by 2015.

During the production of 1,1,1-trichloroethane, there is no intentional venting of the substance to the atmosphere. Releases of 1,1,1-trichloroethane to the atmosphere have dropped significantly in recent years in the U.S. and were reported to be 26 tonnes (57,299 pounds) based on the 2007 Toxics Release Inventory. Approximately one-half of the amount of 1,1,1-trichloroethane released to the atmosphere was from the sole manufacturer with the other releases occurring from processors or others generating 1,1,1-trichloroethane in various chemical processes. Releases to other media reported in 2007 included 10.9 tonnes (24,111 pounds) released to soil and 0.03 tonnes (69 pounds) released to water. Any fugitive emissions are handled in compliance with US federal regulations (US EPA 40 CFR Part 63, Subpart H which defines a fugitive emissions leak detection and repair program). Any waste generated during the production of 1,1,1-trichloroethane is also handled appropriately according to US federal hazardous waste regulations (US EPA 40 CFR Part 265). Limited emissive uses of 1,1,1-trichloroethane are permitted in some countries only, as allowed by the Montreal Protocol. Engineering controls used in the production of 1,1,1-trichloroethane are subject to US EPA HON (Hazardous Organic National Emission Standards for Hazardous Air Pollutants) MACT (Maximum Achievable Control Technology) standards (40 CFR, Part 63) including venting of process streams and storage tanks to on-site incineration, activated carbon beds or refrigerated condensers, implementation of a Leak Detection and Repair program, and use of a closed purge sampling system. Workers are not exposed to non-accidental releases at the facility level; all exposures are maintained below American Conference of Governmental and Industrial Hygienists Threshold Limit Value. Potential routes of accidental exposures for workers are inhalation and dermal. Consumer exposure is not expected as there is no consumer use for 1,1,1-trichloroethane.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7664-38-2
Chemical Name	Phosphoric acid
Structural Formula	$2\text{H}^+\cdot\text{HPO}_4^{2-}$ $\text{H}^+\cdot\text{H}_2\text{PO}_4^-$

SUMMARY CONCLUSIONS OF THE SIAR

Physical and chemical properties

Phosphoric acid is a colourless crystalline substance with a melting point of 42.4 °C and a boiling point of 260 °C, readily absorbing water to form a clear, syrupy liquid. The vapour pressure is 2.75×10^{-9} Pa at 25 °C. The density is 1.87 g/cm³ at 25 °C and phosphoric acid is completely miscible with water at 20 °C, dissociation constants are pK₁=2.15, pK₂=7.09, pK₃=12.32. A log Kow value for an inorganic compound such as phosphoric acid is not relevant.

Human Health

Phosphoric acid can be absorbed by ingestion, inhalation and dermal contact. Absorbed phosphate is widely distributed in the body. Phosphate is present in plasma and extracellular fluid, in cell membranes and intracellular fluid, and in collagen and bone tissue. In the renal phosphate excretion study, more than 90 % of plasma phosphate is filterable, of which 80 % is actively reabsorbed. Phosphate excreted in the urine represents the difference between the amount filtered and that reabsorbed.

An acute inhalation toxicity study was carried out in male rabbits, rats, mice and guinea pigs, exposed for 1 h. to smoke generated from pure unformulated red phosphorus ignited in an air stream. The target concentrations of smoke ranged from 111 to 6,731 mg/m³ as phosphoric acid. Expressed as phosphoric acid, the inhalation LC₅₀ values were 5,337 mg/m³ (rabbit), 3,846 mg/m³ (rat), 856 mg/m³ (mouse) and 193 mg/m³ (guinea pig). Based on 1h-LC₅₀ values, there was a marked species difference in susceptibility to smokes generated from pure red phosphorus. To assess the acute oral toxicity, female rats were gavaged with phosphoric acid at 300 and 2000 mg/kg (6 animals per dose). Among the 6 rats at dose of 2000 mg/kg, 4 cases of salivation, 3 cases of staining around mouth and 2 cases of lacrimation were observed on day 0. On day 1 each one case of staining around mouth and vaginal discharge were observed. No clinical signs were observed in rats treated with 300 mg/kg of the test article. Based on the results, 3 out of 6 rats died by a single oral administration of 2,000 mg/kg phosphoric acid, the acute oral LD₅₀ was approximately 2000 mg/kg bw in rat [OECD TG 423]. The dermal LD₅₀ value was 1,260 mg/kg bw for rabbit (85 % phosphoric acid). The acute toxicity studies suggest high inhalation toxicity to mice and guinea pigs, moderate inhalation toxicity to rats and rabbits and low oral and dermal toxicity.

In general, phosphoric acid solutions of pH < 2.5 should be regarded as corrosive. However, there is conflicting information from non standard studies, which indicates that solutions of 75- 85% are corrosive in skin irritation tests in rabbits following 24-hour exposure under semi-occlusion, but in the same study, 75% and 80% phosphoric acid solutions were non-corrosive after 4-hour exposure. Concentrated phosphoric acid will be corrosive to the eyes. Phosphoric acid (10 % and 17 % in water) caused mild eye irritation in rabbits. In acute inhalation toxicity studies in laboratory animals, phosphoric acid has caused irritation of the respiratory tract.

There were no reliable sensitization studies available.

The repeated dose toxicity of the phosphoric acid has been investigated. In a repeated dose oral toxicity study in rats [OECD TG 422], the substance was administered via gavage to 13 of animals/sex/dose, concentration at 0, 125, 250 and 500 mg/kg bw/day, for 2 weeks. Toxicological changes of the test substance for all males and females were not observed in less than 250 mg/kg. However, two dead females in the 500 mg/kg treatment group were observed, and findings of gaseous distension of gastrointestinal tract were observed. Also, mucous stool, soft stool, and dirty nose were observed in one male of the 500 mg/kg treatment group. Therefore, NOAEL for

repeated dose toxicity was determined at 250 mg/kg in all males and females.

In an *in vitro* bacterial reverse mutation tests, phosphoric acid was negative both with and without metabolic activation in multiple strains of *Salmonella typhimurium* [OECD TG 471]. In a chromosomal aberration test, phosphoric acid did not exhibit clastogenic effects in with or without metabolic activation. Based on these results, phosphoric acid is considered to be non genotoxic *in vitro* [OECD TG 473]. No *in vivo* genotoxicity studies were available.

There was no available data for carcinogenic activity.

The reproductive toxicity of phosphoric acid has been investigated in a reproductive and developmental toxicity screening test in rats [OECD TG 422]. In this study, phosphoric acid was administered via gavage to 13 of animals/sex/dose, concentration at 0, 125, 250 and 500 mg/kg bw/day, for 2 weeks. Based on results of reproductive and development toxicity, no treatment-related effects were observed. At 500 mg/kg bw/day, 2/13 adult females died, indicating parental toxicity at this dose. No effects of test substance were observed on mating, conception, parturition and external of neonates, neonate body weights, and survival rate. Therefore, NOAEL for reproductive and development toxicity was estimated to be 500 mg/kg bw/day, the highest dose tested.

Environment

Photodegradation and distribution modelling for phosphoric acid was not conducted. Phosphoric acid dissociates in water; therefore, a standard hydrolysis study is not relevant. Standard biodegradation tests are not applicable to inorganic substances. Bioaccumulation is not anticipated for inorganic compounds that are miscible with water such as phosphoric acid. This substance has an important eutrophication potential similar to that of inorganic phosphate.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Oryzias latipes*]

96 h LC₅₀ = 75.1 mg/L (measured) without pH adjustment [pH 3.39- 4.45]

Invertebrate [*Daphnia magna*]

48 h EC₅₀ > 376 mg/L (measured) with pH adjustment [pH 7.53 - 7.95]

Algae [*Pseudokirchneriella subcapitata*]

72 h EC₅₀ = 77.9 mg/L (growth rate, measured) without pH adjustment [pH 3.40 - 5.61]

72 h EC₅₀ = 32.0 mg/L (Biomass, measured) without pH adjustment [pH 5.61 - 7.48]

The observed toxicity presented by phosphoric acid for the environment was considered a result of pH effects.

Exposure

In the Republic of Korea, the production, use and import volume was 359,967, 442,152 and 35,312 tonnes in 2006, respectively. Phosphoric acid used for fertilizers, pH-regulating agents, surface-active agents, anti-freezing agents, absorbents and adsorbents in the sponsor country.

Phosphoric acid is not directly found in nature but it exists as phosphate form in phosphate rock. No Toxics Release Inventory (TRI) data are available in the sponsor country. Phosphoric acid could be released into occupational environment during manufacturing processes. According to monitoring data in the workplaces, the 8hr-Time Weighted Average concentrations of phosphoric acid was 0.002 mg/m³, which was below the occupational exposure limit of 1 mg/m³ in the Republic of Korea. The dust containing phosphoric acid in production and processing sites is controlled by ventilation systems and PPEs (personal protective equipments) in the Republic of Korea. Occupational exposure is considered to be minimal in the sponsor country.

The general public may be exposed to small quantities of phosphoric acid in the consumption of food and soft drinks and by using some cleaning agents.

**RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF
FURTHER WORK RECOMMENDED**

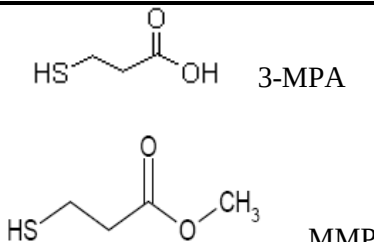
Human Health

This chemical is of low priority for further work. The chemical possesses properties indicating a hazard for human health (acute toxicity to respiratory tract, corrosivity to skin and eye, and moderate repeated dose toxicity). Based on exposure data presented by the Sponsor country exposure to human is expected to be minimal. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment

Phosphoric acid is currently of low priority for further work. Phosphoric acid has properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/l). However, the hazard does not warrant further work as it is related to pH effects. Phosphate has indirect long term effect on the ecosystems due to eutrophication.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Mercapto esters Category
Chemical Names	3-Mercaptopropanoic acid (3-MPA) (CAS No. 107-96-0) 3-Mercaptopropanoic acid methyl ester (MMP) (CAS No. 2935-90-2)
Structural Formula	 <chem>SCCC(=O)O</chem> 3-MPA <chem>SCCC(=O)OC</chem> MMP

SUMMARY CONCLUSIONS OF THE SIAR**Category Rationale**

MMP and 3-MPA are grouped together as a category for human health endpoints based on their structural, physico-chemical and toxicological similarities. Carboxylesterases are ubiquitous enzymes present in many cells (for example, kidney, liver, skin and lung). The metabolic conversion of various acrylates (structurally similar to MMP) to acrylic acid by carboxylesterases has been demonstrated *in vitro* and *in vivo*. MMP is expected to metabolize rapidly to 3-MPA and one mole of methanol (CAS 67-56-1; methanol was previously assessed under the OECD HPV Chemicals Programme-SIAM 19) by carboxylesterases present in multiple species including mammalian species. Thus, data developed on MMP are expected to reflect the toxicity profile for either chemical. The category approach has not been used for the aquatic toxicity endpoints.

Physical-chemical Properties

3-MPA is a liquid with a melting point of 16.8 °C, a measured boiling point of ca. 197 °C and a measured vapour pressure of 0.063 hPa at 25 °C. The measured octanol-water partition coefficient (log K_{ow}) is 0.43, and the measured water solubility is > 603.7 g/L at 22 °C. MMP is a liquid with a measured melting point of <-69 °C, a measured boiling point of 162.8 - 171.5 °C and a measured vapour pressure of 2.86 hPa at 25 °C. The measured octanol-water partition coefficient (log K_{ow}) is 0.9, and the measured water solubility is 21 g/L at 20 °C. The dissociation constant (pKa) for 3-MPA is 4.34.

Human Health

Toxicokinetics data are not available for MMP and 3-MPA. Both MMP and 3-MPA are expected to be well absorbed via all routes of exposure and excreted rapidly because they are highly water-soluble liquids with low molecular weights. The absorbed MMP is expected to metabolize rapidly to 3-MPA by carboxylesterases present in mammalian species. 3-MPA and any unhydrolyzed MMP would be excreted via the urine.

The 4-hour LC_{50} for aerosolized 3-MPA in rats was determined to be approximately 1.81 mg/L (OECD TG 403). All exposure concentrations caused pronounced irritant effects in the upper respiratory tract (nose) including necrosis in the nose and difficult breathing and central nervous system effects including convulsions and tremors. The 4-hour LC_{50} for MMP vapour in rats was 430 ppm (2.11 mg/L) (similar to OECD TG 403). Clinical signs observed in animals that survived included piloerection and hunched posture. The 4-hour inhalation LC_{50} of MMP in rats was 1.80 mg/L (similar to OECD TG 403). Clinical signs at the four highest concentrations (>1.63 mg/L) included tremors, a

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languid appearance, convulsions, laboured respiration and squinted eyes. At necropsy, abnormal findings were seen in the lungs at the three highest dose groups and in the liver in the two highest groups.

The dermal LD₅₀ for MMP in rabbits was 1905 mg/kg bw (similar to OECD TG 402). Clinical signs included depression, laboured respiration, cyanotic appearance, anorexia, and tremors. Erythema ranged from very slight to well-defined, but had mostly cleared by day 7. Necrosis was noted in one male and one female. The only finding at necropsy was dark red lungs in a single female animal that was found dead.

The oral LD₅₀ for 3-MPA in rats was 120 mg/kg bw. There were no signs other than death in this acute oral toxicity study. The oral LD₅₀ for MMP in rats was 194 mg/kg bw (similar to OECD TG 401). Clinical signs included rough coat, depression, salivation, soft feces, urine stains, red stains on the nose and/or eyes, ataxia, convulsions, phonation, tremors, prostration and laboured respiration. Gross pathological findings noted in rats found dead included dark red lungs, compound-like material in the stomach and/or intestines and reddish fluid in the intestines.

3-MPA is corrosive to rabbit skin and an *in vitro* test has demonstrated its potential to be corrosive to human skin; 3-MPA is a severe eye irritant. In the acute dermal toxicity assay, MMP produced erythema ranging from very slight to well-defined irritation and necrosis. 3-MPA and MMP produced signs of respiratory irritation in acute 4-hour inhalation toxicity studies. Labored breathing, nasal discharge and reddened/swollen nose were observed during exposure.

No valid experimental data for 3-MPA or MMP are available for skin sensitisation in animals.

The repeated dose toxicity of one category member (MMP) has been investigated in one study. In a combined oral repeated-dose/reproductive/developmental toxicity screening study following OECD TG 422, MMP was administered via gavage to 10 rats/sex/dose at 0, 25 50 and 100 mg/kg bw/day. Exposure duration in males was at least 28 days. Females were exposed for 14 days prior to mating and through mating and gestation until day 4 post partum. Minimal to slight hyperplasia of the forestomach squamous epithelium, minimal to slight hyperkeratosis and minimal inflammatory cell infiltrations were recorded at 100 mg/kg bw/day. The observed effects were related to the corrosive properties of the test substance. Therefore, the NOAEL and LOAEL for local effects were considered to be 50 and 100 mg/kg bw/day. The NOAEL for systemic effects was 100 mg/kg bw/day (highest dose tested). These data are expected to be representative of 3-MPA.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium* (similar to OECD TG 471), MMP was negative both with and without metabolic activation. In mammalian cell gene mutation assays with L5178Y mouse lymphoma cells, exposure to MMP and 3-MPA (similar to or equivalent to OECD TG 476, respectively) in the presence and absence of metabolic activation did not induce dose-dependent increases in mutation frequency. In *in vitro* chromosomal aberration tests (OECD 473) both with and without metabolic activation, 3-MPA did not induce chromosomal aberrations in human lymphocytes and MMP did not induce chromosomal aberrations in Chinese hamster V79 cells. MMP induced sister chromatid exchanges (SCE; similar to OECD TG 479) in Chinese hamster ovary cells in the presence and absence of metabolic activation. Although SCE were induced in the presence and absence of metabolic activation by MMP *in vitro*, based on the consistent lack of genotoxicity in *in vitro* bacterial and mammalian test system 3-MPA and MMP are considered to be non genotoxic *in vitro*.

No data are available on the evaluation of the carcinogenicity of 3-MPA or MMP.

In the repeated-dose/reproductive/developmental toxicity screening test described above (OECD TG 422), systemic toxicity in parents was seen at 100 mg/kg bw/day. The NOAEL for reproductive/developmental toxicity was considered to be 100 mg/kg bw/day, the highest dose tested. Based on these screening-level results, MMP and 3-MPA are expected to have a low potential for reproductive/developmental toxicity via oral administration.

The chemicals possess properties indicating a hazard for human health (acute inhalation and oral toxicity including central nervous system effects, skin corrosion and severe eye irritation for 3-MPA, potential for respiratory irritation for 3-MPA and MMP, point-of-contact effects from repeated exposures). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The hydrolysis half-life for MMP is 18.5 days at pH 7 at 25 °C. A hydrolysis study was not conducted for 3-MPA as this substance has no hydrolyzable groups.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.3 days for both 3-MPA and MMP. An OECD TG 301B test with MMP resulted in 46% biodegradation after 28 days. MMP is not readily biodegradable under aerobic conditions. In a ready biodegradation study (equivalent to OECD TG 301A), 94% biodegradation was observed at the end of 10-d window, indicating 3-MPA is readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that 3-MPA and MMP will distribute mainly to the soil (65.1 and 59.2 %, respectively) and water (34.5 and 39.8 %, respectively) compartments and negligible amounts in the air and sediment compartments. Henry's law constants for 3-MPA and MMP of 2.6×10^{-8} atm (2.61×10^{-5} hPa)-m³/mole and 8.3×10^{-6} atm (8.4×10^{-3} hPa)-m³/mole at 25 °C suggests that volatilization from the water phase is not expected to be high.

The bioaccumulation potential seems to be low based on a BCF value of 3.16 for both 3-MPA and MMP estimated with BCFWIN.

The following acute toxicity test results have been determined for aquatic species for 3-MPA:

Fish [<i>Brachydanio rerio</i>]	96 h LC ₅₀ = 88 mg/L (measured) (OECD TG 203)
Invertebrate [<i>Daphnia magna</i>]	48 h LC ₅₀ = 9 mg/L (measured) (OECD TG 202)
Algae [<i>Pseudokirchneriella subcapitata</i>]	72 h ErC ₅₀ = 26 mg/L (measured) (OECD TG 201)
Algae [<i>Pseudokirchneriella subcapitata</i>]	72 h EbC ₅₀ = 16 mg/L (area under growth curve method)
Algae [<i>Pseudokirchneriella subcapitata</i>]	72h-NOEC = 4.1 mg/L

The following acute toxicity test results have been determined for aquatic species for MMP:

Fish [<i>Oncorhynchus mykiss</i>]	96 h LC ₅₀ = 1.7 mg/L (measured) (OECD TG 203)
Invertebrate [<i>Daphnia magna</i>]	48 h LC ₅₀ = 0.55 mg/L (measured) (OECD TG 202)
Algae [<i>Scenedesmus subspicatus</i>]	72 h ErC ₅₀ = 0.65 mg/L (measured)(OECD TG 201)
Algae [<i>Scenedesmus subspicatus</i>]	72 h EbC ₅₀ = 0.13 mg/L (area under growth curve method)
Algae [<i>Scenedesmus subspicatus</i>]	72h-NOEC = 0.025 mg/L

These chemicals have properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L for 3-MPA; less than 1 mg/L for MMP). In addition, MMP is not readily biodegradable, however, both substances have a limited potential for bioaccumulation.. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

In the sponsor country (the United States), production volume in 2005 for 3-MPA and MMP was approximately 454 - 4536 tonnes (1-10 million lbs) each. 3-MPA is produced in closed systems and exposure in the workplace is expected to be minimized through the use of recommended engineering controls and personal protective equipment (respiratory protection, goggles and protective clothing). MMP is produced in a closed system with off gasses being directed to the boilers, as well for the inert stream off gas stream as for the contaminated air off gas stream. Both are (separately) directed to the boiler pre-combustion chamber and then combusted.

MMP and 3-MPA are used as chain transfer and cross-linking agents in polymerizations, and as reactive intermediates in the production of PVC stabilizers. They can also be used as reactive intermediates in the production of acidic ion exchange catalysts, coupling agents and in UV-curable formulations. MMP is sold and transported to industrial

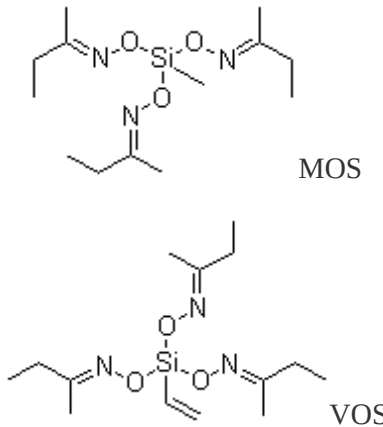
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consumers, that either sell MMP or use it as an intermediate. 3-MPA may be used as a liquid nonhousehold metal cleaner (0.5% by weight); however it is not known whether this is a currently used product, whether 3-MPA appears in the final product (or is a precursor), or to whom the product has been sold.

3-MPA is reacted for use in consumer applications. Final concentrations in consumer products, if found, are expected to be in the low ppm concentration range, and consumer exposure is expected to be primarily low.

No monitoring data for effluents, surface water in occupational settings are available from the production and processing sites in the United States. 3-MPA and MMP are produced in closed systems and sold to industrial consumers. There are no intentional releases to the environment. Stack emissions are estimated to be 0.0000785 lbs MPA/lb MPA produced.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Oximino Silanes Category
Chemical Names and CAS Nos.	2-Butanone, O,O',O''-(methylsilylidyne)trioxime (MOS) (CAS No. 22984-54-9) 2-Butanone, O,O',O''-(ethenylsilylidyne)trioxime (VOS) (CAS No. 2224-33-1)
Structural Formulas	 MOS VOS

SUMMARY CONCLUSIONS OF THE SIAR**Category rationale**

2-Butanone, O,O',O''-(methylsilylidyne)trioxime (MOS) and 2-Butanone, O,O',O''-(ethenylsilylidyne)trioxime (VOS) are grouped together as a category because the chemical structure of these two substances is essentially identical. They each contain three methylethylketoxime groups with the primary difference being methyl or vinyl in the fourth position on the silicon atom. Both substances hydrolyze rapidly (within minutes) to form three moles of methylethylketoxime (CAS No. 96-29-7; MEKO), and one mole reactive methyl or vinyl substituted silanetriol. The methyl or vinyl silanetriol (at concentrations greater than 500 mg/L) can condense to form substituted silanols or disilanols. In aqueous solutions, exposures to the Oximino silanes are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products MEKO, methyl or vinyl substituted silanetriols, and condensed silanetriol materials (high molecular weight polymers). Physical-chemical properties (vapor pressure, melting point and boiling point) are similar for the two substances, thus supporting the category justification. Data from the hydrolysis product MEKO have been presented at SIAM 17 (sponsored by Japan and US). The mammalian toxicity profile of MEKO is similar to that seen for MOS and VOS; data for other hydrolysis products are not available. All human health SIDS endpoints have been addressed by data for MOS. These data are read across to address data gaps for VOS for repeated-dose and reproductive toxicity endpoints.

Reduced Testing Rationale

The oximino silanes (MOS and VOS) undergo rapid hydrolysis in the presence of water; the half life of MOS at pH 7 and 2°C is less than 1 minute. This hydrolysis of MOS is expected to produce 3 moles of methylethylketoxime (CAS No. 96-29-7; MEKO) and 1 mole of methylsilanetriol. The hydrolysis of VOS could not be determined, but is expected to be more rapid than MOS, and to produce 3 moles of MEKO and 1 mole of vinylsilanetriol. Depending on the pH and concentration of the substance, the reactive methyl or vinyl substituted silanetriols may condense to form oligomers and polymers. Because the materials are hydrolytically unstable, water solubility, partition coefficient and biodegradation were not measured. Nonetheless, these endpoints provide

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valuable information on the behaviour of the substance. Therefore, modelled values are provided for water solubility and partition coefficient. The biodegradation data for MEKO are provided in SIAM 17 documents; silanetriols and condensed silanetriol materials are not expected to be readily biodegradable.

The EPISuite program (v4.00) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for silanes that contain silicone in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported below.

Physical-Chemical Properties

MOS is a clear, colourless liquid with a measured melting point of $<-73^{\circ}\text{C}$, a measured boiling point of 250°C at 997 hPa and a measured vapour pressure of 0.085 Pa at 25°C . The calculated octanol-water partition coefficient ($\log K_{ow}$) is 9.83, and the calculated water solubility is 0.00006 mg/L at 25°C . VOS is a clear, colorless liquid with a measured melting point of $<-20^{\circ}\text{C}$, decomposes at high temperatures (calculated boiling point of 359°C) and a measured vapour pressure of 0.025 Pa at 25°C . The calculated octanol-water partition coefficient ($\log K_{ow}$) is 10.19, and the calculated water solubility is 0.00003 mg/L at 25°C .

Human Health

Toxicokinetics data for MOS and VOS are not available. However, data indicate that MEKO, the hydrolysis product, is rapidly absorbed from the gastrointestinal tract and skin, and then it is rapidly metabolized and excreted.

The oral LD_{50} values for MOS were 2260 mg/kg bw for male Fischer 344 rats and 2650 mg/kg bw for female Fischer 344 rats. The substance caused reversible narcotic type effects on the nervous system, significant oxidative destruction of red blood cells, and splenic changes indicative of erythrolysis (at all dose levels [295, 980, 1960, and 2950 mg/kg bw]); generalized hepatocyte cytoplasmic vacuolation and lymphoid depletion/necrosis was observed in some animals that died. The oral LD_{50} values for VOS were >2000 mg/kg bw for male Fischer 344 rats and 1920 mg/kg bw for male Crl: CD (SD) IGS BR VAF/Plus rats and 2610 mg/kg bw for female Crl: CD (SD) IGS BR VAF/Plus rats. Clinical signs included absence of/reduced activity, increased lacrimation, chromodacryorrhea, partially closed eye lids bilaterally, irregular respiration rate, red soiling of the muzzle, bilateral forepaws and/or clear/yellow anal/urogenital staining. No information regarding acute inhalation and acute dermal toxicity is available for MOS or VOS.

MOS was slightly irritating to rabbit skin. Erythema and edema were observed. VOS was moderately irritating to rabbit skin. Reversible, superficial necrosis was observed in 2/6 animals. MOS was slightly irritating to moderately irritating to rabbit eyes producing corneal opacity, circumcorneal injection of the iris, conjunctival redness, chemosis, and discharge, which completely subsided by day 7. VOS was severely irritating to rabbit eyes. Corneal opacity, iritis, conjunctival redness, chemosis, and discharge effects persisted for up to 21 days in 2 animals with eyes “unrinsed”; for those rabbits’ eyes that had been “rinsed”, irritation resolved by day 14. No information is available on the respiratory tract irritation.

No experimental data are available for skin sensitization in animals.

The repeated dose toxicity of the MOS has been investigated in one study. In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422) 10 Wistar rats/sex/dose were administered MOS via gavage at 0, 10, 50 and 250 mg/kg bw/day for at least 28 days. No mortality, treatment-related clinical signs or effects on food consumption, body weights and body weight gain were seen. In the Functional Observational Battery, a decreased number of rearings and decreased mean grip strength of hindpaws was observed in males at 250 mg/kg bw/day. Decreased mean body temperature was observed in both sexes at 250 mg/kg bw/day and in males at 50 mg/kg bw/day. Hematology measurements were not possible for animals at 250 mg/kg bw/day; at 50 mg/kg bw/day, changes in hematology were noted. Changes in clinical chemistry were observed in animals dosed at 250 mg/kg bw/day. Discolored kidneys (250 mg/kg bw) and enlarged spleen (50 and 250 mg/kg bw/day) were observed at necropsy. Heart (250 mg/kg bw/day), liver (50 (males only) and 250 mg/kg bw/day) and spleen (50 and 250 mg/kg bw) weights were increased. At 50 and/or 250 mg/kg bw/day, microscopic

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changes in the liver, spleen, kidneys and bone marrow were observed. Based on hematology, blood chemistry and histopathological findings, the NOAEL for repeated dose oral toxicity was 10 mg/kg bw/day. A similar toxicity profile was observed for MEKO. Similar repeated dose toxicity is expected for VOS.

Gene mutation data are not available for MOS. MOS did not induce chromosomal aberration in Chinese hamster ovary cells *in vitro* with and without metabolic activation. In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium* /*E.coli*, VOS was negative both with and without metabolic activation. In an *in vitro* chromosomal aberration test using OECD 473 and CHO cells, VOS induced chromosomal aberrations. In an *in vivo* micronucleus assay, VOS was negative when administered as a single intraperitoneal injection up to the maximum tolerated dose. Based on these results, VOS is considered to be non genotoxic *in vivo*. MOS and VOS are not expected to be genotoxic *in vivo*.

No data are available for the carcinogenicity of MOS and VOS.

The reproductive and developmental toxicity of the MOS has been investigated in a combined repeated-dose/reproductive/developmental toxicity screening test in rats [OECD 422]. In this study, MOS was administered via gavage to 10 animals/sex/dose at 0, 10, 50 and 250 mg/kg bw/day. Dosing occurred in all groups for at least 28 days. Groups of ten female Wistar rats were dosed for 14 days prior to pairing, through the pairing and gestation periods until the F1 generation reached day 4 post partum. No death was observed in either sex. No adverse effects on reproductive parameters were observed up to the highest dose tested. No test substance-related effects were observed in any of the developmental parameters evaluated. Based on hematology, blood chemistry and histopathological findings, the NOAEL for repeated dose oral toxicity was considered to be 10 mg/kg bw/day. Based on no adverse effects on reproductive parameters NOAEL for reproductive/developmental toxicity was 250 mg/kg bw/day (the highest dose tested). A similar toxicity profile was observed for MEKO. MOS did not cause any reproductive or developmental toxicity; VOS is expected to have a similar profile.

The oximino silanes may present hazard for human health (repeated- dose toxicity; eye and skin irritation). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The hydrolysis half-life for MOS is <1 minute at pH 7 and 2°C. Determination of the hydrolysis rate of VOS was not possible. VOS is expected to rapidly hydrolyze (less than 1 minute at pH 7 and 2 °C); substitution of vinyl for methyl may actually increase the rate of hydrolysis of VOS relative to MOS. Hydrolysis of the oximino silanes is expected to produce 3 moles of MEKO and 1 mole of reactive methyl or vinyl substituted silanetriols. Silanetriols (at concentrations greater than 500 mg/L) can condense to form highly cross-linked, high molecular weight polymers, further reducing the potential for exposure. If the oximino silanes are slowly released such that the concentration of the resulting silanetriol is not high enough to result in polymerization, the silanetriol will exist largely as a monomer. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 27.9 and 4.2 hours, for MOS and VOS, respectively. Based on the rapid hydrolysis of these materials, any potential for biodegradation is likely to be of the hydrolysis products. The hydrolysis products silanetriol and condensed silanetriol materials are not expected to be readily biodegradable. Biodegradation endpoint for MEKO has been addressed at SIAM 17 where it was found to be inherently biodegradable in one test, and not inherently biodegradable in the second test. Level III fugacity model with equal and continuous distributions to air, water and soil compartments suggests that MOS and VOS will distribute mainly to the soil (80 %) and water (18%) compartments with minor distribution to the air compartment (ca. 1%) and negligible amount in the sediment compartment. However, the oximino silanes are unlikely to be found in the environment, as these materials are hydrolytically unstable. A Henry's law constant for MOS and VOS of 500 Pa m³/mole at 25 °C suggests that volatilization of these chemicals from the water phase is expected to be high.

MOS and VOS react to form MEKO and reactive methyl or vinyl substituted silanetriol through hydrolysis. The BCF for the oximino silanes and the methyl or vinyl substituted silanetriol cannot be accurately predicted, but are expected to be low. The measured BCFs for MEKO in fish generally range from 0.5 to less than 2.5, indicating low or no bioaccumulation potential.

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Due to the rapid hydrolysis of the oximino silanes, aquatic organisms are likely exposed to the parent and its hydrolysis products, MEKO, methyl and vinyl substituted silanetriols, and condensed silanetriol materials.

The following acute toxicity test results have been determined for aquatic species for MOS:

Fish [rainbow trout; <i>Oncorhynchus mykiss</i>];	96 h LC50 >120 mg/L (nominal)
Invertebrate [<i>Daphnia magna</i>]	48 h LC50 >120 mg/L (nominal)
Algae [<i>Pseudokirchneriella subcapitata</i>]	72 h ErC50 = 94 mg/L (growth rate, nominal)
	72 h E _b C50 = 50 mg/L (biomass) (nominal)

The oximino silanes may present a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L for MOS and toxicity to aquatic plants). Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

MOS is commercially produced with an annual production volume of approximately 1361 – 2268 tonnes in the Sponsor Country (2005). VOS is commercially produced with an annual production volume of ca. 227 – 907 tonnes in the Sponsor Country (2005). MOS and VOS are not produced in Europe; VOS is commercially produced with an annual production volume of <227 tonnes in Japan (2005). The oximino silanes are used as cross-linking agents in room temperature vulcanizing silicone adhesive sealants. The oximino silanes are used at <10% in formulations.

No monitoring data in occupational settings are available from the production and processing sites in the Sponsor Country. The oximino silanes are produced and used in closed systems [hard-piped]. Necessary engineering controls during production of silicone adhesive/sealants include proper ventilation, containment, safety equipment and actual hardware designed to minimize exposure, through splashing, or exposure to the air. Transfer of this material is in closed pipes or containers rather than in open systems to minimize loss (hydrolysis) although some customers may transfer the material using open systems.

A worker may be exposed during compounding (mixing) of sealant or adhesive to low levels of these silanes. There is no known production process that involves aerosolized material or sprayed material. The vapour pressure of MOS and VOS is low enough that vapour inhalation is not considered a potential route of exposure under normal operating conditions.

Exposure to both MOS and VOS due to non-accidental releases includes cleaning of the mixing vessel and potential routes of exposure are dermal and inhalation. Manufacturers MSDSs recommend general personal protective equipment (PPE) which includes impermeable chemical resistant gloves, goggles, and safety shoes, during the cleaning process. If liquid contact is possible a full face shield is recommended. Recommended engineering controls include flow meters; vacuum; temperature controls; mechanical ventilation devices or a respirator and related equipment. The use of MOS and VOS in the consumer market is limited to use as a cross linker in sealants and adhesives. The substances are used at generally <10% in these formulations and they react with silanol polymers in the formulation during compounding (mixing) and then further react during exposure to atmospheric moisture. After curing, the parent silane is consumed into the polymer matrix and no longer exists, greatly reducing the potential for consumer exposure.

In an experiment conducted to evaluate the potential for exposure to the hydrolysis product, MEKO produced during the curing reaction of adhesive/sealant compositions the maximum concentrations of MEKO in air at the peak of caulk off gassing were the highest (of about 0.011 mg/L or 3 ppm) in the experiment with the lower air exchange rate and hard, non-porous wall surfaces. The lowest concentrations 0.0018 to 0.0027 mg/L (0.5 – 0.75 ppm) were observed with the higher air exchange rate or porous wall surfaces. The manufacturers of MEKO currently recommend an Industrial Hygiene Guideline for inhalation exposure to MEKO. These limits are: 3 ppm (8 hours Time Weighted Average or 8 hours per day, 40 hours a week during normal lifetime exposure) and 10 ppm (15 minutes Short Term Exposure Limit).

MOS and VOS are used in consumer products at <10%. Therefore, the consumer may be exposed while applying the products. However, the substances are reacted during use, losing their chemical identity. Therefore, the final

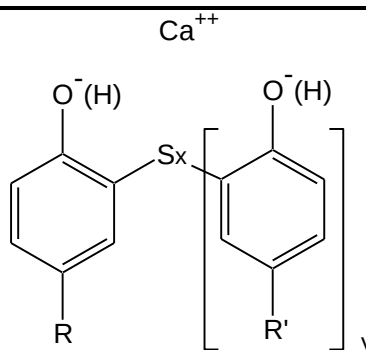
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products generally are expected to contain essentially no MOS or VOS.

No monitoring data for effluents or surface waters are available. However, there are no intentional releases to the environment. Further, the reactive nature of these materials destroys the parent material in water, thus limiting environmental exposure.

SIDS INITIAL ASSESSMENT PROFILE

Category name	Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide category
CAS Nos.	Sponsored Substances 68815-67-8 68855-45-8 122384-85-4 68784-25-8 122384-86-5 68784-26-9 122384-87-6 73758-62-0 122384-84-3 Supporting Substance 68515-93-5
Chemical Names	Sponsored Substances Phenol, thiobis[tetrapropylene-] Phenol, tetrapropenyl-, sulfurized, calcium salts Phenol, tetrapropenyl-, sulfurized, calcium salts, carbonates Phenol, tetrapropenyl-, sulfurized, carbonates, calcium salts, overbased Phenol, tetrapropenyl- and C18-30 alkyl derivatives, sulfurized, calcium salts, overbased Supporting Substance Phenol, nonyl derivatives, sulfides

Structural Formulae

R, R' = median carbon chain length (see text)

x = 1-3 bridging sulfur molecules

y = 1-3 alkyl phen(ol)ate molecules

Sponsored Substances

C36H46O2S1-2

C36H58Ca2O4S1-3

C36H58Ca4O10S1-3

C42-54H70-94Ca4O10S1-3

Supporting Substance

C30H46O2S1-2

SUMMARY CONCLUSIONS OF THE SIAR**Category/analogue Rationale**

The substances that make up the Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide are complex mixtures that can vary in a number of generally predictable ways, and their structural similarities and predictability allow their assessment as a “continuum” category. The members of this category are mixtures of oligomers of alkyl phenol or alkyl phenate molecules that are linked by one to three sulfur atoms. The alkyl phenoxy group that is common to all the members of the category can contain saturated branched chain C10-C15 (predominantly tetrapropenyl) or saturated linear C18-C30 (alpha-olefin) alkyl groups (R and R') attached primarily at the para ring position. Alkyl phenate sulfides are made when the alkyl phenol group is reacted with calcium hydroxide or oxide to form the corresponding calcium salt. Alkyl phenol sulfides are not neutralized with calcium hydroxide during their manufacture.

The category members are produced using highly refined lubricant base oil as solvent. It must be emphasized that the CAS number assigned to each substance refers to the active alkyl phenol sulfide or calcium alkyl phenate sulfide ingredient, but that these substances are never isolated from the highly refined lubricant base oil (present at 40 – 50%); isolation is not technically possible without incurring degradation of the phenate sulfide. Consequently, the measured data presented represent the results of tests conducted with the test substance as manufactured, and the purity of the test substances and amount of highly refined lubricant base oil varies based on the manufacturing processes used by the different manufacturers of these substances. However, calculated data (e.g. QSAR estimates) represent the results of the theoretically purified substance without highly refined lubricant base oil. In general, highly refined lubricant base oils used in the manufacture of alkyl phenol sulfides and alkyl phenate sulfides may cause slight skin irritation, but otherwise have a low order of acute and chronic toxicity. However, the presence of highly refined lubricant base oil can have an impact on the results of aquatic toxicity tests and environmental fate tests where the alkyl phenol sulphide or alkyl phenate sulphide would tend to remain in the lubricant base oil fraction of the mixture and enter the water column to a limited degree in accordance with the log Kow of the substance.

The substances in this category contain the unreacted alkyl phenol and its calcium salts in varying amounts as an unintended residual resulting from the processes involved in manufacture. One example is unreacted tetrapropenyl phenol (TPP, CAS # 74499-35-7) previously assessed in the OECD HPV programme) and its calcium salt (CaTPP), which has been shown to be present in representative samples of the tetrapropenyl phenate sulfide and carbonates (at 3 – 14%). TPP has low solubility in water, high log Kow, and low vapour pressure. It is highly toxic to aquatic organisms, and it causes adverse systemic effects in repeated-dose toxicity studies in mammals. It also causes adverse effects on reproduction parameters and reproductive organs and adverse effects on the developing fetus in mammals. These effects are discussed further below.

The physico-chemical data indicate that the category members demonstrate an orderly progression of changes as one goes from lower molecular weight to higher molecular weight in the category. The physico-chemical information provided indicates that boiling point and log Kow increases across the category, and vapour pressure and water solubility decrease across the category. These physico-chemical properties indicate that the group members are likely to have limited mammalian bioavailability. This is supported by the findings from the single and repeated exposure mammalian toxicity studies indicating minimal general toxicity. All category members have a low vapour pressure indicating that inhalation of vapours is not a likely route of exposure for humans or in the environment. Based on the physico-chemical properties of low water solubility and high octanol-water partition coefficient, these substances are likely to partition largely to sediment and suspended solids in the aquatic environment.

A saturated branched C9 (nonyl) chain substance (CAS 68515-93-5) is used as a supporting substance. This substance is closely related to the category members, differing only in the length of the alkyl chain. Measured data from this supporting substance are used for water solubility and acute inhalation toxicity endpoints.

Physico-Chemical Properties

The substances that are members of the Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide Category are complex reaction mixtures. As stated above, the measured data presented represent the results of tests conducted with the test substance as manufactured, which contains up to 50% highly refined mineral oil that cannot be removed. Calculated data represent the results of the theoretically purified substance without highly refined lubricant base oil, based on the neutral phenol compounds. Therefore calculated values should be viewed as indicative rather than prescriptive. They are liquids with low water solubility (less than 0.206 mg/L, measured, for the supporting substance nonyl phenol sulfide – CAS No. 68515-93-5) and low vapour pressure (calculated range 3×10^{-12} – 6.2×10^{-29} Pa at 25°C). The octanol-water partition coefficient for these substances is high (log Kow > 6.6, measured). Calculated log Kow values range between 8.5 and 14.

Human Health

It is known that these materials have varying levels of residual TPP present and that this substance has demonstrated the potential for toxicity to human health in its own right. This information should therefore be borne in mind as the dataset for this group of materials is considered as it is likely to have some impact for certain endpoints. At this time, however, it is not possible to say with any certainty for which endpoints TPP is a major contributing factor as the evidence is not sufficient to warrant such a statement. It can be stated with some confidence that it is likely to play at least some role in several of the endpoints (e.g. reproductive toxicity) and so considerations to this effect have been included within these sections as a potential explanation for some of the results. Without further testing it would be unwise to speculate on the association between this substance and other endpoints for human health. A summary of the toxicity of TPP is provided in the Appendix to the main SIAR document for reference and comparison.

No experimental data on toxicokinetics of category members are available. The high lipophilicity, high molecular weight, low aqueous solubility, and the lack of adverse findings following oral and dermal dosing indicate that intestinal absorption or absorption through the skin and distribution in the body is likely to be limited. The low vapor pressures of these substances indicate that very little if any absorption occurs via inhalation. Metabolism to (non-toxic) metabolites is predicted to occur mostly in the liver. Excretion is expected to be mainly via the urine and feces.

In general, members of the category are not acutely toxic. In the key acute oral toxicity study (OECD TG 401) for each category member, the LD₅₀ ranged from >5000 to >16000 mg/kg. No deaths occurred in these studies, and signs of toxicity included dirty ruffled fur, soft feces, dark-stained urogenital areas, and red-stained feces at dose levels >5000 mg/kg. The LD₅₀ in the key acute dermal toxicity studies (OECD TG 402) available for all the

category members (except CAS # 68815-67-8) plus the supporting substance (CAS # 68515-93-5) ranged from 2000 to 5000 mg/kg. No deaths occurred in these studies, and signs of toxicity included a decrease in food consumption and clear ocular discharge at dose levels >4000 mg/kg. In two acute inhalation studies (similar to OECD 403) in rodents

with CAS # 122384-87-6 and supporting substance CAS # 68515-93-5, no signs of toxicity occurred at concentrations of up to 1.67 mg/L

In the key eye irritation studies (OECD TG 405) for each category member, animal data indicate that these substances cause slight reversible conjunctival irritation: corneal opacity was observed in only one animal in one study (with CAS # 122384-85-4) and cleared by 24 hours.

Slight reversible irritation to the skin was observed in the key skin irritation studies (OECD TG 404) for each member of the category following a 4-hour application to the skin. In general, skin irritation scores were slightly higher in studies where the test substance was applied to the skin for 24 hours in older studies. In two repeated-dose dermal toxicity studies in rats (CAS # 122384-87-6) and rabbits (supporting substance CAS # 68515-93-5), application of the test substances over a 28-day period resulted in skin irritation at the application site). However, in 2 human repeated-insult patch tests in which the same test substances were applied three times per week for three weeks, no evidence of skin irritation was observed.

Several skin sensitization studies (OECD TG 406) in guinea pigs have been conducted for each member of the category. Findings in animal studies present a contradictory profile, with positive and negative results in some instances obtained with the same substance following identical protocols. However, negative findings were obtained in two human repeated-insult patch tests with CAS # 122384-87-6 and supporting substance CAS # 68515-93-5. Overall, these substances are not considered to be sensitizers in humans.

The repeated-dose toxicity of the members of this category has been evaluated in two 28-day repeated-dose oral (gavage) toxicity studies (OECD TG 422), one repeated-dose dermal toxicity studies (OECD TG 410), two oral (gavage) developmental toxicity studies (based on OECD TG 414), and a 2-generation oral (gavage) reproductive toxicity study (OECD TG 416).

The 28-day repeated-dose oral (gavage) toxicity study with CAS # 122384-85-4 was conducted in rats with dose levels of 0, 50, 300, and 1000 mg/kg bw/day for 7 days/week for 4 weeks. The sample of the test substance used in this study was a commercial sample that contained 54% alkyl phenate sulphide oligomers, 43% highly refined lubricant base oil, and 3% unreacted tetrapropenyl phenol (TPP) and the calcium salt of TPP (CaTPP). Consequently, the animals in the high-dose group were administered 30 mg/kg bw/day of TPP and CaTPP. No deaths occurred, and no signs of toxicity were observed in this study. At study termination, increased mean adrenal weights (absolute and relative to brain weights) were observed at the high dose of 1000 mg/kg bw/day in females only. These changes were accompanied by an increase in the severity of fine vacuolar changes in the cells of the zona fasciculata in the adrenal cortex in the high-dose females. The NOAEL for this study was 300 mg/kg bw/day. Although TPP caused an increase in mean adrenal weights in a 28-day repeated-dose oral (gavage) toxicity study and a 1-generation oral (gavage) reproductive toxicity study, those changes occurred at dose levels >180 mg/kg bw/day in the 28-day study and at the high dose of 125 mg/kg bw/day in the reproductive toxicity study, these changes occurred only in males and was accompanied by a decrease in mean body weight gain. The TPP concentration in the high-dose group in this study was well below the dose levels of TPP that caused adverse effects on the adrenal gland. Hence these findings do not support a possible relationship between the toxicity of TPP and the adverse effects on the adrenal glands observed in this study.

The 28-day repeated-dose oral (gavage) toxicity study with CAS # 122384-87-6 was conducted in rats with dose levels of 0, 50, 200 and 1000 mg/kg bw/day also for 7 days/week for 4 weeks. The sample of the test substance used in this study was a commercial sample that contained 43% alkyl phenate sulphide oligomers, 50.3% highly refined lubricant base oil and calcium carbonate and 6.7% TPP and CaTPP. Consequently, the animals in the high-dose group were administered 67 mg/kg bw/day of TPP and CaTPP. No deaths occurred in this study. Signs of toxicity observed one hour after dosing were limited to salivation, clear material around the mouth, red or yellow staining around the mouth and/or red material around the nose in males and females receiving 1000 mg/kg bw/day. Mean body weight gain was decreased in males and mean adrenal weights (absolute and relative to brain weights) were increased in males and only slightly in females. There were no microscopic changes in any tissues attributable to treatment, and the NOAEL for this study was 200 mg/kg bw/day. The decrease in mean body weight gain and the increase in mean adrenal weight in this study are qualitatively similar to those findings in the repeated-dose studies with TPP. Hence these findings would tend to support a possible relationship between the toxicity of TPP and the

adverse effects on the adrenal glands observed in this study.

The 28-day repeated-dose dermal toxicity study with CAS # 122384-87-6 in rats was conducted with dose levels of approximately 0, 20, 100 and 250 mg/kg bw/day administered for six hours/day, 5 days/week for 4 weeks. The concentration of TPP was not measured in the test sample. No deaths or systemic toxicity was observed in this study, and the systemic NOAEL was 250 mg/kg bw/day.

In the two oral (gavage) developmental toxicity studies in rats, CAS # 122384-87-6 was dosed at levels of 0, 50, 300, 1000 mg/kg bw/day from Days 6-16 of gestation. The TPP concentration was not measured in the sample of commercial test substance used in the screening study. The sample of the test substance used in the definitive study was a commercial sample that contained 43% alkyl phenate sulphide oligomers, 50.3% highly refined lubricant base oil and calcium carbonate and 6.7% TPP and CaTPP. The test substance was administered to 14 or 15 inseminated females at each dose level in the screening study and to 25 inseminated females at each dose level in the definitive study. No deaths or signs of toxicity attributable to the test substance were observed in the screening study, and treatment-related signs of toxicity observed in the definitive study were limited to clear, red, yellow and/or tan staining/matting/material around the nose and mouth in the high-dose group. In both studies, there was a decrease in mean maternal body weight gain on Days 6-16. The NOAEL for systemic toxicity in both studies was 300 mg/kg bw/day.

The 2-generation oral (gavage) reproductive toxicity study in rats with CAS # 122384-87-6 was conducted using dose levels of 0, 50, 200 and 1000 mg/kg bw/day for 7 days/week for 10 weeks prior to mating and all through mating, gestation and lactation for two generations. The sample of the test substance used in this study was a commercial sample that contained 43% alkyl phenate sulphide oligomers, 50.3% highly refined lubricant base oil and calcium carbonate and 6.7% TPP and CaTPP. There were no deaths in this study that could be attributed to the test substance. The predominant signs of toxicity included yellow, red, brown, tan, and/or clear staining/matting/material on various body surfaces, salivation, and red discharge from the vaginal opening at the high dose of 1000 mg/kg bw/day. A decrease in mean body weights in F0 and F1 males in the high-dose group and F1 (but not F0) males in the mid-dose group were observed. There were no effects on mean body weights in females at any dose at any time in the study, except at gestation in the high-dose group. Mean pituitary weights (absolute and relative to final body weight) were increased at the high-dose level in both F0 and F1 males and females and at the mid-dose level in the F0 males only. Mean liver weights (absolute and relative to final body weight) were also increased in the F0 and F1 females at the high dose level. No microscopic lesion attributable to the test substance was observed in these or any other tissue in either sex. The NOAEL for systemic toxicity in this study was 50 mg/kg bw/day.

All of the members of this category are not mutagenic in vitro based on the results of bacterial reverse mutation tests (OECD TG 471) for each member of the category and two mutation assays in cultured mammalian cells (OECD TG 476) with CAS # 68815-67-8 and CAS # 122384-87-6. No positive evidence of in vivo genotoxicity was found in a mouse micronucleus assay (OECD TG 474) conducted with CAS # 122384-85-4 at dose levels up to 5000 mg/kg via intraperitoneal injection.

There is no information on the carcinogenic potential of the any of the category members.

Two members of the category (CAS # 122384-85-4 and CAS # 122384-87-6) were evaluated for reproductive toxicity in oral (gavage) reproductive toxicity screening studies (OECD TG 422) in rats. A 2-generation oral (gavage) toxicity study (OECD TG 416) in rats was conducted with CAS # 122384-87-6 after adverse effects were noted in the reproductive toxicity screening test with this test substance.

In the oral (gavage) reproductive toxicity screening study with CAS # 122384-85-4, the test substance was administered to male and female rats at dose levels of 0, 50, 300 and 1000 mg/kg bw/day for 7 days/week for four weeks prior to mating. The concentration of TPP in the sample of test substance used in this study, the concentration of TPP in the high-dose group, and the systemic toxicity observed in this study have been described above in the repeated-dose toxicity section. There were no adverse effects on any reproductive parameter in this study. The NOAEL for reproductive toxicity is 1000 mg/kg bw/day. The amount of TPP administered in the high dose in this study, 30 mg/kg bw/day, is well below the dose of TPP that caused reproductive toxicity in the 1-generation study.

The oral (gavage) reproductive toxicity screening study with CAS # 122384-87-6 was conducted with dose levels of 0, 50, 200 and 1000 mg/kg bw/day administered to males and females for 7 days/week for 4 weeks prior to mating. The concentration of TPP in the sample of test substance used in this study, the concentration of TPP in the high-dose group, and the systemic toxicity observed in this study have been described above in the repeated-dose toxicity section. The systemic toxicity observed in this study has been described in the repeated-dose toxicity section above.

The test substance caused a decrease in mean live litter size and a decrease in the mean number of corpora lutea for each female at the high dose of 1000 mg/kg bw/day. No other significant effects on reproduction parameters or reproductive organs were observed in this study. The NOAEL for reproductive toxicity was 200 mg/kg bw/day.

In the 2-generation oral (gavage) reproductive toxicity test with CAS # 122384-87-6, the test substance was administered to male and female rats at dose levels of 0, 50, 200 and 1000 mg/kg bw/day for 7 days/week for 10 weeks prior to mating and all through mating, gestation and lactation for two generations. The concentration of TPP in the sample of test substance used in this study, the concentration of TPP in the high-dose group, and the systemic toxicity observed in this study have been described above in the repeated-dose toxicity section. The F0 and F1 fertility indices (number of pregnant females/number of mated females) and F0 and F1 mean live litter sizes were significantly reduced at the high dose of 1000 mg/kg bw/day. In addition, F0 and F1 mean testes, epididymides, and ovary weights were decreased and F0 and F1 mean pituitary weights were increased in males and females. Qualitative spermatogenesis evaluations were performed on all males that did not sire a litter, but no treatment-related changes were observed in gross sperm morphology, apparent relative numbers or motility in the epididymides. The reproductive NOAEL for this study is 200 mg/kg bw/day.

Although the amount of TPP administered in the high dose group in both reproductive toxicity studies with CAS # 122384-87-6, 67 mg/kg bw/day, is lower than the lowest dose of TPP that caused adverse effects on reproduction parameters and reproductive organs in the one-generation reproductive toxicity study, it is also higher than the dose level that did not cause reproductive toxicity. Consequently, the adverse results on reproduction with CAS # 122384-87-6 are consistent with the adverse effects on reproduction produced by TPP.

In two oral (gavage) developmental toxicity studies in rats, CAS # 122384-87-6 was dosed at levels of 0, 50, 300, 1000 mg/kg bw/day from Days 6-16 of gestation. The TPP concentration was not measured in the sample of commercial test substance used in the screening study. The sample of the test substance used in the definitive study was a commercial sample that contained 43% alkyl phenate sulphide oligomers, 50.3% highly refined lubricant base oil and calcium carbonate and 6.7% TPP and CaTPP. The test substance was administered to 14 or 15 inseminated females at each dose level in the screening study and to 25 inseminated females at each dose level in the definitive study. No deaths or signs of toxicity attributable to the test substance were observed in the screening study, and treatment-related signs of toxicity observed in the definitive study were limited to clear, red, yellow and/or tan staining/matting/material around the nose and mouth in the high-dose group. In both studies, there was a decrease in mean maternal body weight gain on Days 6-16. In the screening study, a significant increase in the incidence of fetuses and litters with 14th rudimentary ribs was observed at the high dose of 1000 mg/kg/day. In addition, there was an increased incidence of fetuses with non-ossified and/or incomplete ossification of the hyoid at the mid- and high-dose levels. However, there was no increased incidence of litters with this skeletal variant at any dose level. In the definitive study, there was an increased incidence of litters with bent ribs in the high dose of 1000 mg/kg bw/day. However, the incidence of fetuses with this skeletal variant was not increased. The findings on the ribs in both studies are regarded as minor variations and not major malformations. The delayed ossification of the hyoid may well represent an increase in a finding with a high spontaneous background incidence. The NOAEL for developmental toxicity in the screening study is 50 mg/kg bw/day, and the NOAEL for developmental toxicity in the definitive study is 300 mg/kg bw/day. Overall, minor developmental variations were noted in rats.

In summary, the members of the Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide category, are of a low order of toxicity after acute oral and dermal exposure. These substances cause slight irritation to the eye and skin, and they are not human skin sensitizers. Repeated-dose toxicity studies show some evidence of systemic toxicity at the limit dose of 1000 mg/kg bw/day and at 200 mg/kg bw/day in a 2-generation study. The members of this category are not mutagenic *in vitro*. They are of low concern for developmental toxicity. Alkyl phenate sulfides cause a reduction in fertility in males and female rats, a reduction in mean live litter size, and a reduction in the size of male and female reproductive organs. This may be dependent on the concentration of residual unreacted TPP + CaTPP. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

It can be concluded that the substances that are members of the category do not readily biodegrade. In two studies conducted with CAS # 122384-85-4, the extent of biodegradation after 28 days ranged from 4.7% to 13.4% (OECD TG 301B). They do not undergo hydrolysis. Atmospheric half-lives ranging from 1.41 to 3.00 hours can be calculated based on hydroxyl radical interaction, but the low vapour pressure of these substances and their Henry's Law Constants indicate that partitioning into atmosphere will not be a significant pathway. The Equilibrium

Criterion (EQC) model, part of the EPISUITE program, indicates that these substances are likely to preferentially bind to soil in the terrestrial environment and to sediment and suspended particles in the aquatic environment. While the octanol-water partition coefficient for these substances is high ($\log K_{ow} > 6.6$, measured), calculated bioconcentration factors based on calculated $\log K_{ow}$ values (range 8.5 - 14) generally suggest that these substances have low bioaccumulation potential (estimated BCF range 3.2 – 656). This is supported by an in vitro membrane transport study and the substances' properties indicating low bioavailability in aqueous media.

The substances that make up this category are of low concern for acute toxicity to aquatic organisms. Due to the physico-chemical properties of the substances in this category, water accommodated fractions (WAF) were generally used to produce test media in aquatic studies. Results are quoted relative to WAF loading rates. The WAFs, prepared from loading rates of at least 100mg/l, did not exert acute toxic effects on fish, invertebrates, or algae.

CAS 122384-85-4:

OECD TG 203, *Pimephales promelas* 96h LL50 > 1000mg/l (WAF)

OECD TG 203, *Oncorhynchus mykiss* 96h LL50 > 1000mg/l (WAF)

OECD TG 202, *Daphnia magna* 48h LL50 > 1000mg/l (WAF)

OECD TG 201, *Pseudokirchneriella subcapitata* 96h LL50 > 1000mg/l (WAF)

CAS 122384-86-5:

OECD TG 203, *Pimephales promelas* 96h LL50 (growth rate) > 1000mg/l (WAF)

OECD TG 202, *Daphnia magna* 48h LL50 > 1000mg/l (WAF)

OECD TG 201, *Pseudokirchneriella subcapitata* 96h LL50 > 500mg/l (WAF)

CAS 122384-84-3:

OECD TG 203, *Oncorhynchus mykiss* 96h LL50 > 10,000mg/l (WAF)

These substances are not expected to inhibit wastewater treatment plant microorganisms at typical discharge rates (the 3-hr EC50 is greater than 1,000 mg/L (nominal) in activated sludge respiration inhibition tests). No data on chronic toxicity are available.

The data for this group of materials in this section are not easy to interpret for a number of reasons. These include the unavoidable presence of base oil in the mixtures (which may impact the soluble fractions of the category members and have its own effects on organisms), WAF testing (and variations in WAF methods), and lack of analytical methods to measure the levels and composition of the dissolved fraction for such insoluble materials (making determination of actual exposures tested not possible). A further complication is the presence at varying levels of residual TPP (tetrapropenylphenol, branched C12 alkylphenol) which is known to have a number of effects on test organisms. In WAF preparation it is likely that those components present with higher water solubilities will preferentially dissolve, so that the proportions of the components in the test water are not representative of the proportions of the components found in the test material itself. Relative concentrations will be skewed in favour of the more soluble components. The lower molecular weight/shorter alkyl chain constituents, such as TPP, appear to be more water soluble than the larger components. All of these factors, particularly the TPP presence, make the interpretation of toxicity tests with these substances complex. No acute effects were observed in the valid studies conducted using a WAF technique. There is no data for long term exposure; but it is plausible that the more soluble components (that may be over-represented in the WAF test media, such as TPP) may exhibit effects in long term studies. A summary of TPP toxicity is provided in the Appendix to the main SIAR document for reference and comparison. In the environment the substances are likely to partition to sediment in the aquatic compartment and bind to soil in the terrestrial environment; no data for sediment- or soil-dwelling organisms are available.

In summary, while there are a number of potentially confounding variables within the data, the substances in this category do not appear to present an acute aquatic toxicity hazard for the environment. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

The substances that are members of the Combined Alkyl Phenol Sulfide and Alkyl Phenate Sulfide Category are produced in closed processes in France, the United Kingdom, Singapore, and United States of America. The total global production volume is estimated to be greater than 43,000 tonnes/year.

Members of this category are used to formulate finished lubricant oils including all types of automotive and diesel engine crankcase oils, marine and railroad diesel engine oils, and air-cooled two-cycle engine oils. Typical finished oils contain 1 to 10% alkyl phenol sulfide or alkyl phenate sulfide.

Occupation and consumer exposure to the category members is in general expected to be very low based on their physico-chemical properties, use and handling patterns. Some dermal exposure is expected due to the widespread use of these substances in all types of engine oils. Potential releases of the category members to the environment may occur following production, use to make lubricant additive packages, blending lubricant additives into finished oils, and use and disposal of used lubricants.

SIDS INITIAL ASSESSMENT PROFILE

Category name	Thioglycolic acid and its ammonium salt	
CAS No.	68-11-1	5421-46-5
Chemical Name	Thioglycolic acid	Ammonium thioglycolate
Structural Formula	$\text{HS}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH}$	$\text{HS}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}^{\ominus} \quad \text{NH}_4^{\oplus}$

SUMMARY CONCLUSIONS OF THE SIAR**Analogue/Category rationale**

The category comprises the 2 sponsored substances, thioglycolic acid and ammonium thioglycolate. One analogue of similar structure, sodium thioglycolate (CAS. 367-51-1) is used to fill data gaps where data are not available for the sponsored substances. These chemicals are grouped into a category based on similar molecular structure ($\text{HS}-\text{CH}_2-\text{COO}^-$, R^+ , where $\text{R} = \text{H}^+$, NH_4^+ or Na^+), functionality and (eco)toxicological properties. Both the carboxyl and the mercapto moieties of thioglycolic acid are acidic, in aqueous media, thioglycolic acid and its salts undergo full dissociation into the thioglycolate anion ($\text{HS}-\text{CH}_2-\text{COO}^-$) and the respective cations (H^+ , NH_4^+ or Na^+). The toxicity of each compound is mainly driven by the thioglycolate anion. Sodium sulfate and ammonium chloride, sulfate and phosphate have previously been assessed in the OECD HPV Program¹ and according to the available data, the effect of the counter-ion (sodium or ammonium) on the systemic toxicity and the ecotoxicity of the thioglycolic salts is not expected to be significant.

Physical-chemical properties

Thioglycolic acid is a colorless liquid (with a characteristic sulfide odor) with a $\text{pK}_{\text{a}1(\text{COOH})}$ ranging from 3.55 to 3.82 and $\text{pK}_{\text{a}2(\text{SH})}$ from 9.30 to 10.23, a melting point of -16.2°C , a boiling point of 207.85 to 209.85°C at 1024 hPa (accompanied by decomposition) and a measured vapour pressure of 0.16 hPa at 25°C . The measured octanol-water partition coefficient ($\log K_{\text{ow}}$) is 0.27 at pH 1.7 and 22°C and thioglycolic acid is highly soluble in water (>1000 g/L at 20°C).

The 71% aqueous solution of ammonium thioglycolate is a colorless to faint pink liquid (with a characteristic sulfide odor) with a melting point $<-20^\circ\text{C}$, a boiling point of 115°C at 1021 hPa (decomposition between 165 and 267°C) and an estimated vapour pressure of 11.5×10^{-4} Pa at 25°C for the pure ammonium thioglycolate. The calculated $\log K_{\text{ow}}$ (from the measured value for thioglycolic acid at pH 1.7) is -2.99 at pH 7 and 22°C and ammonium thioglycolate is freely soluble in water at least up to a concentration of 71%.

Human Health

No data is available on the absorption of thioglycolic acid and/or its salts by inhalation or oral exposure. However, the physico-chemical properties of the thioglycolates, small ionisable water-soluble molecules with a very low $\log K_{\text{ow}}$ as well as the acute oral and inhalation toxicity data suggest that thioglycolic acid and/or its salts are significantly absorbed by the inhalation and oral routes. Regarding dermal absorption, no reliable data is available on the pure substances. However, studies performed with cosmetic formulations indicate a low dermal penetration (ca. 1%) for the ammonium salt.

¹ Ammonium chloride (CAS Reg. no. 12125-02-9) was submitted for review at SIAM 17 (JP/ICCA), ammonium sulfate (CAS Reg. no. 7783-20-2) at SIAM 19 (DE/ICCA), sodium sulfate (CAS Reg. no. 7757-82-6) at SIAM 20 (SK+CZ/ICCA) and diammonium phosphate (CAS No. 7783-28-0) at SIAM 24 (US/ICCA). The SIDS Dossiers are available on the OECD website: <http://cs3-hq.oecd.org/scripts/hpv/>

After i.v. injection, ^{35}S -thioglycolate is mainly distributed in the kidneys, lungs, and spleen of a female monkey, and in the small intestine and kidneys of a rat. Residual ^{35}S blood concentrations at 0.5 to 7 h post-injection did not exceed 5.3% in rats. Significant concentrations of dithiodiglycolate were detected in the urine of rabbits 24 h after thioglycolic acid was injected i.p. Negligible concentrations of thioglycolate were detected.

In a study performed according to the OECD Guideline 401, the oral administration of thioglycolic acid to male and female rats resulted to a LD_{50} of 73 mg/kg bw. Its ammonium (71% solution) and sodium salt administered orally to male and female rats gave LD_{50} 's between 50 and 200 mg/kg bw in OECD Guideline 423 studies. Behavioral abnormalities and in some cases, GI tract irritation, were the most common findings after oral administration. In a study performed according to the OECD Guideline 403, the exposure of male and female rats to a vapour/aerosol mixture of thioglycolic acid results in a LC_{50} of 2.172 mg/l for males and 1.098 mg/l for females. Clinical signs included a severe irritation of the respiratory tract and mucuous membranes and behavioural abnormalities, the lungs were discoloured at necropsy. A 7-hour inhalation exposure of male rats to saturated vapours generated at 125°C or ambient temperature produced no mortality or clinical signs of toxicity. In a non-guideline acute dermal toxicity study, the LD_{50} of thioglycolic acid was 848 mg/kg bw in male and female rabbits. The clinical signs were limited to skin irritation and necrosis at the sites of application. For the ammonium (71% solution) and sodium salts, the LD_{50} 's in male and female rats were >2000 mg/kg bw and between 1000 and 2000 mg/kg bw, respectively, in studies performed according to the OECD Guideline 402. No significant clinical signs of toxicity were reported.

Thioglycolic acid was corrosive to the skin in an EpiDerm Skin Model study performed according to Directive 2000/33/EC, B.27. It was also corrosive to the eyes in a study in rabbits compliant with the OECD Guideline 405. The ammonium and sodium salts are only slightly irritating for the skin and the eyes of rabbits in OECD Guideline 404 and 405 studies, respectively. Respiratory tract irritation was observed in rats exposed to a high concentration of a vapour/aerosol mixture, but not when exposed to saturated vapour only.

Due to its corrosive properties, the skin sensitisation potential of not neutralized thioglycolic acid has not been investigated. Thioglycolic acid salts are considered as skin sensitizers. The sensitizing potential of ammonium and sodium salts of thioglycolic acid was investigated in a local lymph node assay in mice performed following the OECD Guideline 429. Both substances were found to be sensitizing to the skin with an EC_{30} value of 0.65% and ca. 6%, respectively. Due to a number of skin sensitisation in hairdressers caused by ammonium thioglycolate and due to positive test results in various dermal clinics the sensitizing effect of ammonium thioglycolate to the skin should be considered as certainty.

No reliable data is available on the repeated dose toxicity of thioglycolic acid and its ammonium salt. The repeated dose toxicity of sodium thioglycolate was evaluated by oral and dermal administrations.

In an oral repeated dose toxicity study compliant with the OECD Guideline 408, sodium thioglycolate was administered by gavage, 7 days per week, for 13 weeks, to male and female rats. Clear but fully reversible effects on some haematological and biochemical parameters and histopathological changes in heart and liver were observed at 60 mg/kg bw/d. These effects may be related to the inhibition of the β -oxidation of fatty acids. The NOAEL was 20 mg/kgbw/d.

In a repeated dose dermal toxicity study completed by National Toxicology Program (NTP) and using a method comparable to the OECD Guideline 411, sodium thioglycolate was administered via dermal route, 5 days per week, for 13 weeks to male and female rats and mice. All animals survived the 13 weeks administration. The only treatment related effect was skin irritation at the site of application. The LOELs for skin irritation were 11.25 and 45 mg/kg bw/d and the NOAELs for systemic toxicity were higher than 180 and 360 mg/kg bw/d in rats and mice, respectively.

In reverse gene mutations assays with multiple strains of *Salmonella typhimurium* performed with methods compliant or comparable to the OECD Guideline 471, thioglycolic acid and its ammonium and sodium salts were not mutagenic in the presence and absence of metabolic activation. In a gene $\text{TK}^{+/-}$ mutation assay in mouse lymphoma L5178Y cells, performed following the OECD Guideline 476, ammonium thioglycolate was also not mutagenic in the presence and absence of metabolic activation. As well, thioglycolic acid was not clastogenic, with or without metabolic activation, in an *in vitro* chromosomal aberration assay in human lymphocytes performed following the OECD Guideline 473. In a micronucleus assay on the peripheral blood of mice treated dermally for 13 weeks with sodium thioglycolate, a slight but statistically significant increase of the frequency of the micronucleated normochromatic erythrocytes was only observed in female mice at the top dose level of 360

mg/kg bw/day. This result seems of doubtful significance because thioglycolic acid did not induce structural chromosomal aberrations *in vitro*, and thioglycolic acid and its sodium salt failed to show any evidence of clastogenic potential when administered by the dermal and oral routes, up to the maximum tolerated dose, in two mouse bone marrow micronucleus assays performed following the OECD Guideline 474. In the sex-linked recessive lethal mutations test, sodium thioglycolate was not mutagenic. The weight of evidence suggests that thioglycolic acid and its salts are not genotoxic.

No data is available on the carcinogenic potential of the category members by the oral and inhalation routes. In a non-standard study by dermal route in mice, sodium thioglycolate was administered as 0, 1.0 and 2.0% solutions (0.02 ml per mice), respectively, until all animals died. Differences in the life span and the incidence of neoplasms between experimental and negative control mice were not statistically significant.

Thioglycolic acid and its salts are not considered to be reproductive toxicants, excepted at dose levels associated with maternal lethality. In a reproduction/developmental toxicity screening test performed following the OECD Guideline 421, sodium thioglycolate was administered by oral administration to rats, 10 weeks before mating and through mating and, for the females, through gestation until day 5 *post-partum*. The NOAEL for parental toxicity was considered to be 20 mg/kg bw/day (based on deaths at 40 and 80 mg/kg bw/day), the NOAEL for reproductive performance (mating, fertility and delivery) was considered to be 20 mg/kg bw/day (based on deaths at 40 and 80 mg/kg bw/day) and the NOAEL for toxic effects on progeny was 40 mg/kg bw/day (based on the dead litter at 80 mg/kg bw/day which cannot definitively be attributed to maternal condition).

In the 13-week dermal subchronic toxicity study in rats and mice with sodium thioglycolate, no treatment-related effects on sperm density and motility, caudal epididymal sperm, spermatid head counts in the testes and testis weights, as well as oestrous cycles, were observed up to dose levels of 180 and 360 mg/kg bw/day, respectively.

Thioglycolic acid and its salts are not considered to be developmental or toxicants, except at dose levels associated with maternal lethality. The developmental toxicity of sodium and ammonium thioglycolates has been investigated in standard oral and dermal studies in rats and/or rabbits compliant or comparable to OECD Guideline 414. Ammonium thioglycolate was administered by gavage to pregnant rats from gestational days 6-19. At 75 mg/kg bw/day, two animals died. The body weight, food and water consumption of the dams were not affected by the treatment. No embryo/fetal toxicity, or treatment-related teratogenicity was observed in any group. The NOAELs for maternal and embryo-foetal toxicity were 15 and 75 mg/kg bw/day, respectively. Sodium thioglycolate was topically applied to pregnant rats from gestational days 6-19 and to pregnant rabbits from gestational days 6-29. In rats, there was one reported maternal death at 200 mg/kg bw/day. Feed consumption, water consumption, and body weights of the dams all significantly increased. The body weights of the foetuses were significantly lower than the controls, however there was no other evidence of embryo/foetal toxicity. In rabbits, moderate to severe erythema occurred at the dosing site in all groups, however no maternal systemic toxicity, embryo/foetal toxicity, or treatment-related teratogenicity were observed in any group. The LOAELs for maternal toxicity was 50 mg/kg bw/day in rats and the NOAEL was 65 mg/kg bw/day (the highest dose tested) in rabbits. The developmental toxicity NOAEL was 100 mg/kg bw/day for rats and 65 mg/kg bw/day for rabbits.

No teratogenic effects were observed.

The mortality and the signs of systemic toxic observed in the oral acute or repeated dose toxicity studies seems primarily linked to the inhibition of the β -oxidation of fatty acids. This inhibition induced secondary effects like a decrease of blood glucose, liver glycogen content, blood and hepatic ketone bodies and liver acetyl-CoA and an increase of plasma free fatty acids and liver triglycerides and acyl-CoA and an enhancement of hepatic pyruvate. The fatty liver induced by thioglycolate was mainly due to an inhibition of acyl-CoA dehydrogenase activity and consequently to a marked depression of the β -oxidation pathway.

Environment

With pK_{a1} ranging from 3.55 to 3.82 and pK_{a2} from 9.30 to 10.23 according to the sources, thioglycolate ion mainly exists in its dissociated form at environmentally relevant pH values. Thioglycolic acid and its salts are expected to oxidize in water but are not expected to photolyse, due to lack of absorption in the environmental spectrum, and to volatilize. Based on thioglycolic acid and salts physico-chemical properties (high solubility and low Log P), it is considered that they are not expected to adsorb to suspended solids, sediments and soils and are mobile in soil.

Usually modeling approach is proposed to roughly estimate possible transport between environmental compartments. This approach cannot necessarily be followed for all categories of substances. Ionizable substances for instance do not fit in relevancy criteria of the common models used. Nevertheless, in some extent, physico-chemical information allows a certain understanding of the behaviour.

With a Henry's Law constant of 1.45×10^{-6} atm-m³/mole, thioglycolic acid is expected to be essentially non-volatile from water and moist soil surfaces. Thioglycolic acid is not expected to volatilize from dry soil surfaces based upon an experimental vapor pressure of 16 Pa .

The main process which will lead to degradation of thioglycolic acid in water is a fast oxidation to dithiodiglycolate as demonstrated by literature and also practical cases. This result combined with available information related to biodegradation process of thioglycolate (OECD Guideline 301 B – 60% of biodegradation after 28 days) and dithiodiglycolate (OECD Guideline 301 B – 80% of biodegradation after 28 days) allows to conclude that thioglycolic acid and its salts are ready biodegradable.

Acute toxicity studies, carried out for thioglycolic acid according to OECD guidelines, reveal 96-hour LC₅₀ of > 100 mg/L for fish (*Oncorhynchus mykiss*) and 48-hour EC₅₀ of 38 mg/L for invertebrates (*Daphnia magna*) expressed as nominal concentrations as concentrations were maintained throughout the tests. Algae and daphnia tests carried out on thioglycolic acid oxidation product (diammonium dithiodiglycolate) demonstrate that the substance is not toxic to algae and daphnia with EC_{50's} > 100 mg/L.

The only one data available for salts is related to fish acute toxicity of ammonium salt. The OECD Guideline 203 test reveals 96-hour LC₅₀ > 100 mg/L (measured concentration) for *Oncorhynchus mykiss*.

Based on physico-chemical properties of the substances (high water solubility > 1000 g/L and low Log P = - 2.99), the bioaccumulation potential is considered to be low.

Exposure

In 2008, the total world market was estimated to be close to 30,000 metric tons of thioglycolic acid equivalents. Thioglycolic acid is manufactured by the reaction of monochloroacetic acid [79-11-8] or its salts with alkali hydrosulphides, eg, NaSH or NH₄SH, in aqueous medium. Ammonium thioglycolate is obtained by neutralisation of the acid with ammonia. Thioglycolic acid is used as a chemical intermediate for the synthesis of esters, which is in turn used as an intermediate for the synthesis of tin stabilizers for PVC. Salts of thioglycolic acid are used in cosmetics like permanents, hair straightening and depilatory preparations, in the leather industry and in some other industrial uses.

Monitoring data measured from effluents at production sites of the two major producers are below the detection limit. In the industry (manufacturer and processor), workers exposure to thioglycolic acid by inhalation and/or dermal contact would be expected to occur primarily during drumming operations. However, due to its corrosive nature, dermal exposure is avoided by the use of personal protective equipment. Limited data on the occupational exposure of professionals (21 hairdressing salons in Finland) to ammonium thioglycolate indicates a very low level of inhalation exposure, well below than the current occupational exposure limit of thioglycolic acid. However, a number of skin sensitisation cases in hairdressers caused by ammonium thioglycolate indicates a potential dermal exposure. Consumer exposure may occur by dermal contact through the use of personal care products. Exposure via the environment is considered negligible.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

Thioglycolic acid and its salts should be considered candidates for further work. The chemicals in this category possess properties indicating a hazard for human health (acute toxicity, corrosivity (acid), sensitization and repeated dose toxicity studies). Thioglycolic acid salts are present in consumer products. Member countries are invited to perform an exposure assessment, and if indicated a risk assessment.

Environment

Thioglycolic acid and its salts are of low priority for further work. The chemicals in this category possess properties indicating a hazard for the environment (toxicity to aquatic invertebrates between 10 and 100 mg/L). However the chemicals are readily biodegradable and possess a limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	109-52-4
Chemical Name	n-Pentanoic acid
Structural Formula	CH ₃ -CH ₂ -CH ₂ -CH ₂ -COOH

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Rationale**

Data from aliphatic acids (or calcium propionate in one case) with structures and carbon chain lengths similar to n-pentanoic acid have been used to satisfy endpoints or supplement available data for n-pentanoic acid. The use of propionic acid as an analogue for n-pentanoic acid is based on the fact that propionic acid is a metabolite of n-pentanoic acid and has similar irritative potential in vivo as n-pentanoic acid. Butyric acid data was also used as an analogue based on similar physical chemical properties and in vivo irritative potential.

For biodegradation and acute toxicity to fish, aquatic invertebrates, and aquatic plants endpoints, data for n-pentanoic acid are supplemented using studies conducted with a commercial mixture of 64% n-pentanoic acid and 36% 2-methyl-1-butyric acid, CAS No. 116-53-0. For human health toxicity endpoints, data for propionic acid (CAS No. 79-09-4) are used to supplement the repeated-dose and reproductive toxicity endpoints. Propionic acid (a 3-carbon carboxylic acid) can be used as an analogue for pentanoic acid (a 5-carbon carboxylic acid) based on similarities of structure with a common functional group. Both compounds are corrosive, which is thought to lead to the similar toxicity observed in repeated-dose studies. Finally, Propionic acid is also a metabolic product of n-pentanoic acid via intracellular oxidation pathways. Calcium propionate (CAS No. 4075-81-4), the calcium salt of propionic acid, is used as support for the developmental toxicity endpoint. Calcium propionate dissociates in water to yield propionate ions. In the stomach, calcium propionate and propionic acid exist as the non-ionized acid.

The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid is being presented at SIAM 29 as a separate case by the United States, and propionic acid has previously been assessed in the OECD HPV Chemicals Programme at SIAM 25.

Physical-Chemical Properties

n-Pentanoic acid is a liquid with a melting point of -33.8°C, a boiling point of 186.1°C and a vapour pressure of 0.1hPa at 20°C. The calculated partition coefficient (log K_{ow}) is 1.39 at 25°C, and the water solubility is 24,000 mg/L at 25°C. As the dissociation constant (pKa) is 4.84, n-pentanoic acid is anticipated to exist primarily in its dissociated form at environmentally relevant pH.

Human Health

n-Pentanoic acid has been demonstrated to be rapidly and extensively metabolized by intracellular β-oxidation pathways at concentrations up to 67 mM without inhibition. The product of beta-oxidation are acetic acid and propionic acid. Propionic acid and acetic acid from pentanoic acid metabolism have been demonstrated to be further metabolized to form glucose and glycogen.

The oral LD₅₀ value for n-pentanoic acid, administered in a 10% aqueous solution, is 1050 mg/kg bw for male rats. Signs of toxicity were not reported, however necropsy of animals that died on study revealed discoloured lungs and

gastrointestinal tracts; the urine of some animals was also discoloured. The dermal LD₅₀ in male rabbits is 657 mg/kg bw; the substance was applied undiluted and produced necrosis at the application site. There were signs of nasal irritation but no mortality among male rats exposed for 8 hours to a substantially saturated vapour of n-pentanoic acid at room temperature.

n-Pentanoic acid is corrosive and causes severe irritation and irreversible injury to the skin and eyes. It is anticipated that high concentrations of n-pentanoic acid, produced as an aerosol or a vapour/aerosol mixture, will result in nasal and/or respiratory irritation. Necrosis was observed in a skin irritation assay performed in rabbits. Severe corneal injury and necrosis were observed in an eye irritation assay performed in rabbits. No experimental data are available for skin sensitisation in animals or humans.

There are short-term repeated-dose toxicity data available for n-pentanoic acid for rabbits via the dermal route of exposure, and for rats via the oral route. In a repeated-dose dermal toxicity study in male and female rabbits, n-pentanoic acid in a mineral oil solution was applied to the skin at a dose of 500 mg/kg bw for a total of 10 applications over fourteen days. Death was observed in one female rabbit; all test animals displayed vocalization upon handling, decreased food consumption, decreased body weight, and severe signs of dermal irritation. In a repeated dose oral toxicity study in female rats, n-pentanoic acid in corn oil was administered by gavage at doses of 0, 125, 250, 500, 750, and 1000 mg/kg-bw/day for 10 consecutive days. Dyspnea or rales were observed in all treated groups. Decreased activity, lethargy, and immobilization were observed at 750 and 1000 mg/kg-bw/day. Mortality occurred at doses of 250 mg/kg-bw/day and greater. All animals died at 1000 mg/kg-bw/day. In a third study, n-pentanoic acid was administered to 10 rats in a rice diet at doses up to 10% of the diet; half were sacrificed at 115 days and the other half at 150 days. Stomachs were examined microscopically if gross lesions were observed. n-Pentanoic acid induced benign hyperplasia, hyperkeratosis, acanthosis and papillomas in the forestomach. No malignant changes were detected and there were no changes in the glandular portion of the stomach.

Repeated-dose oral toxicity data in dogs and rats (in studies similar to OECD TG studies) are available for the analogue propionic acid. Dogs (4 to 8/sex/dose) were exposed to 0, 0.3, 1.0, or 3.0% propionic acid (approximately 0, 196, 660, and 1,848 mg/kg-bw/day for males and 0, 210, 696, and 1,832 mg/kg-bw/day for females) in the diet for 100 days. There was no mortality, no clinical signs of toxicity, and no haematological or clinical biochemical changes. Microscopic examination of tissues revealed no lesions except point-of-contact diffuse epithelial hyperplasia of the mucosa of the esophagus in three dogs in the high-dose group. The incidence of lesions in the esophagus in lower dose animals was similar to controls. The incidence of lesions of the esophagus in the high-dose animals after a 6-week recovery interval was also similar to controls. Based on the point-of-contact effect observed in the esophagus, the LOAEL for this study was determined to be 3% propionic acid (1,848 mg/kg-bw/day in male dogs, and 1,832 mg/kg-bw/day in female dogs) in the diet, and the NOAEL is 1% propionic acid or 660 mg/kg bw/day for males and 696 mg/kg bw/day for females.

In a repeated-dose oral toxicity study, rats (20/sex/dose) received 0, 0.62%, 1.25%, 2.5%, or 5% propionic acid in a pulverized diet for 91 days. There was no mortality. Males in the high dose group (5% in diet) exhibited decreased food consumption and decreased body weight gain. No other clinical signs of toxicity were observed. Point-of-contact effects included acanthosis, hyperkeratosis, and proliferation of the epithelium of the forestomach mucosa in rats in the high dose group; these changes were not observed after a 6-week recovery interval. Based on point-of-contact effects observed in the forestomach, the NOAEL for male and female rats in this study is 2.5% propionic acid in the diet, or approximately 1600 mg/kg bw/day.

Additional studies focused on the site-of-contact effect of the analogue propionic acid on the stomach; other tissues were not examined. Male rats (6 /dose) were fed a control diet or a pellet diet containing 4% propionic acid (approximately 2,700 mg/kg bw/day) for 24 weeks. Macroscopic and histopathological examination of the stomach revealed no adverse effects. Male rats (6/dose) were also given a control powdered diet, or a powdered diet containing 4% propionic acid for 12 weeks. Rats displayed severe hyperplastic changes and ulcerations in the forestomach but not in the glandular stomach.

In another study, groups of 30 male rats were fed 0, 0.4 or 4% propionic acid in ground rat feed for 20 weeks or lifetime. Of the rats fed 0.4% propionic acid (approximately 270 mg/kg bw/day), hyperplasia and hyperkeratosis were observed histologically in the forestomach. Among rats fed 4% propionic acid, forestomach epithelial changes such as hyperplasia and hyperkeratosis were noted at 20 weeks, and hyperplasia with ulceration, dyskeratosis and papillomatous elevations (one with unspecified "carcinomatous" changes) were noted after lifetime exposure. No histopathological changes were observed in the glandular stomach in these studies. The consistency of the diet appeared to influence the incidence of lesions observed. The point-of-contact effects observed in the rat forestomach

in response to feeding high doses of short-chain fatty acids are likely to be the result of severe irritation and inflammation and the associated hyperplastic proliferative repair response.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium*, and in an *in vitro* HGPRT forward mutation assay using Chinese hamster ovary (CHO) cells, n-pentanoic acid was negative with and without metabolic activation. An *in vitro* chromosomal aberration test using CHO cells was positive with and without metabolic activation. An *in vitro* sister chromatid exchange assay in CHO cells was negative without metabolic activation and positive with metabolic activation. The effect of pH in these studies is uncertain because it was not measured. An *in vivo* micronucleus assay in mice was negative at doses of 25%, 50% and 80% of the LD₅₀ via intraperitoneal injection that were determined in a range-finding study. Cytotoxicity (PCE/NCE ratios) was seen in females (but not males) in the rangefinding test at 200 mg/mL, but was not observed in the definitive test at concentrations up to 266 mg/mL. Based on these data, n-pentanoic acid did not induce gene mutations but induced chromosomal aberrations in *in vitro* tests, and did not induce an increase in micronuclei when tested *in vivo*.

There are no valid carcinogenicity studies for n-pentanoic acid. In an 80-week dermal toxicity assay in mice with significant methodological deficiencies, repeated dermal application of undiluted n-pentanoic acid (25 mg/mouse or approximately 950 mg/kg bw applied two times per week) induced mortality (66%), severe skin ulcerations, chronic inflammation, and regenerative repair with disproportionate cell proliferation which resulted in scar tissue formation with subsequent dysplasia, hyperplasia, and skin tumours. The controls also showed high mortality (48%). There is some uncertainty regarding the skin tumors observed in the repeated exposure dermal toxicity study and the positive *in vitro* genotoxicity results. However, these effects were likely due to the low pH of the test solutions.

There are no fertility studies available for n-pentanoic acid. Repeated-dose data are available regarding effects on reproductive organs from for the structural analogue, propionic acid. In repeated-dose oral toxicity studies, there were no effects on reproductive organ weights, and reproductive organs and tissues were normal in male and female rats exposed to n-propionic acid at doses up to 5% in the diet (approximately 3300 mg/kg bw/day) for 91 days with a NOAEL of 3300 mg/kg bw/day for reproductive organ toxicity. Similarly, there were no effects on reproductive organs in dogs fed propionic acid at doses up to 3% in the diet (1848 mg/kg bw/day for male dogs; 1832 mg/kg bw/day for female dogs) for up to 106 days, with a NOAEL of 1832 mg/kg bw/day for reproductive organ toxicity.

There are three developmental toxicity studies for n-pentanoic acid. Fetal malformations were not observed. However, significant maternal mortality limited the ability to make firm conclusions from these studies. In the most robust study, n-pentanoic acid in corn oil was administered by oral gavage to rats on gestation days 6 through 15 at doses of 0, 50, 100, and 200 mg/kg bw/day. Rales and vocalization during dosing were reported in dams at all doses. Mortality of dams occurred in all treated groups and was greater than 10% at 100 and 200 mg/kg bw/day. Necropsy of dams dying on study revealed respiratory tract congestion, distention of the gastrointestinal tract, and gastric irritation. Decreased fetal body weights were observed at 100 and 200 mg/kg bw/day. Developmental toxicity, as evidenced by an increased incidence of reduced ossification of late-developing sternebrae, was observed at 50 and 100 mg/kg bw/day. Developmental effects may have been confounded by maternal toxicity.

The analogue, calcium propionate is the non-corrosive salt of propionic acid, and does not induce significant point-of-contact toxicity typical of the parent acid. Calcium propionate was administered via oral gavage to pregnant mice and rats during gestation days 6-15 at doses of 0, 3, 14, 65, and 300 mg/kg-bw/day and to pregnant rabbits and hamsters at doses of 0, 4, 19, 86, and 400 mg/kg-bw/day during gestation days 6-18 (rabbits) or 6-10 (hamsters). Dams were sacrificed on gestation day 17 (mice), 20 (rats), 14 (hamsters), or 29 (rabbits). In all species, there was no effect on maternal or fetal survival, or on fetal or litter size and no increases in fetal or skeletal abnormalities were observed. Both NOAELs for maternal toxicity and developmental effects were the highest doses tested (300 mg/kg-bw/day mice and rats; 400 mg/kg-bw/day for rabbits and hamsters).

n-Pentanoic acid possesses properties indicating a hazard for human health (severe skin and eye irritation, repeated-dose toxicity associated with point of contact effects). Adequate screening-level data are available to characterize the hazard for the human health purposes of the OECD HPV Programme.

Environment

n-Pentanoic acid is not expected to undergo hydrolysis in the environment, due to the lack of hydrolyzable functional groups. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with an estimated half-life of 2.6 days. An aerobic biodegradation test, similar to OECD TG 301D, using n-pentanoic acid resulted in 72% biodegradation after 30 days. Similar results (73% biodegradation in 28 days) were obtained in an

OECD TG 301D study using a commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid. n-Pentanoic acid is readily biodegradable under aerobic conditions.

Based on Level III fugacity modelling with equal and continuous distributions to air, water and soil compartments, it is estimated that the majority of n-pentanoic acid will distribute mainly to the soil (61.8%), and water (33.8%) compartments with minor distribution to the air compartment (4.33%) and a negligible amount to the sediments compartment. When released to water, this chemical will remain in the water compartment. Biodegradation half-lives in water, soil and sediment were 208 h, 416 h, and 1873 h, respectively. The Henry's law constant for n-pentanoic acid is 4.48×10^{-7} atm-m³/mol (0.045 Pa-m³/mol) at 25°C. This value suggests that volatilization of pentanoic acid from the water phase is not expected to be high. The K_{oc} for n-pentanoic acid was calculated to be 4.084 L/kg. This K_{oc} value indicates low potential for accumulation in soil. The bioaccumulation potential for n-pentanoic acid is anticipated to be low based on the preferred Log K_{ow} value of 1.39. The BCF value of 3.16 is estimated using BCFWIN (v 3.00).

The following acute toxicity test results* have been determined for aquatic species for n-pentanoic acid:

Fish**	<i>Pimephales promelas</i>	Static test systems	96 h LC ₅₀ = 39 mg/L 96 h LC ₅₀ = 77 mg/L
Invertebrate***	<i>Daphnia magna</i>	Static test system	48-hr EC ₅₀ = 45 mg/L
Algae**	<i>Pseudokirchneriella subcapitata</i>	Static test system	72-hr E _b C ₅₀ = 10.7 mg/L (biomass) 72 hr NOEC = 6.38.mg/L

*Results for fish and invertebrates are based on nominal test concentrations; results for algae are based on measured test concentrations. **In these studies, test solutions were unbuffered.

*** Reliability = 4; however, supported by the analogue data.

The following acute toxicity test results* have been determined for aquatic species for a commercial mixture of 64% n-pentanoic acid and 36% 2-methyl-1-butyric acid:

Fish	<i>Oncorhynchus mykiss</i>	OECD 203	TG	96 h LC ₅₀ = 75.9 mg/L
Fish	<i>Pimephales promelas</i>	Static test system		96 h LC ₅₀ = 29 mg/L 96 h LC ₅₀ = 34 mg/L
Invertebrae	<i>Daphnia magna</i> Straus	OECD 202	TG	48-hr EC ₅₀ = 88.1 mg/L
Algae	<i>Pseudokirchnerilla subcapitata</i>	OECD 201	TG	96-hr E _b C ₅₀ = 51.8 mg/L (biomass) 96-hr ErC ₅₀ = 66.2 mg/L (growth rate) 96- hr NOEC = 12.8 mg/L (biomass and growth rate)

*All results are based on measured test concentrations. In all studies test solutions were unbuffered.

n-Pentanoic acid possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L in unbuffered systems). However, the chemical is readily biodegradable, has low bioaccumulation potential, and the observed aquatic toxicity is due to

reductions in pH. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

n-Pentanoic acid had a production and/or import volume in the United States between 4,540 and < 22,680 tonnes during 2005. n-Pentanoic acid is produced in an enclosed, continuous process by an air-oxidation reaction of valeraldehyde.

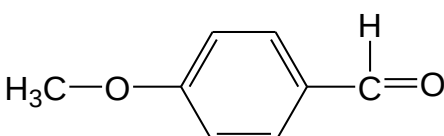
n-Pentanoic acid is used primarily as an industrial intermediate in the manufacture of neopolyol ester (NPE) base stocks for synthetic lubricants; it is also used as an intermediate in the production of isoamyl valerate. Reported minor uses are as an intermediate for the manufacture of plasticizers, pharmaceuticals, vinyl stabilizers, fragrances, and flavourings. Pentanoic acid has been identified as a naturally-occurring volatile emitted from cooked foods and it has been detected in foods at low ppm concentrations. n-Pentanoic acid is a GRAS (generally accepted as safe) direct food additive. Because it is a product of metabolism, it can also be found in sewage and animal waste.

No monitoring data within production and processing sites in the United States are available. n-Pentanoic acid is a corrosive, combustible liquid with a flammable range of 2.7 to 7.6 volume % in air (27,000 – 76,000 ppm) and a flash point of 89°C (193°F). It has a very low odour threshold (0.0026 ppm) and a strongly disagreeable, penetrating odor. n-Pentanoic acid is manufactured in an enclosed, continuous process and engineering controls and vapour collection systems are used during production, transfer, and loading operations. These measures are used to minimize workplace exposure and odour complaints.

Consumer exposure occurs during ingestion of foods that contain n-pentanoic acid as a natural product or as an added flavouring agent, but is not expected to occur from other products because n-pentanoic is primarily used as an intermediate.

Because of its objectionable odour, additional scrubbers and other emission controls are usually employed to minimize release of n-pentanoic acid during manufacture and use. However, n-pentanoic acid may be released to the environment as a fugitive emission during production and use and may be found in the environment as naturally-occurring emissions from food products, microorganisms, animal wastes, and diesel exhaust.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-11-5
Chemical Name	<i>p</i> -Methoxybenzaldehyde
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

p-Methoxybenzaldehyde is a colourless to pale yellow liquid with sweet odour of hawthorn. Melting point and boiling point are 0 °C and 248 °C respectively. Water solubility and vapour pressure are 4.4 g/L at 25 °C(measured) and 4 Pa at 25 °C respectively. Partition coefficient between octanol and water (Log K_{ow}) is 1.76 (measured). Estimated Log K_{oc} is 1.37.

Human Health

As for the metabolism, available experimental data suggest that *p*-methoxybenzaldehyde is demethylated to a small extent and the aldehyde group is oxidized to the acid. The resulting metabolite anisic acid would be conjugated with glucuronic acid and/or glycine, and excreted in the urine. Although there is no other experimental data on the toxicokinetics of *p*-methoxybenzaldehyde, the physicochemical properties and the reproduction/developmental toxicity screening test via oral gavage suggest that this substance could be absorbed via the gastrointestinal tract.

In an acute toxicity study (OECD TG 401) of *p*-methoxybenzaldehyde in rats, the oral LD₅₀ value was considered to be more than 2,000 mg/kg bw in both sexes. At the lethal doses, there were dyspnea, apathy, abnormal position, staggering gait, atonia, arthrogryposis, tremor, skin redness, ruffled fur and poor general state. Based on a inhalation test, the inhalation LC₅₀ value was considered to be more than 0.32 mg/L (vapour) in rats for both sexes. During exposure, snout wiping and attempts to escape were observed. No reliable acute dermal studies are available for *p*-methoxybenzaldehyde.

A human patch test (190 subjects as total) of *p*-methoxybenzaldehyde was negative. A dermal irritation study in 3 rabbits (similar to Federal Register 38 No. 187, § 1500.41) showed that the substance was slightly irritating after application for 4 hours under occlusive conditions, but the effects were fully reversible within 8 days for 2 of 3 animals. *p*-Methoxybenzaldehyde was slightly irritating in the eye irritation assay in 3 rabbits (similar to Federal Register 38 No.187, §1500.41), but the effects were fully reversible within 72 h. *p*-Methoxybenzaldehyde is considered to be non irritating to the skin and eye.

In a maximisation test on 25 male volunteers, 10 % *p*-methoxybenzaldehyde was not sensitizing. The result of animal experiments performed according to the OECD TG 429 and EPA OPPTS 870.2600 was also negative. *p*-Methoxybenzaldehyde is considered to be non sensitizer to the skin.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), rats were given *p*-methoxybenzaldehyde by gavage at 0, 20, 100 or 500 mg/kg bw/day. Males were dosed for 42 days from 14 days before mating and females were dosed from 14 days before mating to day 4 of lactation throughout the mating and pregnancy period. No animals died in any group. Temporary salivation after administration was observed in males and females in the 500 mg/kg bw group. Body weight tended to be increased in males in the 500 mg/kg bw group and females in the 100 and 500 mg/kg bw groups. Decrease in platelets was observed in males in 500 mg/kg bw group and in females in the 100 and 500 mg/kg bw groups. Hyperplasia of squamous epithelium was detected in males and females given 100 or 500 mg/kg bw. In the 500 mg/kg bw group, the liver weight was increased in males and females. Histologically, centrilobular hypertrophy or hepatocytes was detected in these animals. On biochemical analysis, the A/G ratio, GOT activity and inorganic phosphorus concentration were found to be increased in males in the 500 mg/kg bw group. Therefore,

the NOAEL for repeated dose oral toxicity was considered to be 20 mg/kg bw/day in both sexes

p-Methoxybenzaldehyde did not induce gene mutations in bacterial *in vitro* tests (OECD TG 471) or chromosomal aberrations in non-bacterial *in vitro* tests (OECD TG 473). The test substance showed positive results in *in vitro* studies using the mouse lymphoma and the induction of SCE in the *in vitro* study using human lymphocytes at non-cytotoxic doses. Equivocal results exist concerning genotoxicity based on *in vitro* reports and QSAR predictions, suggesting some concerns for genotoxicity of *p*-methoxybenzaldehyde. No valid *in vivo* genotoxicity study of *p*-methoxybenzaldehyde is available for clarification of the positive results reported *in vitro*. However, an *in vivo* micronucleus test on the closely related structural analogue, i.e. 4-ethoxybenzaldehyde, was negative up to the maximum tolerated dose in mice. Based on the available data, *p*-methoxybenzaldehyde was not considered to raise a health concern about *in vivo* genotoxicity.

There is no reliable information on carcinogenicity either for *p*-methoxybenzaldehyde or for 4-ethoxybenzaldehyde.

In the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), the rats were given *p*-methoxybenzaldehyde by gavage at 0, 20, 100, or 500 mg/kg bw/day for 42 days beginning 14 days before mating in males, and from 14 days before mating to day 4 of lactation throughout the mating and pregnancy period in females. In the 500 mg/kg bw group, the number of non-pregnant females was increased although all pairs copulated. The fertility index was also reduced, and the number of pups, the delivery index and the number of live pups on lactation day 0 and 4 were lower than in the controls at 500 mg/kgbw/day. Therefore, the NOAEL for reproductive and developmental toxicity in rats was considered to be 100 mg/kg bw/day.

***p*-Methoxybenzaldehyde possesses properties indicating a hazard for human health (repeated dose, reproductive and/or developmental toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.**

Environment

p-Methoxybenzaldehyde is stable in water: a hydrolysis test according to OECD Guideline 111 showed no hydrolysis at pH 4, 7 and 9 at 50 °C for five days. Using AOPWin (version 1.91), a calculated half-life time of 5.2 hours is obtained for the indirect photo-oxidation of *p*-methoxybenzaldehyde by reaction with hydroxyl radicals in air.

A test result with activated sludge shows 99 % degradation by BOD after two weeks cultivation period according to OECD Guideline 301C. A test result according to OECD Guideline 301E with activated sludge shows 97 % of biodegradability after 7 days. These results show that *p*-Methoxybenzaldehyde is readily biodegradable. A bio-concentration factor (BCF) of 4.5 was obtained by BCFWin using a log K_{ow} of 1.76, showing a limited potential for bioaccumulation of *p*-methoxybenzaldehyde.

Fugacity level III calculations with EPISuite show that *p*-methoxybenzaldehyde is mainly distributed to the water compartment (34.3 %) and the soil compartment (64.5 %) with negligible amounts in air and sediment compartments if equally and continuously released to the air, soil and water. A Henry's law constant of 7.94×10^{-7} atm.m³/mole at 25 °C suggests that volatilization of *p*-methoxybenzaldehyde from the water phase is expected to be low.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ = 40 mg/L (measured)
Invertebrate [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 45 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ = 61 mg/L (measured; growth rate)
	72 h EbC ₅₀ = 59 mg/L (measured; biomass)

The following chronic toxicity test results have been determined for aquatic species:

Invertebrate [<i>Daphnia magna</i>]:	21 d NOEC = 0.71 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOEC = 0.65 mg/L (measured; growth rate)
	72 h NOEC = 0.65 mg/L (measured; biomass)

***p*-Methoxybenzaldehyde possesses properties presenting a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L for fish, invertebrate and algae, and chronic toxicity lower than 1 mg/L for invertebrate and algae) however the substance is readily biodegradable and has low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.**

Exposure

Production and import volume of *p*-methoxybenzaldehyde in the sponsor country was 100 ton – 1000 ton in 2007. Production and import volume in USA was 1 – 10 million pounds (454 ton – 4540 ton) in 2006 according to IUR information. In Germany, production volume of 500 – 3000 ton/year was reported. According to SPIN database, total volume of the use of *p*-methoxybenzaldehyde in the Nordic countries was less than 1 ton in 2007. Worldwide production volume of *p*-methoxybenzaldehyde was not available. *p*-Methoxybenzaldehyde is produced by methylation of the raw material *p*-cresol followed by further oxidation. Another method of the production is from oxidation of anethole with either chromic acid or sulphuric acid.

p-Methoxybenzaldehyde is used as a fragrance compound for soaps, shampoos and toiletry products, an intermediate of pharmaceutical products and a surface treatment agent for metalizing plating process in the sponsor country. *p*-Methoxybenzaldehyde is also used as a flavoring in food and beverages as this chemical is designated as a food additive in the sponsor country. According to SPIN database, the main use patterns in the Nordic countries in 2007 are odour agents, cleaning/washing agents and industry perfumes.

p-Methoxybenzaldehyde may be released to the waste water during the manufacturing and packing process. However, waste water is treated in the waste water treatment plant with activated sludge before it is released to the environment in the sponsor country. As *p*-methoxybenzaldehyde is readily biodegradable, production and packaging are unlikely to lead to environment exposure. However, as *p*-methoxybenzaldehyde has a number of dispersive uses such as components in soaps, shampoos and toiletry products, emissions to the environment from some downstream uses are possible.

p-Methoxybenzaldehyde is a naturally occurring substance as it is a metabolic product of fungal organisms. Therefore, human and non-human organisms will be naturally exposed with non-quantifiable amount of this substance.

Occupational exposure to this chemical through inhalation of mist or vapor is possible. Dermal exposure is also possible, but effect of dermal exposure may be small.

p-Methoxybenzaldehyde may be contained in food and beverage as this chemical is allowed to use as a food additives in the sponsor country. Therefore, consumer exposure through consumer products and foods/beverages is expected. No other information on the consumer exposure in the sponsor country is available.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-86-4
Chemical Name	n-butyl acetate
Structural Formula	CH ₃ -COO-CH ₂ -CH ₂ -CH ₂ -CH ₃

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Data from n-butanol (BA) toxicity studies have been included in the assessment of butyl acetate (BAc). Data from n-butanol is useful when assessing the hazards associated with the systemic toxicity of n-butyl acetate (BAc) exposure due to the rapid and complete hydrolysis of BAc to BA *in vivo*. Exposure to BAc via dermal, inhalation, and water or dietary administration results in the rapid appearance of BA in the systemic circulation due to metabolism of the acetate ester within barrier tissues. Since exposure to either BAc or BA results in systemic exposure to BA, systemic toxicity data from studies that administer BAc directly are useful in identifying hazards associated with BA exposure. Endpoints of BAc toxicity that are associated with direct contact-mediated effects (e.g. eye, skin, and respiratory tract irritation) cannot be extrapolated from BA data due to the difference in physical-chemical properties of the two materials.

Human Health

n-Butyl acetate (BAc) exhibits low acute toxicity by the oral, dermal, and inhalation routes. The oral LD₅₀ ranges from 3,200 mg/kg in rabbits to 14,130 mg/kg in rats. Dermal LD₅₀ values range from >5,000 mg/kg to 17,600 mg/kg in rabbits. Inhalation LC₅₀ values for vapour exposures were >8,000 ppm (38,320 mg/m³) in well-controlled studies. Nose-only inhalation studies using atomizers to generate a mixture of aerosols and vapour yielded conflicting and nonreplicable data with deaths below 8,000 ppm in some instances. In these acute studies, the major sign of toxicity observed were depressed central nervous system function, which is documented to be well known to alcohols and esters of alcohols. BAc is not a dermal sensitizer or an eye or skin irritant. In repeat-dose inhalation toxicity studies, (9 days to 13 weeks), NOAELs of 500 ppm (2395 mg/m³) and higher were observed in rats. Effects observed included decreased activity during exposure, decreases in motor activity immediately post-exposure, decreases in body weights and rate of weight gain, and degeneration of olfactory epithelium in the nose. Repeated exposures for 13-weeks to concentrations as high as 3000 ppm (1437 mg/m³) did not find any evidence of cumulative neurotoxicity when motor activity, functional observational batteries, and scheduled controlled operant behaviour were assessed. Therefore, other than transient reversible sedation during exposure, BAc should not be considered a neurotoxicant. The degeneration of the olfactory epithelium within the nose is a common lesion in rats exposed by inhalation to acetate esters of short-chain alcohols due to the liberation of acetic acid in these cells from the hydrolysis of the ester linkage. Since rats are obligate nose-breathers, the delivered dose to this portion of the nose is higher in rats than humans and the significance of this lesion in human health is questionable. Pharmacokinetic studies have demonstrated an elimination half-life for BAc of 0.41 minutes in blood *in vivo* in rats. The rapid appearance of the n-butanol (BA) metabolite allows the use of studies conducted directly with BA to be used in hazard identification and assessment for BAc.

In the 13-week inhalation study using BAc, no effects on homogenisation-resistant sperm or spermatid head counts collected from the testes and epididymides, respectively were observed. Developmental

toxicity studies have been conducted in rats and rabbits exposed via inhalation to 1500 ppm (7185 mg/m³) BAc. In rats, reduced fetal size was observed after exposure to BAc during gestation days 1-16 or 7-16 and decreased body weight was seen in dams exposed from GD 1-16. Therefore, the maternal and developmental LOAEC was determined to be 7185 mg/m³ in rats. In rabbits, there was an increase in the incidence of “misaligned sternebra” and “retinal folds” in the group exposed from GD 1-19. A single increased incidence of a morphologic variation (“clear gallbladder”) was also seen in this group of rabbits. A maternal NOAEC and developmental LOAEC of 7185 mg/m³ were determined for rabbits. No teratogenicity was observed in rats or rabbits. These results indicate that BAc may result in developmental toxicity at high doses.

In vitro mutagenicity and chromosomal aberration studies indicate that BAc is not a genotoxicant. In addition, BA was negative in an *in vivo* mouse micronucleus study. Inhalation of 200 ppm (958 mg/m³) BAc or higher has been reported to cause slight irritation to the throat of human subjects, while lower exposure concentrations were without effects. In humans, eye irritation occurs at levels > 1400 mg/m³.

Environment

The available physicochemical data are adequate to describe the properties of n-butyl acetate (BAc). BAc has a vapour pressure of 12-21 hPa at 20°C, a water solubility of 14 g/l at 20°C and a Log K_{ow} of 1.82. The photochemical removal of n-butyl acetate from the troposphere occurs at a slow rate with the total tropospheric lifetime of n-butyl acetate expected to be about 50 hours. BAc is readily biodegradable under aerobic conditions. However, the primary mode of removal from surface water is volatilisation. BAc is not persistent in the environment and is not likely to bioaccumulate in food webs. Based on fugacity-dependent modelling it is estimated that the majority of BAc released to the environment will partition into air (97.2 %), with a smaller amount in water (2.4%). The stability of BAc in water is pH dependent, at neutral pHs (7) the T_{1/2} = 3.1 years at 20°C and at higher pHs (8 and 9) the T_{1/2} is shortened to 114 days and 11.4 days respectively. Based on acute aquatic toxicity data, the most sensitive species appears to be in fish (*Pimephales promelas*) which has a 96h LC50 of 18 mg/L. Terrestrial data are not available, but based on negligible soil release and low potential for bioaccumulation, adverse terrestrial outcomes are considered unlikely.

Exposure

Approximately 132,000 tonnes (290 million pounds) of BAc were manufactured in the USA in 1993, using a continuous, closed process. Environmental release from production facilities is low. BAc is used as a solvent in liquid formulation products, typically lacquers, solvent mixtures, inks, coatings, and adhesives. Application of these materials results in exposure via the dermal and inhalation routes, and release of BAc into the environment through volatilisation. Due to the physical-chemical properties of BAc, the material is not typically present as an aerosol. In regards to physical hazard, the chemical has a low flash point and a flammable range of 1.7 to 7.6% volume in air. Monitoring of lacquer spray booths (believed to represent a worst-case occupational exposure) provided breathing zone measurements of BAc in the 1-10 ppm (.21 – 2.1 mg/m³) range. BAc is also a product of normal intermediary metabolism in mammals and a natural component of apple, potatoes, and nuts.

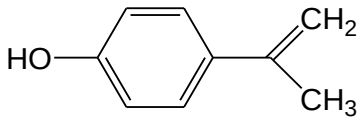
NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos	124-38-9
Chemical Names	Carbon dioxide
Structural Formulae	CO ₂
This chemical is considered of low priority for further work at the OECD, due to its intrinsic properties indicating a low hazard	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	4286-23-1
Chemical Name	4-(1-Methylethenyl)phenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

4-(1-Methylethenyl)phenol is a white to pale yellow crystal with a water solubility of 1.39 g/L at 20 °C. Melting point and boiling point are 83.1 – 85.0 °C and 276.0 – 277.0 °C respectively. A measured partition coefficient between octanol and water (Log K_{ow}) is 2.90. An estimated value of vapour pressure with MPBPWIN is 0.0911 Pa at 25 °C. A measured dissociation constant in water (pK_a) is 9.54. The estimated Log K_{oc} is 3.12.

Human Health

There is no experimental data available on toxicokinetics. However, the physicochemical properties and repeated dose oral gavage studies of 4-(1-methylethenyl)phenol in animals provide strong support in determining the ADME profile for this substance. Based on these data, 4-(1-methylethenyl)phenol is considered to be absorbed via the gastrointestinal tract and well distributed in the mammalian body. It may be metabolized by conjugation pathways and excreted via urines and feces.

In an acute toxicity study of 4-(1-methylethenyl)phenol in rats [OECD TG 401], the oral LD_{50} values were considered to be 585.8 mg/kg bw in both sexes. No acute inhalation or dermal studies were available for 4-(1-methylethenyl)phenol.

There were no experimental data on irritation or sensitisation.

In the 28-day repeated dose toxicity test [OECD TG 407], male and female rats were given 4-(1-methylethenyl)phenol by gavage at 0, 30, 100, 300 or 400 mg/kg bw/day for 28 days. Suppression of body weight gain and a decrease in food consumption were apparent in females at 300 mg/kg bw and above after day 7 of the administration period. Haematological, clinical chemistry and organ weight changes were observed at 300 mg/kg bw/day and above in both sexes. Histopathological examination revealed squamous cell hyperplasia of the forestomach in females at 100 mg/kg bw and above. Squamous cell hyperplasia of the limiting ridge of the stomach was also observed in males and females at 100 mg/kg bw/day and above. The NOAEL for this repeated dose toxicity study was considered to be 30 mg/kg bw/day.

In the reproduction/developmental toxicity screening test [OECD TG 421], Crj:CD (SD)IGS rats (13 animals/sex/dose) were given 4-(1-methylethenyl)phenol by gavage at a dose of 0 (vehicle: 0.5CMC Na solution), 4, 15, or 60 mg/kg bw/day. Dose levels were determined according to a 5-day preliminary study. Males were dosed for a total of 47 days from 14 days before mating and females were dosed from 14 days before mating to day 3 of lactation throughout the mating and pregnancy period. Thickening of the mucosa in the forestomach accompanied by diffuse squamous hyperplasia was found in the 60 mg/kg bw/day group. A decrease in thymus weights and an increase in extramedullary haemopoiesis in spleen were observed at the LOAEL of 60 mg/kg bw/day in females. Based on these results, the NOAEL for repeated dose toxicity was considered to be 15 mg/kg bw/day.

A reverse gene mutation assay [OECD TG 471] and a chromosomal aberration test in cultured Chinese hamster lung (CHL/IU) cells [OECD TG 473] were conducted. 4-(1-Methylethenyl)phenol did not induce gene mutations in the bacterial *in vitro* test, but induced chromosomal aberrations in the mammalian *in vitro* test. An *in vivo* oral (by gavage) micronucleus assay [OECD TG474] in rats was negative up to the dose of 600 mg/kg bw, which is similar to the LD_{50} , and represent a cytotoxic dose to the bone marrow. Based on these results,

weight of evidence suggested that 4-(1-methylethenyl) phenol is not genotoxic *in vivo*.

There was no experimental data available on carcinogenicity.

In the reproduction/developmental toxicity screening test [OECD TG 421], rats were given 4-(1-methylethenyl)phenol by gavage at 0, 4, 15 or 60 mg/kgbw/day for 47 days beginning 14 days before mating in males, and for 14 days before mating to day 3 of lactation throughout the mating and pregnancy period in females. There were no adverse effects on reproductive and developmental indices in any groups. Therefore, the NOAEL for reproductive and developmental toxicity in rats was considered to be 60 mg/kgbw/day, the highest dose tested.

4-(1-Methylethenyl)phenol possesses properties indicating a hazard for human health (repeated dose toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The pK_a of 9.54 indicates that most 4-(1-methylethenyl)phenol will exist in its neutral form in water under environmental conditions. 4-(1-Methylethenyl)phenol is not stable in water at low pH according to OECD Guideline 111. Half-life times in water are 1.7 days for pH 4 at 25 °C, 15.6 days for pH 7 at 25 °C and 157 days for pH 9 at 25 °C.

4-(1-Methylethenyl)phenol was not readily biodegradable under aerobic conditions after 4 weeks cultivation period according to OECD Guideline 301C. Measured bio-concentration factors (BCF) of 4-(1-methylethenyl)phenol with Japanese carp were 14 with test concentration of 50.0 µg/L and 19 with test concentration of 5.0 µg/L according to OECD Guideline 305. These results show a limited potential for bioaccumulation of 4-(1-methylethenyl)phenol. Using AOPWin (version 1.91), a calculated half-life time of 1.546 hours is obtained for the indirect photo-oxidation of 4-(1-methylethenyl)phenol by reaction with hydroxyl radicals in air.

Fugacity level III calculations with EPISuite show that 4-(1-methylethenyl)phenol is mainly distributed to the water compartment (25.7 %) and the soil compartment (73.8 %) with negligible amounts in air and sediment compartments if equally and continuously released to the air, soil and water. A Henry's law constant of 4.51×10^{-7} atm.m³/mole (0.0457 Pa.m³/mole) at 25 °C suggests that volatilization of 4-(1-methylethenyl)phenol from the water phase is expected to be low.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ = 9.2 mg/L (measured)
Invertebrate [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 4.1 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ = 5.4 mg/L (measured; growth rate)
	72 h EbC ₅₀ = 5.0 mg/L (measured; biomass)

The following chronic toxicity test results have been determined for aquatic species:

Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOEC = 1.3 mg/L (measured; growth rate)
	72 h NOEC = 1.3 mg/L (measured; biomass)

4-(1-Methylethenyl)phenol possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L for fish, invertebrate and algae and not readily biodegradable). However the substance has low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

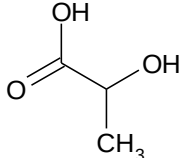
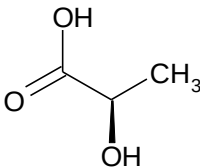
Annual production volume of 4-(1-methylethenyl)phenol in the sponsor country is less than 100 tonnes although this used to be a high production volume chemical. Worldwide production volume of 4-(1-methylethenyl)phenol is not available. 4-(1-Methylethenyl)phenol is produced from the residue of a manufacturing process of another chemical in the sponsor country. 4-(1-Methylethenyl)phenol is used as a raw material of light-sensitive resin used in several industrial processes in the sponsor country. No other information on the use pattern is available.

Although 4-(1-methylethenyl)phenol may be released to the environment during the manufacturing process, all vent gases in the plant are released into the air after the scrubber treatment. The whole manufacturing process is conducted in a closed system in the sponsor country. In the packing process, powder dusts of 4-(1-methylethenyl)phenol may be dispersed. However, packing places are equipped with exhaust equipment. Therefore, no significant emission into the environment is foreseen.

Occupational exposure to this chemical through inhalation of dusts and dermal contact is possible. Inhalation of vapour may be negligible due to its low vapour pressure at room temperature.

4-(1-Methylethenyl)phenol is not used in general consumer products in the sponsor country. Therefore, no consumer exposure is foreseen in the sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	50-21-5
Chemical Name	Lactic Acid
Structural Formula	 Lactic Acid  L(+)-Lactic Acid

SUMMARY CONCLUSIONS OF THE HAZARD CHARACTERIZATION

NOTE: The conclusions in this document are based on consideration of comments from OECD member countries and the final Hazard Characterization and Robust Summary documents published in August 2008 by the United States in the US HPV Chemicals Program (http://www.epa.gov/chemrtk/hpvis/rbp/Lactic%20Acid_Web_SuppDocs_August%202008.pdf). The SIDS endpoints requested in the US HPV Chemicals Program are equivalent to those evaluated in the OECD HPV Chemicals Program.

Justification for Supporting Chemical

The sponsored chemical, lactic acid (CAS No. 50-21-5), is the racemic mixture. However, only the natural form of lactic acid—L(+)-lactic acid (CAS No. 79-33-4)—is usually manufactured. L(+)-Lactic acid is biologically important; therefore, most available hazard data have been developed for the L(+)-form. L(+)-lactic acid is used as a supporting chemical for racemic lactic acid. The calcium salt (calcium lactate) of lactic acid was also used as a supporting chemical for repeated dose toxicity and carcinogenicity.

Physical-Chemical properties

Lactic acid is a clear to slightly yellow liquid with a melting point of 16.8°C, a boiling point of 258°C at 1,000 hPa, a vapour pressure of 0.004 hPa at 20 °C, the octanol-water partition coefficient (log K_{ow}) of -0.62 and water solubility of 876 g/L. As the dissociation constant (pKa) is 3.68, lactic acid is anticipated to exist primarily in its dissociated form at environmentally relevant pH.

Human Health

No data were provided for reproductive toxicity and limited data are available for some other endpoints. However, testing was not deemed necessary because the substance is a normal component of human intermediary metabolism.

L(+)-Lactic acid is a natural, functional metabolite in mammals, and serves as mammalian fuel. According to the "lactate shuttle" concept, L(+)-lactic acid represents a major means of distributing carbohydrate potential energy

for oxidation and gluconeogenesis. The concept of a "lactate shuttle" is that during hard exercise, as well as other conditions of accelerated glycolysis, glycolic flux in muscle involves L(+)-lactic acid formation regardless of the state of oxygenation. The production rate of endogenous L(+)-lactic acid in the resting human is about 1.3 mol (70 kg/bw) 24 h⁻¹ (equals 117 g/day).

The acute oral LD₅₀ value for L(+)-lactic acid is 3543 – 4936 mg/kg-bw for male and female Charles River rats. Lethargy, ataxia, prostration, irregular breathing, piloerection, squinting, lacrimation, salivation, crusty eyes and muzzle, loose stools, damp or yellow/brown stained fur and moribund were the clinical signs observed as early as 0 – 1 hour after dosing and as late as day 2. Necropsy of animals found dead and the four surviving females at 3162 mg/kg-bw included discoloured lungs; firm texture of lungs; green foci on one lung; several stomach lesions; discoloured liver; white foci on the liver; pale capsular areas, superficial erosion, or mottled liver; discoloured kidney and red-brown exudates in the nasal and/or oral regions. The acute dermal LD₅₀ value in male and female New Zealand white rabbits is > 2000 mg/kg bw following 2 hour exposure of L(+)-lactic acid to clipped, abraded skin. No mortality or clinical signs of toxicity were seen. Severe erythema and edema were observed at the application sites of all animals on day 1. Both erythema and edema decreased in severity by observation day 14. Blanching, necrosis, eschar formation, atonia, desquamation and denuded areas were also seen at some application sites. At necropsy, A dark red focus was observed on the lung of one male; no other abnormalities were observed. In a 4-h acute inhalation study in male and female Fischer rats via nose-only exposure to L(+)-lactic acid aerosol, the LC₅₀ was > 7.9 mg/L. Rapid breathing, lacrimation, hunched posture, ruffled fur and unkempt appeared with soiled fur were observed in the exposed animals. Female rats appeared lethargic during exposure. By 24 hours, most animals appeared to have recovered from lethargy and unkempt fur. Exposed females (4/5) had ruffled and ungroomed fur until post-treatment day 4. One exposed female died on day-8 post-treatment. No gross lesions were observed at necropsy.

L(+)-Lactic acid is severely irritating and corrosive to rabbit skin [OECD TG 404], slightly irritating to guinea pig skin and not irritating to pig skin. L(+)-Lactic acid is not a dermal sensitizer in guinea pigs [Buehler method].

The repeated-dose toxicity was evaluated as follows: Experiment I: F344 rats (5/sex/dose) were administered calcium lactate via drinking water at 0, 0.3, 0.6, 1.25, 2.5 and 5% (corresponding to 0, ~30, 60, 125, 250 and 500 mg/kg-bw/day) for 13 weeks. In all groups, basic diet (CRF-1) was given ad libitum. No mortalities occurred. A slight decrease in body weight gain (less than 10%) compared to controls was observed at all concentrations. Changes in some haematological and biochemical parameters were observed. On histological examination, however, no severe toxicological findings were noted in any of the treated groups. Experiment II: Rats were fed synthetic diet B, containing 0, 5, 10, 20 or 30 % calcium lactate. At the highest dose, body weight-gain was decreased compared to the control group. Histological examination revealed nephrocalcinosis in all groups, including the control group and the degree of occurrence was dose-dependent. Females exhibited this lesion to a greater extent than males. In a follow-up study, rats were given CRF-1 or synthetic diet B for 8 weeks. Nephrocalcinosis was observed only in the group given diet B. It was concluded that the nephrocalcinosis observed in Exp. II was dependent on the low Ca/P ratio (less than 1) of the synthetic diet B. The NOAEL was 500 mg/kg bw/day (highest dose tested).

In an Ames test with multiple strains of *Salmonella typhimurium*, L(+) lactic acid was negative both with and without metabolic activation and up to concentrations of 10,000 µg/plate. Positive controls were tested concurrently and responded appropriately. In an *in vitro* chromosomal aberration test using Chinese hamster ovary cells, L(+) lactic acid did not induce clastogenic activity with and without metabolic activation when the medium was neutralized to physiological pH 6.4. Pseudo-positive reactions were seen as a result of low pH. Limited details were available regarding this study. Overall, L(+) lactic acid was not mutagenic.

F344 rats (50/sex/dose) were given calcium lactate in the drinking water at levels of 0, 2.5 or 5% for 2 years. The high-dose animals (males and females) showed a significant reduction in mean body weight gain. There was no evidence of organ-specific toxicity and there was no evidence of carcinogenicity. Limited data are available regarding this study.

No data were provided for the reproductive toxicity endpoint. In a developmental toxicity study, lactic acid was neither toxic to dams or offspring when administered orally to pregnant CD-1 mice via gavage at doses of 0 or 570 mg/kg bw/day during days 6-15 of gestation. The NOAEL for maternal and developmental toxicity was 570 mg/kg bw.

Lactic acid does not present a hazard for the human health based on its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD

HPV Programme.**Environment**

Lactic acid is not susceptible to hydrolysis under environmental conditions. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a calculated half-life of 22 hours. A biodegradation test resulted in 67% biodegradation in 20 days; therefore, lactic acid is readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that lactic acid will partition primarily into water (46.3%) and soil (50.5%), with minor distribution to the air (3.2%) and sediment (0.07%). A Henry's law constant of 9.6×10^{-9} atm-m³/mol (9.74×10^{-6} hPa-m³/mol) by VP/WSol estimation method at 25 °C suggests that volatilisation of lactic acid from the water phase is expected to be low.

The bioaccumulation potential seems to be low based on a log K_{OW} of -0.62, supported by an estimated BCF value of 3 (BCFBAF v 3.0). The following acute toxicity test results for L(+)-lactic acid have been determined for aquatic species:

Fish (Zebrafish; <i>Brachydanio rerio</i>)	OECD TG 203	96 h LC ₅₀ = 320 mg/L*
Fish (Bluegill sunfish; <i>Lepomis macrochirus</i>)	OECD TG 203	96 h LC ₅₀ = 130 mg/L*
Invertebrate (<i>Daphnia magna</i>)	OECD TG 202	48 h EC ₅₀ = 240 mg/L*
Algae (<i>Pseudokirchneriella subcapitata</i>)	OECD TG 201	70-h EC ₅₀ (growth) = 3500 mg/L 70-h EC ₅₀ (biomass) > 2800 mg/L

*The test solutions were not neutralized.

Lactic acid does not present a hazard for the environment based on its low hazard profile. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

Lactic acid and its supporting chemical L(+) lactic acid have an aggregated production volume in the range from 51 million to 110 million pounds (23133 to 49895 tonnes). These chemicals are used as solvents, pH-regulating agents or intermediates in a variety of industries, including the manufacturing of basic organic chemicals, paints and coatings, soaps and cleaning agents as well as textiles and fabrics. Both chemicals are used in commercial settings or consumer products. Lactic acids are naturally occurring in foods, and are used as an acidulant in foods, mordant in printing woolen goods, solvent, and in textile, leather and many other applications.

L(+)-Lactic acid is a natural, functional metabolite in mammals, and serves as mammalian fuel; therefore, humans and animals will be exposed internally to lactic acid.

Environmental exposure to lactic acid is expected based on environmental release information from manufacturing, processing and uses.

Exposures of the general population, workers, consumers and children to lactic acid is also expected based on the wide variety of uses including commercial and consumer uses.

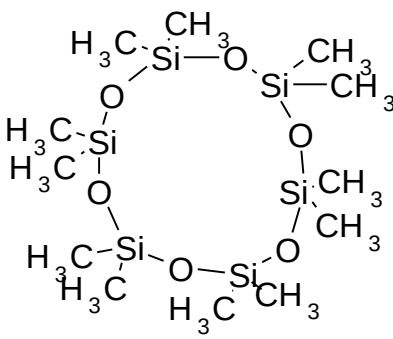
SIDS INITIAL ASSESSMENT PROFILE

CAS Nos	50-70-4
Chemical Names	D-glucitol
Structural Formulae	$C_6H_{14}O_6$
This chemical is considered of low priority for further work at the OECD, due to its intrinsic properties indicating a low hazard	

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos	50-99-7
Chemical Names	Glucose
Structural Formulae	$C_6H_{12}O_6$
This chemical is considered of low priority for further work at the OECD, due to its intrinsic properties indicating a low hazard	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	540-97-6
Chemical Name	Dodecamethylcyclohexasiloxane (D6)
Structural Formula	
SUMMARY CONCLUSIONS OF THE SIAR Physical-Chemical Properties D6 is a clear, odorless liquid with a melting point of -3°C, a boiling point of 245 °C (at 1013 hPa) and a measured vapor pressure of 4.6 Pa at 25 °C. The measured octanol-water partition coefficient (log K_{ow}) is 8.82 (at 23.7 °C) and the measured water solubility is 0.00513 mg/L at 23 °C. Human Health The absorption, distribution, metabolism and excretion of D6 has been studied in rats. In rats after oral exposure, the majority of ¹⁴C-D6 was eliminated in the feces within 48 hours, unchanged. Approximately 12-15% was absorbed; 11-13% was excreted as volatiles; and a small amount of the substance was systemically available and distributed to the liver, brown fat and bone marrow. <i>In vitro</i> dermal absorption studies using human skin under semi-occluded conditions showed that the majority of the applied dose was found on the skin surface or volatilized from the dosing site, suggesting that D6 does not penetrate the skin. The oral and dermal LD₅₀ values for male and female rats were determined to be >2000 mg/kg-bw. No mortality or changes in clinical signs were observed. D6 does not cause skin or eye irritation in rabbits and it does not cause skin sensitisation in guinea pigs. The repeated-dose toxicity of D6 has been investigated in two studies. In an OECD TG 422 study, rats (10/sex) were administered D6 in corn oil via oral gavage at 0, 100, 330 and 1000 mg/kg-bw daily for 29 days. Increases were observed in the relative weights of the liver and kidneys in both sexes and in the adrenal glands in females at all doses, although only the liver weight increase in females (seen at all dose levels) showed a dose-related response. Pulmonary granulomatous inflammation (focal, multifocal and/or widespread) was observed in 0, 5, 4 and 7 animals at 0, 100, 330 and 1000 mg/kg bw/day, respectively. Neither incidence nor severity increased with increasing dose levels of the test article. With the exception of the liver in females, there were no other changes in organ weights that appeared to have a dose response relationship. A LOAEL via the oral route was determined to be 100 mg/kg bw/day for systemic toxicity based on dose-responsive relative liver weight increases (14%), and periportal lipidosis in the female rat livers. In another oral gavage repeated-dose toxicity study, rats were exposed to 1500 mg/kg bw/day D6 in distilled water for 28 days. The study revealed no treatment-related effects in either sex. Based on no effects observed, the NOAEL in this study was considered to be 1500 mg/kg bw/day. In a bacterial reverse mutation assay with multiple strains of <i>Salmonella typhimurium</i>, and a strain of <i>Escherichia coli</i>, D6	

SIDS INITIAL ASSESSMENT PROFILE

was negative both with and without metabolic activation. D6 tested negative in both *in vitro* chromosomal aberration assay (Chinese hamster ovary cells) and *in vivo* mouse bone marrow erythrocyte micronucleus assay. Based on these results, D6 is not genotoxic either *in vitro* or *in vivo*.

No data were available for the carcinogenicity of D6.

The reproductive toxicity of D6 was investigated in a combined reproductive/developmental screening test in rats [OECD TG 422]. D6 in corn oil was administered via gavage to 10 female rats each at 0, 100, 330 and 1000 mg/kg bw/day for 14 days prior to mating, during mating, gestation and postpartum for a total exposure duration of 45 days. Ten male rats per dose group were exposed to D6 14 days prior to mating and during mating. Based on the results of this screening study, the LOAEL for maternal toxicity of D6 via repeated oral dosing was determined to be 100 mg/kg bw/day, based on effects in the liver. The NOAEL for reproductive/developmental toxicity was 1000 mg/kg bw/day. Overall, D6 did not show evidence of reproductive/developmental toxicity based on screening level data.

D6 possesses properties indicating a hazard for human health (repeated-dose toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The EPISuite program developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain siloxanes in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values reported below and they should be used with caution.

The hydrolysis half-life for D6 at 25 °C and pH = 7 has been estimated at > 1 year based upon extrapolation of the hydrolysis rates determined at 40 °C and pH = 10, and 60 °C and pH = 9. A hydrolysis half-life of 401 days has been estimated for D6 based upon the correlation between OH and H ion catalyzed hydrolysis rates and water solubility of D3, D4 and D5.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 5.96 days (EPISuite estimation using AOPWIN v 1.92). An OECD TG 310 study resulted in 4.47 % biodegradation after 28 days. D6 is not readily biodegradable under aerobic conditions. Level III fugacity modeling for D6 using loading rates for air, soil, and water of 1000 kg/h for each media shows environmental distributions of 0.5% in air, 1.4% in water, 28.1% in soil, and 70.0% in sediment. Due to its low water solubility, higher volatility and partitioning properties, D6 released into air or soil is expected to remain in that compartment, while D6 released into water is expected to partition primarily to the sediment (98.0%), based on the estimated log K_{oc} value of 6.03. Measured Henry's Law constant of 2.25×10^6 Pa·m³/mole (2.22×10^1 atm·m³/mole) at 23.7 deg C suggests that volatilization of D6 from the water phase is expected to be high. Based on available experimental data, D6 will degrade in dry soil (with half-lives ranging from hours to several months depending on soil type) into low molecular weight linear silanols that further degrade to dimethylsilanediol. D6 will ultimately degrade to inorganic silicate (sand), water, and carbon dioxide.

Bioaccumulation studies with freshwater fish (*Pimephales promelas*) and the aquatic invertebrate, *Daphnia magna*, resulted in BCF values of 1160 and 2400 L/kg, respectively. The fish BCF is based on total radioactivity (parent compound, any retained metabolites and assimilated carbon), representing a worst case condition. A sediment bioaccumulation study with the oligochaete, *Lumbriculus variegatus*, provided BAF values of 0.66 and 0.70 mg a.i./kg (dry weight) with a depuration half-life of 4.1 – 5.2 days. In a recent field study, as yet unpublished, lower concentrations of D6 were observed at increasingly higher trophic levels in an aquatic food chain.

Chronic toxicity studies with freshwater fish (*Pimephales promelas*, 49 days) and the water flea (*Daphnia magna*, 21 days) showed no observed effects (NOEC) at the limits of water solubility (4.4 and 4.6 µg/L, respectively); based on total radioactivity using radiolabeled ¹⁴C-D6. D6 also showed no adverse effects (NOEC ≥ 2 µg/L) on the yield or growth rate of the freshwater alga, *Pseudokirchneriella subcapitata* in a closed bottle study at the functional limit of water solubility (2 µg/L). Likewise, no toxicity to *Lumbriculus variegatus* was observed during the sediment BAF study at the two concentrations tested, 28 and 484 mg/kg (dry weight; measured concentrations).

D6 does not possess properties indicating a hazard to the environment based on its low hazard profile (i.e. no aquatic

SIDS INITIAL ASSESSMENT PROFILE

toxicity at the limit of water solubility). D6 is not readily biodegradable and has the potential to bioaccumulate. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

In 2007, the United States production volume was 7303 tonnes and accounted for 61% of global production.

D6 is widely used. It is used in the formulation of cosmetics and personal hygiene products, as an ingredient for manufacture of processing aids such as defoamers, surfactants and mold release agents, lubricants, polishes and coatings on a range of substrates including textiles, carpeting and paper, sealants, architectural coatings, mechanical, heat transfer and dielectric fluids and reprography.

The presence of D6 in the environment depends on its uses and the compartment into which it is released. The major route of entry into the environment is expected from its release into the atmosphere due to the volatility of D6 and can occur during manufacturing, via personal care products, or from atmospheric releases during wastewater treatment. Partitioning to sludge will compete with volatilization during wastewater treatment. D6 has been detected in the livers of marine fish, common mussels, flounder livers and fillets and in cod stomach contents in Europe as well as in ambient and indoor air, sludge, soil, sediment and coastal waters.

Producers, processors and formulators of personal care products may be exposed to D6 as may barbers and beauticians. Consumer exposure may occur through dermal, inhalation or oral pathways. Environmental exposure is possible. Although the majority of testing covered in the above mentioned health and environmental studies was conducted with D6 at greater than 99.5% purity, the D6 that is in commerce can contain impurities that can be up to 4% which include Octamethylcyclotetrasiloxane (D4), Decamethylcyclopentasiloxane (D5) and tetradecamethylcycloheptasiloxane (D7) and greater methylcyclsiloxanes. D4 and D5 are generally less than 2% individually in the commercial D6 product.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos	57-50-1
Chemical Names	Sucrose, pure
Structural Formulae	$C_{12}H_{22}O_{11}$
This chemical is considered of low priority for further work at the OECD, due to its intrinsic properties indicating a low hazard	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	61898-95-1
Chemical Name	Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester
Structural Formula	

SUMMARY CONCLUSIONS OF THE HAZARD CHARACTERIZATION

NOTE: The conclusions in this document are based on considerations of comments from OECD member countries and the Hazard Characterization and Robust Summary documents published in September 2008 by the United States in the US HPV Chemicals Program (http://www.epa.gov/chemrtk/hpvis/rbp/61898-95-1_Web_SuppDocs_Sept2008.pdf). The SIDS endpoints requested in the US HPV Chemicals Program are equivalent to those evaluated in the OECD HPV Chemicals Program.

Reduced Testing Rationale

Testing for the repeated-dose and reproductive toxicity endpoints was waived because cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester is a closed-system intermediate (CSI); the chemical is isolated at the production plant, is shipped in drums or tank trucks and is then used as a starting material for the production of pyrethroid insecticides in the sponsor country. However, reproductive toxicity was assessed in the reproductive/developmental toxicity screening test [OECD TG 421].

Physical-Chemical Properties

Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester is a clear, colourless liquid at room temperature with a melting point of 28 °C (estimated), a boiling point of 78 °C at 0.6 mm Hg (0.80 hPa) and a measured vapour pressure of 0.04 hPa at 25 °C. The measured octanol-water partition coefficient (log K_{ow}) is 3.66 and the water solubility is 53 mg/L (measured) at 25 °C.

Human Health

Toxicokinetics data are not available.

The oral LD₅₀ value for cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester was > 5000 mg/kg bw in male and female rats following gavage administration. Clinical signs included abdominogenital staining, ataxia, chromodacryorrhea, chromorhinorrhea, cyanosis, diarrhea, exophthalmos, lacrimation, decreased locomotion, oral discharge, prostration and recumbency. One female died within 3 days following dosing. The inhalation LC₅₀ value was > 0.35 mg/L in male and female rats following 6 hours of exposure to saturated vapour of cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester. Clinical signs included squinting eyes, excessive lacrimation, red perinasal fur and irregular breathing patterns.

No experimental data are available for irritation or sensitisation studies in animals.

Repeated-dose toxicity data are not required in the U.S. HPV Chemical Challenge Program because the chemical is a CSI.

In a bacterial reverse mutation assay (Ames test) with multiple strains of *Salmonella typhimurium*, cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester was negative both with and without metabolic activation. An *in vitro* chromosomal aberration test [OECD TG 473] using cultured Chinese hamster lung cells was negative with and without metabolic activation. Based on these results, cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester is considered to be non genotoxic *in vitro*.

No data are available for the carcinogenicity of cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester.

Although not required because the chemical is a CSI, the reproductive toxicity was assessed in the reproductive/developmental toxicity screening test in rats [OECD TG 421]. In this study, cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester was administered via gavage to rats of both sexes at 0, 50, 450 or 900 mg/kg-bw/day. Male rats were administered the test substance from 2 weeks before mating to the end of mating period (28 days total). Females were administered the test substance from 2 weeks before mating, during mating through gestation and up to day 3 post partum (54 days total). There was a high incidence of salivation in both sexes at 450 and 900 mg/kg-bw/day. Two moribund females were sacrificed at 900 mg/kg-bw. There were no treatment-related changes in body weight, food consumption, necropsy finding, male reproductive organ weights or histopathological findings. An increase in perinatal deaths, decreased number and body weights of live young at birth, and decreased litter size were observed at 900 mg/kg-bw/day. No treatment-related effect was seen in gestation length, viability index, sex ratio, number of pups with gross lesions, or pups with abnormally low body weights. Based on mortality, the NOAEL and LOAEL for maternal toxicity was considered to be 450 and 900 mg/kg- bw/day, respectively. The NOAEL and LOAEL for developmental toxicity was considered to be 450 and 900 mg/kg-bw/day, respectively, based on decreased litter size and body weights and increased mortality in offspring.

Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester possesses properties indicating a hazard for human health (developmental toxicity only at high doses). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The hydrolysis half-life for cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester is 17 years at pH 7 (estimated). In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 2.4 days. A closed bottle OECD TG 301D resulted in 0 % biodegradation after 28 days. Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester is not readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-,methyl ester will distribute mainly to the soil (73.7 %) and water (21.4%) compartments with minor distribution to the air compartment (3.53%) and sediment compartment (1.42%). An estimated Henry's law constant of 1.63×10^{-4} atm-m³/mol (16.5 Pa- m³/mol) suggests that a potential for volatilization from the water phase is not expected to be high. A K_{oc} of 285.7 was estimated. The bioaccumulation potential seems to be low based on a log K_{ow} of 3.66 supported by an estimated log BCF value of 0.803 (BCFBAF v3.00).

The following acute toxicity test results have been determined for aquatic organisms:

Fish [<i>Oncorhynchus mykiss</i>]	96 h LC ₅₀ = 3.01 mg/L (measured)
Aquatic Invertebrate [<i>Daphnia magna</i>]	48 h LC ₅₀ = 7.04 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i>]	72 h ErC ₅₀ = 8.3 mg/L (measured)

Algae [*Pseudokirchneriella subcapitata*] 72 h EbC₅₀ = 5.2 mg/L (measured)

Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, methyl ester possesses properties indicating a hazard for the environment (acute toxicity to fish, invertebrates and algae from 1 to 100 mg/L). Although this chemical is not readily biodegradable, it has a limited potential for bioaccumulation. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-methyl ester is commercially produced with an annual production volume of approximately 4536 metric tons (2002) in the United States. Worldwide production volume is not available. Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-methyl ester is only used as a closed system intermediate.

The chemical is manufactured and processed in systems that are expected to reduce the potential for worker exposure and environmental releases. No commercial or consumer uses have been identified. Therefore, consumer exposure is not expected.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos	69-65-8
Chemical Names	D-mannitol
Structural Formulae	$C_6H_{14}O_6$
This chemical is considered of low priority for further work at the OECD, due to its intrinsic properties indicating a low hazard	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7758-87-4
Chemical Name	Tricalcium phosphate
Structural Formula	$2[\text{PO}_4^{3-}] \ 3[\text{Ca}^{2+}]$

SUMMARY CONCLUSIONS OF THE SIAR**Physical and chemical properties**

Tricalcium phosphate is amorphous, odourless, tasteless powder substance with a melting point of 1670 °C and density of 3.14 g/cm³. It has a low water solubility of ≤ 20 mg/L at 20 °C and negligible vapour pressure. The boiling point and partition coefficient for tricalcium phosphate are not applicable to an inorganic salt.

Human Health

Calcium is required for the proper functioning of muscle contraction, nerve conduction, hormone release, and blood coagulation. In addition, proper calcium concentration is required for various other metabolic processes. Calcium stores depend on dietary intake, absorption of gastrointestinal (GI) tract and renal calcium excretion. Phosphorus is one of the most abundant elements in the human body. Most phosphorus in the body is complexed with oxygen as phosphate. Phosphate is absorbed from, and to a limited extent secreted into, the GI tract. Transport of phosphate from the gut lumen is an active, energy-dependent process that is modified by several factors. As an example, vitamin D stimulates phosphate absorption, an effect reported to precede its action on calcium ion transport. In adults, about two thirds of the ingested phosphate is absorbed, and then almost entirely excreted into the urine. In growing children, phosphate balance is positive. Concentrations of phosphate in plasma are higher in children than in adults. Collapse of phosphate balance as 'hyperphosphatemia' decreases the affinity of hemoglobin for oxygen and is hypothesized to explain the physiological 'anemia' of childhood.

In an acute oral toxicity study [OECD TG 423], tricalcium phosphate was administered via gavage to 2 groups of 3 female rats at dose level of 2,000 mg/kg bw. No death and abnormal clinical signs were observed. Body weights increased normally. There were no macroscopic abnormalities at necropsy in the oral study. The acute oral LD₅₀ value was >2,000 mg/kg bw for rats. Depending on the relative absorption of calcium versus phosphate, a rise in serum phosphorus could stimulate parathyroid hormone (iPTH) secretion. The absorption and acute metabolic effects of oral tricalcium phosphate (TCP) and calcium carbonate (CC) were evaluated with 10 women, aged 22-40 years. The subjects were fasted overnight for 12 hours, 1,200 mg calcium (as CC or TCP) was ingested. Serum and urine calcium, phosphorus, and creatinine, urine cyclic adenosine monophosphate (cAMP) were determined. iPTH levels following TCP were also measured. Calcium absorption was determined by the postload rise in urine calcium above baseline. Urine calcium excretion increased significantly and was accompanied by significant rises in serum calcium after both preparations. Following tricalcium phosphate administration, serum and urine phosphorus increased. Urinary cAMP did not change after either preparation, and iPTH levels fell after oral tricalcium phosphate. Tricalcium phosphate administered orally is absorbed and does not stimulate parathyroid gland function. No acute inhalation and dermal toxicity studies were available.

No experimental data are available for skin and eye irritation in animals. Trisodium phosphate has however skin and eye irritation properties, therefore it can be anticipated that tricalcium phosphate may also have skin and eye irritant properties.

There were no experimental data available for skin sensitization in animals.

In a repeated dose oral toxicity study according to the OECD Guideline 422, tricalcium phosphate was administered via gavage at dose levels of 0, 250, 500 and 1,000 mg/kg bw/day to male rats from 2 weeks before mating to the end of the mating period, for at least 28 days, and to females from 2 weeks before mating to day 4 of lactation including the mating and gestation periods. Ten animals/sex/dose were assigned to the main group and 6 animals/sex/dose were used in the recovery group. No death was observed in either sex. There were no treatment-related changes in clinical signs, body weight, food consumption, urinalysis, hematology, serum biochemistry, necropsy finding and organ weights. At histopathological examination, slight tubular

degeneration/regeneration was observed in kidney in males and mineralization in kidney in females at 1,000 mg/kg bw/day. However, these findings were not considered to be toxicologically significant, since no treatment-related changes were observed in serum biochemistry due to kidney dysfunction. Based on these results, the NOAEL for repeated dose oral toxicity was considered to be 1,000 mg/kg bw/day in both sexes (the highest dose tested).

In an *in vitro* bacterial reverse mutation test, tricalcium phosphate was not considered to be mutagenic both with and without metabolic activation in multiple strains of *Salmonella typhimurium* and *Escherichia coli* strain [OECD TG 471]. In a chromosomal aberration test, tricalcium phosphate did not exhibit clastogenic effects in with or without metabolic activation. There was no increase as compared with the negative control. Based on these results, tricalcium phosphate was considered to be non genotoxic *in vitro* [OECD TG 473]. No *in vivo* genotoxicity studies were available.

There was no reliable data for carcinogenic activity of tricalcium phosphate.

The reproductive toxicity of the tricalcium phosphate has been well investigated in a reproductive and developmental toxicity screening test in rats [OECD TG 422]. Tricalcium phosphate was administered via gavage at dose levels of 0, 250, 500 and 1,000 mg/kg bw/day to male rats from 2 weeks before mating to the end of the mating period, for at least 28 days, and to females from 2 weeks before mating to day 4 of lactation including the mating and gestation periods. Ten animals/sex/dose were assigned to the main group and 6 animals/sex/dose were used for the recovery group. No death was observed in either sex. There were no treatment-related changes in clinical signs, body weight, food consumption, necropsy finding and organ weights. There were no treatment-related adverse effects on reproductive parameters, including precoital time, mating index, fertility index and pregnancy index. No treatment-related effects on F1 pups were observed in the number of corpora lutea, gestation length, delivery index, number of live and dead pups at birth, litter size, percentage of live and dead pups to implantations, sex ratio, viability index and body weights of pups on post-natal day 0 and 4. There were no externally malformed neonates in any groups. Therefore, the NOAEL for reproductive toxicity and developmental toxicity are considered to be 1,000 mg/kg bw/day

Tricalcium phosphate does not present a hazard for human health due to its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

Environmental fate analysis based on log K_{ow} and log K_{oc} is not applicable for inorganic substances such as tricalcium phosphate. Photodegradation and biodegradation are not applicable to metal-containing inorganic substances like tricalcium phosphate. The current state of the science does not allow for the unambiguous interpretation of the significance of various measures of bioaccumulation (e.g., BCF, BAF) for metal-containing inorganic substances.

The substance has a significant eutrophication potential, similar to that of inorganic phosphate.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Oryzias latipes</i>]	96 h LC ₅₀ > 2.14 mg/L (highest concentration measured in solution)
Invertebrate [<i>Daphnia magna</i>]	48 h EC ₅₀ > 5.35 mg/L (highest concentration measured in solution)
Algae [<i>Pseudokirchnerella subcapitata</i>]	72 h ErC ₅₀ > 1.56 mg/L (growth rate) (highest concentration measured in solution)
	72 h EbC ₅₀ > 1.56 mg/L (area under growth curve method) (the highest concentration measured in solution)

This chemical does not possess properties indicating a hazard to the environment based on its low hazard profile (no aquatic toxicity at the limit of water solubility) . Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

In the Republic of Korea, the production, use and import volume of tricalcium phosphate was 21,600, 1,546 and 76 tonnes in 2006, respectively. Tricalcium phosphate is used as a raw material for formula feed, enrichment agent with P and Ca of livestock, food/foodstuff additives and dispersing agents for styrene acrylonitrile resin etc. in the sponsor country.

In the sponsor country, tricalcium phosphate is handled in a closed system. No monitoring data are available from the wastewater. The dust containing tricalcium phosphate in production and processing sites is controlled

by ventilation systems and PPEs (personal protective equipments) in the Republic of Korea. The 8hr-TWA concentrations of dust for workplaces in tricalcium phosphate were 0.61 ~ 1.82 mg/m³, which were less than occupational exposure limit of 10 mg/m³. Occupational exposure is considered to be negligible in the sponsor country.

Tricalcium phosphate can be absorbed into the body by ingestion. The consumer could be exposed to small quantities of tricalcium phosphate in the consumption of food and by using some food/foodstuff additives. Consumer exposure is considered to be minimal in the sponsor country.

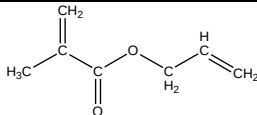
SIDS INITIAL ASSESSMENT PROFILE

CAS Nos	8029-43-4
Chemical Names	Syrups, hydrolyzed starch
Structural Formulae	-
This chemical is considered of low priority for further work at the OECD, due to its intrinsic properties indicating a low hazard	

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos	9050-36-6
Chemical Names	Maltodextrin
Structural Formulae	$[\text{C}_6\text{H}_{10}\text{O}_5]_n$
This chemical is considered of low priority for further work at the OECD, due to its intrinsic properties indicating a low hazard	

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos	96-05-9
Chemical Names	Allyl Methacrylate
Structural Formulae	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties**

Allyl methacrylate is a clear, colorless liquid with a melting point of -75 °C, boiling point of 141 °C, and measured vapor pressure of 7.7 hPa (5.77 mmHg) at 25 °C. The measured octanol-water partition coefficient (log K_{ow}) is 2.15 at 25°C, and water solubility is 2200 mg/L.

Human Health

No data were identified related to metabolism of allyl methacrylate. In general, methacrylates are readily absorbed and metabolized to methacrylic acid and the appropriate alcohol. Therefore, allyl methacrylate is expected to be metabolized to methacrylic acid and allyl alcohol.

In a 4-hour acute inhalation toxicity study in male and female rats exposed to allyl methacrylate vapour via whole body, the LC_{50} was 1.56 mg/L (310 ppm). Clinical signs included secretory responses (chromodacryorrhea, nasal discharge, excessive lacrimation, excessive salivation) and respiratory responses (labored breathing, gasping and moist rales) and signs of CNS depression (decreased motor activity and effects that included flattened posture, drooping eyelids, ataxia or tip-toe gait, decreased or no locomotor activity, stupor, no response to external stimulation, abnormal air righting reflex and decreased grip strength) that were considered to be general effects of allyl methacrylate exposure and not specific neurobehavioral effects; the surviving animals showed no such effects at 1 or 2 weeks after exposure. In a second study (nose only exposure), rats were exposed to allyl methacrylate vapour at 1.02 and 2.13 mg/L (198 and 414 ppm). Clinical signs during exposure included initial exaggerated breathing for approximately 2 hours followed by a decreased breathing rate. No treatment-related findings were noted at necropsy of surviving rats. The 4-hour inhalation LC_{50} from this study was estimated to be 1.47 mg/L (the geometric mean of the two concentrations tested). The oral LD_{50} of allyl methacrylate in male rats was 470 mg/kg bw. In the oral study, rats exhibited lacrimation (high-dose group) and piloerection. Necropsy findings in the survivors included dark yellow liver lesions and adhesions of the stomach and/or liver peritoneum. These oral data are adequate for SIDS because there is no indication in studies with acrylates/methacrylates in general that toxicity is greater in females than males, and the results from acute inhalation toxicity studies indicate that female rats are not more sensitive, and possibly slightly less sensitive, than male rats to allyl methacrylate. In two limited acute dermal toxicity studies in rabbits, LD_{50s} were 210 and 467 mg/kg bw.

Allyl methacrylate was not irritating to slightly irritating to rabbit skin and eyes. A case report indicated skin irritation in three of 11 humans exposed to 3% allyl methacrylate in olive oil. Acute inhalation studies with allyl methacrylate suggest the substance is a respiratory irritant. In a 4-hour acute inhalation toxicity study clinical signs included respiratory responses (labored breathing, gasping and moist rales). In a second study with nose only exposure, clinical signs during exposure included initial exaggerated breathing for approximately 2 hours followed by a decreased breathing rate. Allyl methacrylate was not a skin sensitiser in guinea pigs (OECD TG 406).

Repeated-dose toxicity of allyl methacrylate has been investigated in two studies. In a combined repeated-dose/reproduction/developmental toxicity screening test (OECD TG 422), the test substance was administered via gavage to 10 rats/sex/dose at 0 (corn oil), 3, 15 or 60 mg/kg bw/day. Males were treated once daily during the pre-mating and mating periods for a minimum of 4 weeks. Females were treated once daily during pre-mating, mating and gestation and through post natal day (PND) 5 (the day of birth was designated PND 1). Males were sacrificed after the mating period, and females were sacrificed with their litters on PND 6. Hypersalivation was observed in a dose-related manner in males and females given 15 or 60 mg/kg bw/day. Treatment-related effects at 60 mg/kg bw/day included one female with hypotonia and half-closed eyes on PND 5, one

female with increased total bilirubin concentration and another with increased biliary acid concentration that correlated with pathological findings in the liver (yellowish areas in 2/5 animals and foci of degenerated/necrotic hepatocytes, together with slight periportal fibrosis, slight biliary proliferation, and greenish-pigment-laden macrophages in 3/5 females). Other treatment-related findings included increased absolute thymus weights in the 15 and 60 mg/kg bw/day males group ($p < 0.05$). Based on liver effects, the LOAEL was 60 mg/kg bw/day and the NOAEL was 15 mg/kg bw/day.

In a 28-day dermal toxicity study, the test substance was administered under occlusive condition to rabbits (6 animals/sex/dose) at 0, 25, 50 or 100 mg/kg bw for 6 hrs/day, 5 days/week, for 4 weeks. A recovery high dose group was monitored for three additional weeks after dosing. Four female rabbits, two from the 50 mg/kg bw/day group and two from the 100 mg/kg bw/day group, died during the dosing phase of the study. Body weights and food consumption of the high-dose males were decreased throughout the dosing phase. No treatment-related clinical signs or changes in hematology, blood chemistry, or urine measurements were observed. Slight hemorrhage in the fascia of the skin at the treatment site in the high dose group animals was the only observation at termination. Microscopic effects were hyperplastic thickening of the epidermis with hyperkeratosis of the treatment-site skin, primarily in the high dose group. Following the recovery period, the animals from the high dose group appeared normal. A NOEL of 25 mg/kg bw/day was identified from this study.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium*, allyl methacrylate was negative both with and without metabolic activation. In an *in vitro* chromosomal aberration test using human lymphocytes allyl methacrylate was negative. Based on these results, allyl methacrylate is not considered genotoxic *in vitro*. No *in vivo* mutagenicity studies were identified for allyl methacrylate.

No data are available for the carcinogenicity of allyl methacrylate.

In the repeated-dose/reproductive/ developmental toxicity screening test in rats (OECD TG 422) described above, no effects were observed following oral exposure of males and females to allyl methacrylate on reproductive performance, fertility or development in pups. The NOAEL for reproductive performance and developmental toxicity was 60 mg/kg bw/day (the highest dose tested).

The developmental toxicity of allyl methacrylate has also been investigated in rats via inhalation in an OECD TG 414 developmental toxicity study. Pregnant rats (19-25/group) were exposed to allyl methacrylate vapour via whole body inhalation for 6 hrs/day during gestation days 6 to 20 at 0, 12, 25, 50, and 100 ppm (corresponding to 0, 0.063, 0.131, 0.262, 0.524 mg/L). Maternal weight gain was reduced at ≥ 12 ppm. The mean number of implantation sites and number of live fetuses was comparable across all groups. Although slight increases in the incidence of non-live implants and of resorptions at 50 and 100 ppm were observed, these were not statistically significant. There was a concentration-related decrease in fetal body weight that achieved a statistical significance at 100 ppm. No compound-induced teratogenic effects were observed. The NOAEL for maternal toxicity was not achieved. The NOAEL for developmental toxicity was 50 ppm (0.262 mg/L/day) based on decreased fetal body weight. Based on these data, allyl methacrylate may result in developmental toxicity via inhalation (decreased fetal body weights).

Allyl methacrylate possesses properties indicating a hazard for human health (skin, respiratory and slight eye irritation, acute toxicity, repeated-dose toxicity, and developmental toxicity via the inhalation route). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

Hydrolysis of allyl methacrylate, as with other methacrylates, is not expected to occur at pH values below 9; therefore, hydrolysis does not occur under normal environmental conditions. In the atmosphere, indirect photo-oxidation of allyl methacrylate is predicted to occur with an estimated half life of 2.8 hours with an OH-rate constant of 4.59×10^{-11} cm³/molecule-sec. obtained using EPISuite. Allyl methacrylate does not contain photolytically active groups and, therefore, direct photolysis by absorption of light > 290 nm will not occur. A test conducted according to OECD TG 301D with allyl methacrylate resulted in 67.3% degradation over 28 days and met the 10-day window criterion. Allyl methacrylate is readily biodegradable under aerobic conditions.

The level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that allyl methacrylate will partition primarily into soil (57.3%) and water (40.8%), with smaller amounts in air (1.75%) and sediment (0.1%). A Henry's law constant of 1.90×10^{-4} atm-m³/mole (19.3 Pa-m³/mole) (bond method) suggests that volatilization of allyl methacrylate from the water phase is expected to be moderate.

The bioaccumulation potential is estimated to be low based on a BCF value of 12.2 calculated with BCFWIN based on the low

log K_{ow} of 2.15.

The following acute toxicity test results have been determined for allyl methacrylate in aquatic species:

Fish [<i>Pimephales promelas</i>]	96-h LC_{50} = 0.61 mg/L (measured)
Invertebrates [<i>Daphnia magna</i>]	48-h EC_{50} = 2.4 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i>]	72-h ErC_{50} = 59.6 mg/L (growth rate) (measured)
	96-h ErC_{50} = 77.2 mg/L (growth rate) (measured)
	72-h EbC_{50} = 19.3 mg/L (biomass) (measured)
	96-h EbC_{50} = 28.8 mg/L (biomass) (measured)

Allyl methacrylate possesses properties indicating a hazard for the environment (acute toxicity to fish, invertebrates and algae from <1 to 100 mg/L). However, allyl methacrylate is readily biodegradable and has a limited potential for bioaccumulation. Adequate screening-level data are available to characterize the environmental hazards for the purposes of the OECD HPV Programme.

Exposure

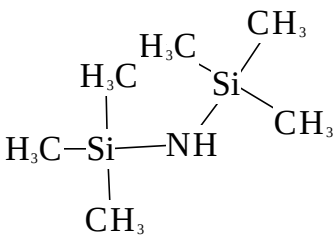
The world-wide estimated total annual production volume of allyl methacrylate is 1,000 to 10,000 metric tons.

Allyl methacrylate is manufactured using closed systems and can be produced by two different methods: (1) reaction of allyl alcohol and methacrylic acid and (2) trans-esterification of allyl alcohol and methyl methacrylate. It is further purified through distillation. Allyl methacrylate is a reactive monomer intermediate that is used in the production of polymers. The monomer is both manufactured and processed in closed systems. These closed systems are process units where most, if not all, of the equipment is vented to a scrubbing system or flare. Allyl methacrylate is primarily used as a cross-linking agent to improve the hardness and heat resistance of resins. In addition, it can be used as a rubber improver and coating modifier. Allyl methacrylate can also be used to manufacture intermediate compounds, which are then used to produce polymers. Methacrylate polymers have an uninterrupted carbon backbone and are very stable. With the additional cross-linking provided by reactions of the allyl side chain, the polymers can only be destroyed by a very high supply of energy (e.g. pyrolysis). Therefore, the polymer will not revert back to its original monomeric form during degradation under usual industrial and environmental conditions.

The monomer is both manufactured and processed in closed systems, which limits occupational exposure. Since there is potential inhalation exposure to allyl methacrylate and it has an offensive odor, special measures are taken to minimize or prevent worker exposure. There are no current occupational exposure limit values for allyl methacrylate. All customers are major resin or chemical producers with fully developed industrial hygiene procedures and equipment to minimize potential exposure. After initial manufacture of the resin, the material may be washed to remove residual monomers. In the production of water borne primary dispersions, the residual monomers are reacted away by a boost (addition of peroxide) or a distillation step, which is expected to limit consumer exposure. A typical residual monomer level of allyl methacrylate in finished resins is 1 - 2 ppm.

Since allyl methacrylate is a chemical intermediate that is both manufactured and processed in closed systems and wastes are incinerated or treated biologically, exposure from releases to the environment is expected to be limited.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	999-97-3
Chemical Name	1,1,1,3,3,3-Hexamethyldisilazane (HMDZ)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties****Reduced Testing rationale**

HMDZ undergoes rapid hydrolysis in the presence of water; the half life at pH 7 and 1.5°C is <0.5 minutes. Based on the chemical structure of HMDZ, this hydrolysis is expected to produce ammonia (CAS No. 7664-41-7) and trimethylsilanol (CAS No. 1066-40-6). Ammonia was previously assessed in the OECD HPV Chemicals Programme. Because HMDZ is hydrolytically unstable, water solubility and partition coefficient were not measured; modeled values are provided. In aqueous solutions, exposures to HMDZ are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products.

The EPISuite program (v. 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

HMDZ is a liquid with a melting point of -76.2 +/- 1.9 °C, a boiling point of 125 °C at 1013 hPa and a measured vapour pressure of 22 hPa at 25 °C. The calculated octanol-water partition coefficient (log K_{ow}) is 2.62, and the water solubility is 761 mg/L at 25 °C. The water solubility and log K_{ow} values may not be applicable because the chemical is hydrolytically unstable.

Human Health

No data are available on the toxicokinetics, metabolism or distribution of HMDZ.

In an OECD TG 403 study, the 6-hr LC₅₀ of HMDZ was 10 mg/L in rats, when exposed whole body to a vapour atmosphere. Clinical observations noted for the 7.8 mg/L group animals were consistent with respiratory and nervous system effects. Similar signs were also observed at 5.9 mg/L. In two studies conducted in a manner similar to OECD TG 402, the 24-hr dermal LD₅₀ in rabbits was reported to be 547 (females) and 589 (males) mg/kg bw in one study and 1350 (combined sexes) mg/kg bw in the second study. Clinical signs were consistent with nervous system effects; local skin effects included severe irritation and necrosis. In a study conducted in a manner similar to OECD TG 401, the oral LD₅₀ of HMDZ in rats was 1416 (males) and 1904 (females) mg/kg-bw, respectively. Clinical signs were consistent with nervous system effects and general signs of toxicity. The acute oral LD₅₀ in another rat study was 774 mg/kg bw; clinical signs were consistent with nervous system effects and general signs of toxicity. In a final acute oral study in rats, the oral LD₅₀ was determined to be 851 mg/kg bw. Clinical signs were consistent with nervous system effects at > 774 mg/kg bw, as well as reduction in body weight and a general poor condition.

HMDZ was not irritating to the skin in rabbits in an OECD TG 404 study. In three 4-hr studies conducted

under occlusive conditions according to U.S. Department of Transportation regulations, the substance caused necrosis of the skin; use of the occlusive cover is likely to have increased the severity of the effect. HMDZ was slightly or not irritating to the eyes in standard irritation studies (OECD TG 405 or similar) in animal tests. Acute inhalation studies with HMDZ suggest the substance is a respiratory irritant. In an OECD TG 403 test, rats exposed for six hours to 5.9 mg/L and above exhibited slow/noisy respiration. One group of five rats/sex was exposed for one hour at approximately 6.7 mg/L in a test conducted according to DOT guidelines. Clinical signs of toxicity were observed only during exposure and included respiratory difficulties (abdominal breathing). No experimental data are available for skin sensitisation in animals.

The repeated-dose toxicity of HMDZ has been investigated by the inhalation route in a combined repeated-dose/ reproductive/developmental toxicity screening study (OECD TG 422). The test article was administered to groups of 10 rats/sex via whole-body vapour inhalation for six hours/day, seven days/week to target concentrations of 0 (filtered air), 25, 100 and 400 ppm (0.16, 0.66, and 2.66 mg/L). Males were exposed throughout the 15 day pre-mating period and during the mating and post-mating periods, for a total of at least 4 weeks. Females were exposed throughout the pre-mating and mating periods and during pregnancy and lactation, until day 4 post-partum (or until sacrifice for un-mated females). Un-mated females were used in the repeated-dose portion of the study. Clinical signs were consistent with nervous system effects immediately after exposure at 2.66 mg/L. Significantly decreased body weight [15%] and food consumption were observed at 2.66 mg/L and absolute body weights of 0.66 mg/L females were decreased [7%; $p < 0.02$]. Effects on haematology and serum chemistry parameters were noted at 2.66 mg/L. Decreases in absolute epididymides weight of 2.66 mg/L males and absolute lung weights of 2.66 mg/L females were observed. Increases in relative kidney weight were observed at 0.66 and 2.66 mg/L (females) and 2.66 mg/L (males). Increased relative liver weight was observed in 2.66 mg/L females. Centrilobular hypertrophy in the liver of 2.66 mg/L females was the only microscopic finding. Based on the clinical observations, body weight changes, serum chemistry, haematology and histological findings following whole body inhalation exposure, the systemic toxicity NOAEC was 0.66 mg/L and the LOAEC was 2.66 mg/L.

In bacterial reverse mutation assays with *Salmonella typhimurium* and *E. coli*, HMDZ was negative both with and without metabolic activation. Mammalian gene mutation assays with L5178Y mouse lymphoma cells were negative both with and without metabolic activation. An *in vitro* chromosomal aberrations test using HMDZ was negative both with and without metabolic activation. Based on these results, HMDZ is considered to be non-genotoxic *in vitro*.

No data are available regarding the carcinogenicity of HMDZ.

In the combined repeated-dose/reproductive/developmental toxicity screening study [OECD TG 422] with HMDZ, the NOAEC for reproductive/developmental toxicity for HMDZ was 2.66 mg/L (highest dose tested). The NOAEC for maternal toxicity was 0.66 mg/L. Overall, HMDZ did not show evidence of reproductive/developmental toxicity based on screening level data.

HMDZ possesses properties indicating a hazard for human health (acute and repeated dose toxicity, skin and respiratory irritation). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The hydrolysis half-life for HMDZ is < 0.5 minutes at 1.5 °C and pH7 following OECD TG 111. HMDZ is expected to form ammonia and trimethylsilanol. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 11.9 days. The biodegradation of HMDZ was investigated following EU Directive 92/69/EEC, C.4-E; HMDZ achieved a breakdown rate of 15.3% in 28 days, indicating the test substance is not readily biodegradable. This result is more likely to reflect the biodegradation potential of trimethylsilanol than it is parent substance.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that HMDZ will distribute mainly to the soil (70.8%) compartment with minor distribution to the water compartment (21.8%) and negligible amount to the air (7.08%) and sediment (0.31%) compartments. However, HMDZ is unlikely to be found in the environment, as this material is hydrolytically unstable. Henry's Law constant of 8.69×10^{-5} atm-m³/mole (8.8 Pa-m³/mole) suggests that volatilisation from the water phase for HMDZ is not expected to be high. The bioaccumulation potential of the parent compound is considered to be low based on the chemical reactivity of HMDZ. The estimated BCF value is 24.77 L/kg wet-wt

using BCFBAF v3.00.

No information on the environmental fate of trimethylsilanol was found. Trimethylsilanol is relatively stable. Although at high concentrations (>5%) trimethylsilanol is known to condense forming hexamethyldisiloxane, at environmentally relevant concentrations this is not expected to be a significant reaction pathway. However, based on studies of related monomeric silanols, the adsorption of trimethylsilanol onto surfaces is expected. Trimethylsilanol is expected to partition primarily to water, soil, and sediment due to its high water solubility and have the potential to bind to mineral surfaces. Slow biodegradation in water and soil might also occur.

Due to the rapid hydrolysis of HMDZ, aquatic organisms are likely exposed primarily to its hydrolysis products, ammonia and trimethylsilanol. The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Brachydanio rerio</i>]	96 h LC ₅₀ = 88 mg/L (measured as Total Organic Carbon; (TOC); EU Directive 92/69/EEC, C.1)
Aquatic invertebrate [<i>Daphnia magna</i>]	48 h EC ₅₀ = 80 mg/L (measured as TOC; EU Directive 92/69/EEC, C.2)
Algae [<i>Scenedesmus subspicatus</i>]	72 h EbC ₅₀ =19 mg/L (biomass) (measured as TOC; EU Directive 92/69/EEC, C.3)
Algae [<i>Scenedesmus subspicatus</i>]	72 h ErC ₅₀ =50 mg/L (cell growth)(measured as TOC; EU Directive 92/69/EEC, C.3)

HMDZ possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). The substance is not readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

HMDZ is commercially produced with an annual production volume of 454 - 2268 tonnes in 2005 in the United States of America. Worldwide production volume was estimated to be 2722-11340 tonnes/year in 2005.

Industrial uses of HMDZ include surface treatment of silica, as an intermediate; sold into the semiconductor industry as an adhesion promoter or silylating agent; chemical modification of inorganic fillers; water scavenger in some silicone sealants. HMDZ is a universal silylating agent used for the derivatization of alcohols, carboxylic acids, amines, amides, mercaptans and other compounds. HMDZ is a popular monofunctional silane that many researchers have found useful for deactivating and coating HPLC or GC chromatographic supports. HMDZ is a popular choice for silylation of sugars and related substances. HMDZ is also used for deactivating glass wool and for treating GC injection port glass inserts. HMDZ, used as a blocking agent by the pharmaceutical industry to produce antibiotics, is completely consumed and does not become part of the final product. In other applications, the sponsored substance is reacted during use and is not expected to be present in the final product.

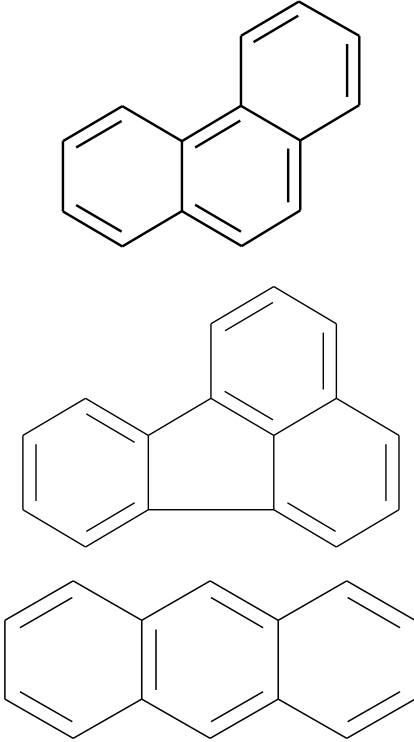
HMDZ is manufactured in closed systems (hard-piped); engineering controls are routinely used. Dermal and inhalation are possible routes of occupational exposure (manufacturing and industrial consumer).

HMDZ is added to several silicone home maintenance sealants at 1-5% as a scavenger for free water or methanol. During use as a sealant applied to a substrate, HMDZ is expected to very rapidly react with moisture and no longer be available unless used in environments with unusually low moisture or in cases where there is excess HMDZ.

Some healthcare adhesives are manufactured using HMDZ as the endcapping (chain terminating agent) of the polymer. During the manufacture of these polymers residual HMDZ is removed by vacuum stripping. There is no residual HMDZ expected to remain in the pressure-sensitive adhesives.

There are no intentional releases to the environment.

INITIAL TARGETED ASSESSMENT PROFILE (Enviroment)

CAS No.	Anthracene oil 90640-80-5 Anthracene oil, anthracene paste, distn. Lights 91995-17-4 Anthracene oil, anthracene paste, anthracene fraction 91995-15-2 Anthracene oil, anthracene-low 90640-82-7 Anthracene oil, anthracene paste 90640-81-6
Chemical Name	Anthracene oils
Structural Formula	The anthracene oil derivate are complex and have variable compositions. Structures of some components: 
SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT NOTE: The present assessment is targeted to address the following environmental endpoints: stability in water and biodegradability, bioaccumulation potential, screening information on acute and chronic toxicity to aquatic organisms. It cannot be considered as a full SIDS Initial Assessment. Human health endpoints are not addressed in this assessment. It should be noted that some components of the Anthracene oils are classified as carcinogenic and mutagenic in the European Union. The full targeted assessment will be published under the responsibility of the European Chemicals Agency (ECHA). Rationale for Targeting the Assessment Under Regulation (EC) No 1907/2006 (REACH-Regulation) substances can be identified as substance of “very high concern” (SVHC) and then included in the Candidate List. Substances from the Candidate List are subject to	

information requirements for articles and can be included in Annex XIV (Authorisation List).

The dossiers to identify a substance as a SVHC focus on the relevant endpoints. Germany proposed to identify some anthracene oils as SVHCs based on the PBT- and vPvB (persistent, bioaccumulative and toxic; very persistent and very bioaccumulative) properties.

The Anthracene oils were investigated in the EU PBT working group before entry into force of the REACH-Regulation. Germany prepared Annex XV-Dossiers to transfer the result from the EU PBT working group to the REACH-Regulation.

More information about the identification of SVHC can be found here:

http://guidance.echa.europa.eu/authorisation_en.htm

Note: More data about the components is available in the EU transitional dossier for Pitch, coal tar, high-temp [http://echa.europa.eu/chem_data/transit_measures/annex_xv_trans_reports_en.asp]

Analogue/Category rationale

Category assessments:

Anthracene oils are UVCB (Unknown, of Variable Composition, or of Biological Origin) substances consisting of a complex mixture of hydrocarbons. Major constituents are three- to five-fused aromatic rings. Minor constituents are three- to four-fused aromatic sulphur-, nitrogen- or oxygen-heterocycles. Anthracene oils are produced from distillation of coal tars, which are condensation products obtained by cooling of the gas evolved by carbonization of coal. The physical state of anthracene oil (CAS 90640-80-5) at 20 °C is an oily liquid with a colour ranging from yellow over dark green to brown. Derivatives from anthracene oil may be either oily liquids (anthracene low, CAS 90640-82-7) or solids (anthracene paste, distn. lights, CAS 91995-17-4; anthracene paste, CAS 91995-15-2 and 90640-81-6). The main components in anthracene oil and its derivatives are the following:

Substance	main components and its concentration range [% w/w]
anthracene oil, CAS 90640-80-5	Acenaphthene: 0.2-16 Anthracene: 3-25 Phenanthrene: 10-35 Fluorene: 1-16 Fluoranthene: 2-15 Pyrene: 1-10 Carbazole: 1-10 Dibenzofurane: 0.1-8
anthracene low, CAS 90640-82-7	Acenaphthene: 1-10 Anthracene: 1-6 Phenanthrene: 10-30 Fluorene: 4-10 Fluoranthene: 5-15 Pyrene: 2-8 Carbazole: 1-3
anthracene oil, anthracene paste, distn. lights, CAS 91995-17-4	Anthracene: 0.5-25 Phenanthrene: 10-45 Fluorene: 15-45 9,10-Dihydroanthracene: 3-15 Carbazole: 0.1-5 Dibenzothiophene: 2-7
anthracene paste, CAS 91995-15-2	Anthracene: 50-70 Phenanthrene: 25-45 Carbazole: 1-5
anthracene paste, CAS 90640-81-6	Anthracene: 15-50 Phenanthrene: 5-30 Carbazole: 5-30

Anthracene was identified in the EU as a SVHC in 2008.

[http://echa.europa.eu/doc/candidate_list/svhc_supdoc_anthracene_publication.pdf]

Physical-chemical properties

Anthracene oil CAS-No 90640-80-5 is a solid or liquid with a melting point $<80^{\circ}\text{C}$, a boiling point of $>270^{\circ}\text{C}$ and a vapour pressure of $<100\text{ Pa}$ at 20°C . The octanol-water partition coefficient ($\log K_{ow}$) is 3.45-4.8, and the water solubility is 0.041-1.98 mg/L at 20°C .

Anthracene oil, anthracene paste CAS-No 90640-81-6 is solid with a melting point of $150-200^{\circ}\text{C}$, a boiling point of $300-350^{\circ}\text{C}$ and a vapour pressure of $9.4 \cdot 10^{-4} - 0.091\text{ Pa}$ (20°C). The octanol-water partition coefficient ($\log K_{ow}$) is 4.57-4.68, and the water solubility is 0.047-1.6 mg/L at 25°C .

Anthracene oil, anthracene-low CAS-No 90640-82-7 is liquid or solid with a melting point of $20-70^{\circ}\text{C}$, a boiling point of $230-400^{\circ}\text{C}$ and a vapour pressure of $\leq 200\text{ Pa}$ at 25°C . The octanol-water partition coefficient ($\log K_{ow}$) is 3.84-5.20, and the water solubility is $<100\text{ mg/L}$ at 20°C .

Anthracene oil, anthracene paste, anthracene fraction, CAS-No 91995-15-2 is solid with a melting point of $170-200^{\circ}\text{C}$, a boiling point of $300-350^{\circ}\text{C}$ and a vapour pressure of $<0.01\text{ Pa}$ at 25°C . The octanol-water partition coefficient ($\log K_{ow}$) is 3.84-4.68, and the water solubility is $<1.29\text{ mg/L}$ at 20°C .

Anthracene oil, anthracene paste, distn. lights CAS-No 91955-17-4 is solid with a melting point of $<109^{\circ}\text{C}$, a boiling point of $<333^{\circ}\text{C}$ and a vapour pressure of $<100\text{ Pa}$ at 20°C . The octanol-water partition coefficient ($\log K_{ow}$) is 3.84-4.68, and the water solubility is $<1.98\text{ mg/L}$ at 20°C ."

Human Health

Not part of the targeted assessment

Environment

Hydrolysis as a way of abiotic degradation can be considered as not relevant for the main components of the anthracene oils because of their chemical structures. E.g. the component anthracene (CAS-No 120-12-7) is stable against hydrolysis. This has been observed in laboratory and in "in situ" experiments. Because of the similar chemical structure (consisting of aromatic rings) similar assumptions for hydrolytic behaviour of the other components can be made. Half-lives for primary photodegradation in water have been reported in the range of 20 minutes to 125 hours depending on the experimental conditions used. The highest value corresponds to photolysis in winter conditions. Anthraquinone has been identified as the main abiotic degradation product of anthracene.

Anthracene oil contains hardly degradable Polycyclic Aromatic Hydrocarbons (PAHs). Biodegradation screening tests with sludge indicate that anthracene is not readily degradable. Biodegradation tests employing water and sediment-water mixtures are available showing slow to very slow mineralization. Mineralization half-lives up to 210 days have been reported for aerobic sediment, whereas under anaerobic conditions anthracene is completely recalcitrant. In addition, a half-life of 7.9 years has been observed in soil in a field study. Based on these data, anthracene is considered to have very high biodegradation half lives in water, sediment and soil.

Screening studies (OECD TG 301C) show, that acenaphthene, fluorene and carbazole – components present in anthracene oil - are not readily biodegradable.

Further laboratory studies show relatively long dissipation times for fluoranthene (DisDT50 $> 173\text{ d}$), pyrene (DisDT50 $> 131\text{ d}$), and carbazole (Degradation half-life: DegDT50 $> 184\text{ d}$) in soil.

Additionally in a field study half lives of 5.7 years for phenanthrene, 7.8 years for fluoranthene, and 8.5 years for pyrene, have been measured in soil.

Anthracene oils are expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor of >5000 for the main components (Anthracene [Fish], Phenanthrene [fish], Fluoranthene [Mollusca], Pyrene [Mollusca, Fish]).

According to the components' Henry' Law constants, anthracene oils are appreciated to be moderately volatile. Anthracene oils have a high potential to adsorb to organic matter and are only little mobile in soil and sediment.

The following acute toxicity test results have been determined for aquatic species with the main components:

Anthracene

Fish [*Lepomis macrochirus*]; 96 h LC₅₀ = 0.026 mg/L (nominal)

Invertebrate [*Daphnia magna*] 48 h EC₅₀ = 0.0095 mg/L (nominal)

The following chronic toxicity test results have been determined

Invertebrate [*Daphnia magna*] 21 d, NOEC = 0.0068 mg/L (nominal)

Fluoranthene

Fish [*Pseudopleuronectes*]; 96 h LC₅₀ = 0.0001 mg/L (nominal)

Invertebrate [*Americamys bahia*] 96 h EC₅₀ = 0.0014 mg/L (nominal)

Anthracene oils possess properties indicating a hazard for the environment (acute and chronic toxicity to fish, invertebrates < 1 mg/L; long biodegradation half lives and high potential for bioconcentration in aquatic organisms.

Exposure

Not part of the targeted assessment

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	68515-42-4														
Chemical Name	1,2-Benzenedicarboxylic acid, di-C₇₋₁₁-branched and linear alkyl esters (Di(heptyl, nonyl, undecyl) phthalate)														
Structural Formula	$R_1 = C_7H_{15} \text{ or } C_9H_{19} \text{ or } C_{11}H_{23}$ $R_2 = C_7H_{15} \text{ or } C_9H_{19} \text{ or } C_{11}H_{23}$ $R_1 \text{ and } R_2 \text{ can be linear or branched}$														
SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT NOTE: The present assessment is targeted to address the following human health endpoints: reproductive and developmental toxicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment are included in the Canadian screening assessment but have not been agreed upon by OECD member countries, and thus are not included in this profile. The final screening assessment has been published under the responsibility of the Government of Canada. [http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/batch-lot-6/index-eng.php#final] Rationale for Targeting the Assessment The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its <i>Canadian Environmental Protection Act, 1999</i> (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: inherently toxic to humans or to the environment and that might be persistent and/or bioaccumulative; and substances to which people might have greatest potential for exposure. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release. The substance 1,2-Benzenedicarboxylic acid, di-C₇₋₁₁-branched and linear alkyl esters or di(heptyl, nonyl, undecyl) phthalate, abbreviated as DHNUP, was identified as a high priority for assessment of human health risk because it was considered to present intermediate potential for exposure and had been classified by the European Commission on the basis of reproductive and developmental toxicity (Category 2 for developmental toxicity with risk phrase R61 ("May cause harm to the unborn child") and as a Category 3 for reproductive toxicity with risk phrase R62 ("Possible risk of impaired fertility"). Substance Identity DHNUP, Chemical Abstracts Service Registry Number (CAS RN) 68515-42-4, is a mixture of phthalates containing the following six components: <table border="1"> <thead> <tr> <th>CAS RN</th> <th>Name</th> </tr> </thead> <tbody> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> </tbody> </table>		CAS RN	Name												
CAS RN	Name														

3648-20-2	1,2-Benzenedicarboxylic acid, diundecyl ester, linear only
68515-44-6	1,2-Benzenedicarboxylic acid, diheptyl ester, branched and linear
68515-45-7	1,2-Benzenedicarboxylic acid, dinonyl ester, branched and linear
111381-89-6	1,2-Benzenedicarboxylic acid, heptyl nonyl ester, branched and linear
111381-90-9	1,2-Benzenedicarboxylic acid, heptyl undecyl ester, branched and linear
111381-91-0	1,2-Benzenedicarboxylic acid, nonyl undecyl ester, branched and linear

There is variation regarding the nomenclature used to represent this mixture. In Europe, the composite CAS RN 68515-42-4 is used most commonly to represent DHNUP. However, CAS RNs in the list above are also made reference to in Europe. In the United States, DHNUP is more frequently represented by listing together all the individual CAS RNs provided above. The US EPA considers the test substance for commercial DHNUP to be a mixture of the above six CAS RNs and not described by CAS RN 68515-42-4.

It should be noted that some common names or trade names for DHNUP may also represent different CAS RNs for similar mixtures of phthalates or individual phthalates. For example, the common name 711P may refer to DHNUP or to 1,2-benzenedicarboxylic acid, (C7,C11) ester, branched and linear (CAS RN 111381-90-9). The components of DHNUP, except for CAS RN 111381-90-9, are known to be commercially sold as separate products. It is notable that, due to the variable composition of DHNUP, no single discrete molecular structure may be considered truly representative of DHNUP, and thus use of the representative structure provided above was limited to physicochemical property modelling.

Physical-chemical properties

The substance, DHNUP, is a liquid at room temperature with a measured melting point of -57°C, measured boiling points of 235 to 278°C and measured vapour pressure of <10 Pa at 20°C. The measured octanol-water partition coefficient (log K_{ow}) is 4.8, and the measured water solubility is 0.1 mg/L at 20°C.

Human Health Targeted Endpoints

Most of the *in vivo* studies were conducted in rats, and only a few of them were conducted in mice. Whereas most of the studies were reported on CAS RN 68515-42-4, there are some that pertain to CAS RN 3648-20-2, which is just one of the six components of DHNUP. No toxicological data were identified for the remaining components of DHNUP.

No guideline studies on reproductive toxicity were identified. Data on potential effects on fertility were obtained from repeated-dose studies. Reproductive toxicity in the form of slight testicular atrophy and reduced testis weights following dietary administration of CAS RN 68515-42-4 to rats for 21 days was observed at 2416 mg/kg-bw per day (LOEL = 2416 mg/kg bw/day), suggesting an LOAEL > 2416 mg/kg bw/day. No effects were observed at 1159 mg/kg-bw per day (no-observed-effect level [NOEL]). For CAS RN 3648-20-2, the NOEL in rats was reported at 2495 mg/kg-bw per day.

High incidences of teratogenic and embryotoxic effects were observed following oral administration of di-711-phthalate (considered to comprise the following CAS RNs: 111381-89-6, 111381-90-9, 111381-91-0, 68515-44-6, 68515-45-7 and 3648-20-2) to female rats at 1000 mg/kg-bw per day (lowest-observed-adverse-effect level [LOAEL]) during gestation (in a developmental toxicity study). Other effects observed at this dose included reduced maternal body weight and body weight gain, increased relative liver and kidney weights and markedly reduced uterus weight. These effects were not observed at 200 mg/kg-bw per day (no-observed-adverse-effect level [NOAEL]). Another study on rats using Santicizer 711 (Santicizer 711 has been ascribed CAS RN 68515-42-4 by the authors of the study) reported a lowest-observed-effect level (LOAEL) of 5000 mg/kg-bw per day based on significant mean fetal body weight reduction in the absence of maternal toxicity.

DHNUP possesses properties indicating a hazard for the human health endpoints, developmental and reproductive toxicity (teratogenic and embryotoxic effects, testicular atrophy and reduced testes weights).

Exposure Summary Information

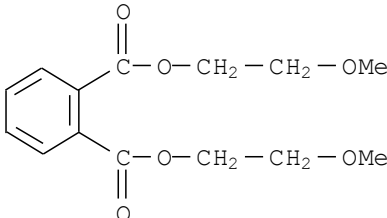
DHNUP is used principally for plasticizing applications. A single use was identified in Canada as on-going after the 2006 reporting year, namely plasticization of electrical and communication wire insulation. As a plasticizer, DHNUP is compatible with several polymer resins, including copolymer and homopolymer vinyl resins, nitrile, chlorinated and styrene-butadiene rubber, cellulose, neoprene, polyurethane, acrylic latex, alkyd resins and rosin-modified polyester resins of maleic anhydride and glycerine.

DHNUP was introduced worldwide in the early 1970s. The following uses of DHNUP were identified as global or historical in nature; however, they were not determined to be on-going in Canada after the 2006 reporting year. For vinyl applications, DHNUP plasticizes polyvinyl chloride (PVC) coatings of mine brattice cloth and

metal coils. Industrially, DHNUP plasticizes polyurethane prepolymers for foam applications. For automotive use, DHNUP is used as a low-volatility sealant in addition to functioning as a plasticizer in primerless urethane adhesive, glass and transmission adhesive, vibration-damping coatings and exterior trim. In terms of construction materials, DHNUP has been used as a plasticizer in elastomeric roof and barrier coatings, geomembranes, tarpaulins, flashing cement, wood filler, wood and stone hardener, caulk, sanding sealer and high-solids lacquer. Finally, DHNUP has been reported to be used to plasticize high-end luggage.

In response to a survey conducted in Canada, less than 10 kg of DHNUP was reported to be released to each of air and water in the 2006 calendar year. Some transfers of DHNUP to non-hazardous waste facilities occurring in the 2006 calendar year were also reported. DHNUP is not reportable to the National Pollutant Release Inventory in Canada or to the US Toxics Release Inventory Program; therefore, no release information was available from these sources.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	117-82-8
Chemical Name	1,2-Benzenedicarboxylic acid, bis(2-methoxyethyl) ester (Di(methoxyethyl)phthalate)
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address the following human health endpoints: reproductive and developmental toxicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment are included in the Canadian screening assessment but have not been agreed upon by OECD member countries, and thus are not included in this profile.

The final screening assessment has been published under the responsibility of the Government of Canada.

[<http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/batch-lot-6/index-eng.php#final>]

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its *Canadian Environmental Protection Act, 1999* (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: **inherently toxic** to humans or to the environment and that might be **persistent** and/or **bioaccumulative**; and substances to which people might have **greatest potential for exposure**. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release.

The substance 1,2-benzenedicarboxylic acid, bis(2-methoxyethyl) ester or di(methoxyethyl)phthalate, abbreviated as DMEP, was identified as a high priority for assessment of human health risk because it was considered to present intermediate potential for exposure and had been classified by the European Commission on the basis of reproductive and developmental toxicity (Category 2 for developmental toxicity with risk phrase R61 ("May cause harm to the unborn child") and as a Category 3 for reproductive toxicity with risk phrase R62 ("Possible risk of impaired fertility")).

Physical-chemical properties

The substance DMEP is a liquid at room temperature with a measured melting point of -45°C, measured boiling points of 313 and 340°C and modelled vapour pressures of 0.03 and 0.07 Pa at 25°C. The measured octanol-water partition coefficient (log K_{ow}) is 0.04, and the measured water solubility is 8500 mg/L at 15-25°C.

Human Health Targeted Endpoints

There is a limited dataset on DMEP, but it is supported by the fact that DMEP is metabolized quickly to a well-characterized reproductive and developmental toxicant, 2-methoxyethanol (2-ME). A health risk assessment on

2-ME was completed by the Government of Canada earlier.

Few adequate studies were identified in which DMEP was administered to laboratory animals by routes that are relevant to human exposure (i.e., oral, dermal or inhalation). A five-generation oral study with very limited data reported did not reveal any signs of reproductive toxicity induced by DMEP in rats given up to 900 mg/kg diet per day (45 mg/kg-bw per day: original report did not state clearly what the actual dosage was. This dose was estimated based on the assumption that DMEP was applied to rats in diet). DMEP-induced testicular effects were observed in rats following acute or 2-week gavage administration. Significant reductions in absolute and relative testis weights with seminiferous tubule atrophy and sperm degeneration and the appearance of giant spermatids were observed at 1000 mg/kg-bw per day in the 2-week study; a no-observed-adverse-effect level (NOAEL) of 100 mg/kg-bw per day for testicular effects was identified. In addition, haematological effects as well as thymic effects, exhibiting a limited dose-response relationship, were observed in the 2-week oral study at 100 mg/kg-bw per day and above in male rats. The purity of the test material in this study was 78%, which may have introduced some confounding factors. Significantly reduced testis weights and increased abnormal sperm levels were also observed in the single gavage dosing study at a higher dose level (1500 mg/kg-bw) following single dosing.

Significantly reduced relative testis weights were observed in mice administered DMEP by intraperitoneal (i.p.) injection for 6 weeks at a dose level of 250 mg/kg-bw per day, the only dose tested and determined to be the lowest-observed-adverse-effect level (LOAEL). Thus, based on a weight of evidence approach in which oral and i.p. exposures resulted in similar testicular effects, a hazard to fertility cannot be excluded.

Developmental effects of DMEP were observed in rats following oral (gavage) administration on gestation days 6 to 16. Significantly reduced pup body weight gain and slightly reduced pup survival from day 1 to 5 postpartum were observed at the lowest dose tested (60 mg/kg-bw per day, LOAEL). At a higher dose level (180 mg/kg-bw per day), significantly reduced pup survival and pup body weight gain as well as pup abnormalities including a shortened lumbosacral region, acauda (i.e. no tail) and filamentous tails were observed. At the highest dose tested (600 mg/kg-bw per day), a complete resorption of the litters was observed accompanied by maternal toxicity such as significantly reduced body weight gain and mean body weights as well as food consumption. A NOAEL for maternal toxicity was identified at 180 mg/kg-bw per day. Similar teratogenic and fetotoxic effects were also observed in a number of i.p. developmental toxicity studies in rats and mice.

DMEP possesses properties indicating a hazard for the human health endpoints, developmental and reproductive toxicity (teratogenic and embryotoxic effects, testicular atrophy, reduced testes weights and sperm abnormalities).

Exposure Summary Information

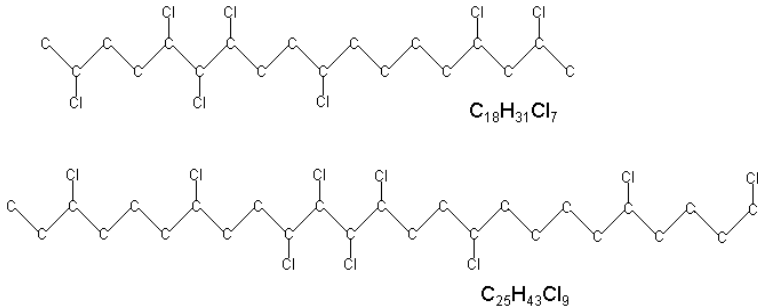
No information regarding any current uses of DMEP in the Canadian marketplace has been identified. Based on the global decline of manufacture of DMEP and the information reported under a survey conducted in Canada, use of DMEP in Canada is not expected to be significant.

The general applications of DMEP have included its use as a plasticizer in the production of nitrocellulose, acetyl cellulose, polyvinyl acetate, polyvinyl chloride and polyvinylidene chloride intended for contact with food or drink, giving these polymeric materials good light resistance, and as a solvent. DMEP can improve the durability and toughness of cellulose acetate and can be used in enamelled wire, film, high-strength varnish and adhesive. It can also be used in pesticide products.

There was no manufacture or import of DMEP in a quantity greater than or equal to the 100 kg reporting threshold or use of DMEP in a quantity greater than or equal to the 1000 kg reporting threshold in Canada in 2006; therefore, industrial releases are not expected to be significant. DMEP is not a reportable substance under the National Pollutant Release Inventory in Canada, the US Toxics Release Inventory, the Australian National Pollutant Inventory or the Japanese Chemical Survey.

The historical uses of DMEP as a plasticizer and as a solvent suggest that DMEP may be released to the environment through various waste streams.

SIDS INITIAL ASSESSMENT PROFILE

CAS Numbers and Chemical Names	63449-39-8 Paraffin waxes and hydrocarbon waxes, chloro 85535-86-0 Alkanes, C ₁₈ - 28, chloro 85422-92-0 Paraffin oils, chloro
Example Structural Formulae	$C_nH_{2n+2-y}Cl_y$, where $n = 18$ to 30 and $y = \sim 4$ to ~ 30  $C_{18}H_{31}Cl_7$ $C_{25}H_{43}Cl_9$

SUMMARY CONCLUSIONS OF THE SIAR**Analogue/Category Justification**

The Long-Chain Chlorinated Paraffins (LCCP) category contains complex commercial substances whose chemical components are predominantly in the range of carbon chain lengths from C₁₈ to C₃₀ with chlorine content in the range of approximately 35-72% by weight. Chlorinated paraffins (CP) are derived from the chlorination of straight-chain hydrocarbon substances (i.e., n-paraffins, n-alkanes) and are generally divided into three categories based on their carbon chain-length:

- Short-Chain Chlorinated Paraffin (SCCP): C₁₀ to C₁₃
- Mid-Chain Chlorinated Paraffin (MCCP): C₁₄ to C₁₇
- Long-Chain Chlorinated Paraffin (LCCP): C₁₈ to C₃₀

For purposes of this assessment, the LCCPs are being divided into 3 subgroups to reflect differences in carbon chain length (those derived from the C₁₈-C₂₀ hydrocarbon feedstock and those from the C₂₀-C₃₀ hydrocarbon feedstock), and physical state (as a result of degree of chlorination). Both factors have an influence on use pattern, which adds to the usefulness of this approach. These subgroups are:

- C₁₈-C₂₀ LCCPs: ca. 40 – 52% Cl (liquid)
- C₂₀-C₃₀ LCCPs: ca. 40 – 54% Cl (liquid)
- C₂₀-C₃₀ LCCPs: ca. 70% Cl (solid)

LCCP purity is related to the purity of the n-paraffin feedstock. In North America and Western Europe, n-paraffin feedstocks contain no more than 1-2% isoparaffins and <100 ppm (<0.01%) aromatics (which are specifically removed from the paraffins feedstock by hydrosulfurisation). The feedstocks may contain n-alkanes beyond the nominal or predominant carbon number range reported for the feedstock. The carbon number range (C₁₈-C₃₀) of the LCCP category is generally fully encompassing of the main commercial products, though some C₁₈₋₂₀ products may contain a significant (10-20%) amount of C₁₇ chlorinated alkane.

The substances in this category have a predictable range of physico-chemical properties and physical forms. As chain length and degree of chlorination increases, pour (melting) points and octanol-water partition coefficients increase and water solubilities decrease. While there are ranges to the physico-chemical properties, LCCPs all still display similar characteristics – very low water solubility, very low vapour pressure, and high K_{ow} values. Environmental fate modelling indicates that all LCCPs are anticipated to partition almost entirely to the soil or sediment, depending on release patterns, indicating that fate and behaviour are likely be very similar for all LCCPs. Data from the related substance MCCPs, which have similar physico-chemical properties, are structurally analogous and, where known, have a similar toxicological profile to C₁₈₋₂₀ LCCPs, are used to address human health hazards for C₁₈₋₂₀ LCCPs, including acute toxicity, irritation, repeated dose toxicity, toxicity for reproduction (effects on fertility) and developmental

toxicity. Data from liquid C₂₀₋₃₀ LCCPs is read across to solid C₂₀₋₃₀ LCCPs for acute *Daphnia magna* toxicity.

Physico-chemical Properties

Measured data for commercial LCCPs usually give a range of values for single endpoints owing to the complex nature of the substance. Estimated values have been predicted using representative individual structures. LCCPs can vary from free-flowing mobile liquids, through highly viscous glassy liquids, to waxy solids and powders. Distinct melting points are not evident; liquid LCCPs generally exhibit pour points (approximate range -30 to 10 °C) and solid LCCPs softening points (103 – 115 °C). Higher values correspond with a greater degree of chlorination. LCCPs decompose at temperatures above 210 °C before boiling occurs. Vapour pressures range from 1.4×10^{-15} to 5.3×10^{-4} Pa (estimated at 25 °C) for C₂₀₋₃₀ (ca. 70% Cl) and C₁₈₋₂₀ (ca. 40% Cl), respectively. Estimated octanol-water partition coefficients (log K_{ow}) range from 7.5 – 11.5 for C₁₈₋₂₀, from 7.6 -17.5 for liquid C₂₀₋₃₀ and from 16.9 – 20.1 for solid C₂₀₋₃₀ LCCPs. The estimated water solubility ranges from 1.6×10^{-11} – 6.6 µg/L at 20 °C for LCCPs.

Human Health

Toxicokinetics, metabolism and distribution

No information was available on the metabolism of the LCCPs.

Ninety-day studies, in which ¹⁴C radio-labelled LCCPs were administered orally to rats, showed that an average of 77% of the administered radio-activity was excreted in the faeces within seven days. Less than 1% was excreted in urine or expired air. This suggests that the compound was either poorly absorbed or that a significant quantity was excreted in the bile, either unchanged or as a metabolite. Up to about 4% remained in the tissues, mainly the liver. There have been no studies on absorption through the skin. It is known that both SCCPs and MCCPs are absorbed via this route to only a very small extent (~0.7 % for MCCPs). It is anticipated that based on the larger molecule size of LCCPs, they would be less likely than MCCPs to be absorbed through the skin. Similarly, there are no studies on the absorption of LCCPs through the respiratory tract, either as vapour, aerosol or dust, although it is reasonable to assume that absorption via the lungs is unlikely to be higher than the assumed rate of oral absorption, i.e. 50%.

Acute toxicity

There is adequate data to assess the acute toxicity of LCCPs. C₂₀₋₃₀ LCCPs (both solid and liquid) are of very low acute toxicity, having oral LD₅₀ values in excess of 5.0 g/kg bw in the rat and other species. MCCPs are also of very low acute toxicity, with oral LD₅₀ >2.0 g/kg bw in the rat. As such it is likely that C₁₈₋₂₀ liquid grade LCCPs are of very low acute toxicity.

There are no data on the acute toxicity of LCCPs following dermal administration. However, as it is anticipated that they would not be absorbed to any significant extent via this route, it is considered unnecessary to conduct such tests. Similarly, there are no data on the acute toxicity of LCCPs following inhalation.

Irritation

There is adequate data to assess the irritant potential of LCCPs. In a study of liquid C₂₀₋₃₀ LCCPs, 0.5 ml neat LCCP, which included several stabilisers, was applied as a single occlusive application for 24 hours to abraded and non-abraded skin of rabbits. Erythema and oedema was scored after 24 and 72 hours. Slight erythema was observed on both the abraded and non-abraded skin in two out of six rabbits at 24 hours. In another study, up to 6 applications of 0.1ml of either liquid or solid LCCPs, either neat or in a non-irritating vehicle, were applied to the shorn back of three female rats on alternate 24-hour periods. It was concluded that these test materials were non-irritant. Single exposure to MCCPs also caused slight irritation in standard tests, but somewhat more pronounced irritation has been reported following repeated exposure, presumably due to the defatting properties of MCCPs. There are no data on respiratory irritation of LCCPs. Overall the only concern regarding skin irritant properties of LCCPs relates to read across data from MCCPs which may be applicable to C₁₈₋₂₀ LCCPs. C₂₀₋₃₀ LCCPs do not possess irritating properties.

Sensitisation

Valid skin sensitisation studies on LCCPs in guinea pigs have shown no evidence of sensitising potential. These findings, together with the lack of sensitisation activity shown by SCCPs and MCCPs, support the conclusion that LCCPs are unlikely to have any significant potential to sensitise the skin.

Repeat-dose toxicity

There are valid oral 90-day repeat dose toxicity studies in the rat on a C_{23(average)}, 43%Cl LCCP, a C₂₂₋₂₆, 43 % Cl LCCP (both liquid grades) and a C₂₂₋₂₈, 70% Cl LCCP (a solid grade) which have been conducted to protocols which are broadly consistent with modern guidelines. There are also a valid oral 90-day repeat dose toxicity study in the mouse and valid 2-year repeat dose studies in both the rat and the mouse on the C_{23(average)}, 43%Cl LCCP.

Studies in rats: The principal target organ in the rat for 90-day and 2-year studies was the liver, with the lymphatic system and kidneys in male rats and the haematological system in female rats also identified as target organs. The

female rat was the most sensitive sex and species. In the 90-day study of C₂₂₋₂₈, 70% Cl solid LCCP, the NOAEL for both male and female rats was 900 mg/kg bw/day based on hepatotoxicity at 3750 mg/kg bw/day (LOAEL). In a 90-day study of C_{23(average)}, 43%Cl LCCP, no significant adverse effects were observed in the male rats (NOAEL = 3750 mg/kg bw/day), but effects in the liver (granulomatous inflammation) were observed in all dose groups for the females (LOAEL of 235 mg/kg bw/day). In a 90-day study of C₂₂₋₂₆, 43 % Cl liquid LCCP, there was evidence of liver toxicity in all exposed females (increased absolute liver weight, dose-dependent multifocal granulomatous hepatitis accompanied by an increase in the intensity of ORO staining, a slight increase in microsomal Lowry protein and a concomitant increase in microsomal enzyme levels). There were no effects in the livers of treated male rats, although trace/mild nephrosis was reported in male rats receiving 3750 mg/kg/day. The NOAEL for male rats from this study was 900 mg/kg bw/day and the LOAEL for female rats was 100 mg/kg bw/day (no NOAEL could be established). In the 2-year study of rats with C_{23(average)}, 43%Cl LCCP, increased liver weights were seen in both male and female rats, the effect being seen after 6 months dosing in female rats and after 12 months dosing in male rats. The effects were accompanied by a slight elevation in several serum enzyme levels and, in females only, variations in haematological parameters. The primary pathological lesion reported was a diffuse lymphohistiocytic inflammation of the liver and the pancreatic and mesenteric lymph nodes. The LOAEL for effects in the liver was 1875 mg/kg bw/day in male rats and 100 mg/kg bw/day in female rats.

Studies in mice: In the mouse, oral administration of the C_{23(average)}, 43 % Cl LCCP for either 90-days or 2-years caused no effects on body or organ weights, no clinical signs of toxicity and no treatment-related histopathological effects (90-day NOAEL = 7500 mg/kg bw/day; 2-year NOAEL = 5000 mg/kg bw/day).

The LOAEL for C₂₀₋₃₀ LCCPs in 90 day and 2 year studies in the rat was 900 mg/kg bw/day in males and 100 mg/kg bw/day in females, based on hepatotoxicity. The NOAEL for males in the 90 day study was 300 mg/kg bw/day, but no NOAEL was obtained for females.

There was no valid repeat-dose toxicity study on a C₁₈₋₂₀ liquid grade LCCP, though available data on MCCPs, C₁₄₋₁₇, was used for read across purposes. In a 90-day rat dietary study, using MCCP, decreased plasma triglycerides and cholesterol, and increased kidney weights were observed at 222 mg/kg bwt/day, and the NOAEL was 23 mg/kg bw/day. This NOAEL can be read across to C₁₈₋₂₀ LCCPs.

Mutagenicity

There is adequate data to assess the mutagenic potential of LCCPs. LCCPs, like the SCCPs and the MCCPs, do not induce mutations in bacteria. There is some evidence of weak clastogenic potential *in vitro* in mammalian cells, with chromosomal aberrations observed in CHO cells (with metabolic activation) and also sister chromatid exchanges (at 5-5000 µg/mL with and without activation); however, no evidence of chromosomal aberrations was seen in a well-conducted *in vivo* study in rat bone marrow cells, in which the rats received doses of up to 5000 mg/kg bw/day for 5 days by gavage. There was also a negative mouse lymphoma assay conducted by the NTP on C_{23(average)} liquid LCCP. Taking all of the data on LCCPs into account and considering what is known about shorter chain CPs, it is concluded that LCCPs, as a group, are without significant genotoxic potential.

Carcinogenicity

There are valid studies on the carcinogenic effects of a C_{23(average)} 43%Cl LCCP in rats and mice. The only convincing evidence of carcinogenicity was an increased incidence of malignant lymphoma in male mice reported at the highest dose of 5000 mg/kg bw/day. Marginal increases in the incidence of adrenal medullary pheochromocytomas were observed in female rats from 100 to 5000 mg/kg bw/day and in hepatocellular carcinomas in female mice at 5000 mg/kg bw/day.

These changes were only observed at exposure levels that are so high (5000 mg/kg bwt/day) that the relevance of this property to a human health is doubtful.

There is no information on the carcinogenic potential of C₁₈₋₂₀ LCCPs or C₂₀₋₃₀ solid grade LCCPs. However, given the results on the studies in rats and mice on the C₂₀₋₃₀ liquid grade LCCP and the fact that CPs, in general, are without significant genotoxic potential, it is considered that LCCPs present a low carcinogenic potential for humans.

Toxicity for Reproduction

Effects on Fertility: There are no fertility studies available, conducted with the LCCPs. No evidence of toxicity to the reproductive organs has been found in standard repeated dose studies conducted with LCCPs. In addition, no evidence of an adverse effect on fertility (standard reproductive/fertility parameters were unaffected) has been found in a well-conducted fertility study conducted oral gavage study of MCCPs. However, in this study, MCCPs did cause maternal deaths around the time of parturition, and neonatal mortalities from internal hemorrhaging as a consequence of reduced maternal vitamin K levels; it is possible that similar effects could be observed with LCCPs. These changes in vitamin K levels were only observed at doses of 74 mg/kg bw/day and above, which is significantly greater than the NOAEL of 43 mg/kg bw/day identified for repeated dose effects established for the MCCPs. Overall, it is anticipated that the LCCPs are unlikely to pose a hazard to fertility.

Developmental Toxicity: There are valid oral gavage developmental toxicity studies on both solid and liquid grade C₂₀₋₃₀ LCCP. There is no evidence that these grades of LCCP cause developmental effects in either rats or rabbits; NOAELs for developmental toxicity range from >1000 to >5000 mg/kg bw/day. There was some evidence that these grades of LCCP might impact on implantation and foetal survival in the rabbit in the absence of overt maternal toxicity, although the effect was not toxicologically significant even at 5000 mg/kg bw/day, the highest dose tested.

There was no valid developmental toxicity study on a C₁₈₋₂₀ liquid grade LCCP. However, given the results of the studies on the C₂₀₋₃₀ LCCPs and the fact that MCCPs have shown no adverse effects in prenatal developmental toxicity studies, it is concluded that the C₁₈₋₂₀ liquid grade LCCPs are also likely to be devoid of developmental toxic effects.

Overall, the LCCPs are not considered to be developmental toxicants.

LCCPs possess properties indicating a hazard for human health (repeated dose toxicity and for C₁₈₋₂₀ LCCPs, potential for skin irritation). Adequate screening-level data are available to characterise the hazard to human health for the purposes of the OECD HPV Chemicals Programme for C₂₀₋₃₀ LCCPs and read across data from MCCPs were used to characterise missing SIDS endpoints for the C₁₈₋₂₀ LCCPs.

Environment

LCCPs have very low volatility and water solubility. LCCPs are hydrolytically stable as they contain no hydrolysable functional groups. Based on Mackay Level III fugacity modelling, in the environment LCCPs are expected to remain almost entirely in the soil when released to soil and migrate to the sediment when released to water. This is also supported by the high Kow values for LCCP, which suggest a strong affinity for soil and sediment. Estimated Koc values for LCCPs range between 2.93×10^6 and 1×10^{10} L/kg (the upper limit of the model). Any limited amount of LCCPs in the air may adsorb to particulates or aerosols. Unadsorbed LCCPs in air would break down via photooxidation, mediated primarily by hydroxyl radicals with a calculated degradation half-life range of 18 to 112 hours (based on a 12-hour day and a hydroxyl radical concentration of 5×10^5 OH/cm³). Data indicate some potential for biodegradation with acclimated microorganisms, though limited biodegradation in non-acclimated organisms. The potential for biodegradation appears to increase with decreasing chlorine content. There is also information to suggest that biodegradation of LCCPs may occur under anaerobic conditions. However LCCPs are not considered to be readily biodegradable. LCCPs do not appear to be toxic to microorganisms in the available study data.

Studies performed mostly in excess of water solubility have shown LCCPs to bioaccumulate in fish and mussels; it is not possible to obtain a reliable BCF value from these data. The potential for uptake and accumulation of LCCPs by fish and other aquatic and terrestrial organisms appears to decrease with increasing carbon chain length and increasing degree of chlorination. Model estimated BCFs in fish are as follows based on representative log Kow values (EU Technical Guidance Document parabolic equation, applicable for substances with log Kow >6 and molecular weight < 700 g/mol: $\log BCF = -0.2 \times (\log Kow)^2 + (2.74 \times \log Kow - 4.72)$):

C ₁₈₋₂₀ liquid LCCP	BCF = 1,096 L/kg (based on log Kow 9.7)
C ₂₀₋₃₀ liquid LCCP	BCF = 192 L/kg (based on log Kow 10.3)
C ₂₀₋₃₀ solid LCCP	BCF <1 L/kg (based on log Kow 17)

Results of dietary exposure studies in fish show that uptake from food occurs in the laboratory, and that this uptake in some cases can be significant. The degree of uptake appears to be highest for the C₁₈₋₂₀ LCCPs, but uptake of C₂₀₋₃₀ LCCPs has also been demonstrated. The uptake of the highly chlorinated C₂₀₋₃₀ solid LCCPs from food appears to be minimal.

There is a relatively large amount of aquatic toxicity data available for LCCPs. Aquatic toxicity testing is problematic due to the very low water solubility of LCCPs. In many instances, it is uncertain whether saturated test solutions contained undissolved test substance. It is likely that the methods used in some tests (e.g., water accommodated fraction) to prepare test solutions may result in the more soluble components (ie those with shorter chain lengths) present in the commercial LCCP being preferentially represented in the resultant solution. These, and the fact that any effects observed were near the limit of water solubility, complicate interpretation of test results. The substances in the category generally show little or no toxicity at concentrations well in excess of their water solubility in acute tests. Available acute test results are as follows.

C₁₈₋₂₀ LCCPs

Fish (96h): no effects at limit of solubility.

Daphnia magna (48-h): no effects at solubility limit in one of two studies; 15% immobilisation in another study in a saturated solution (400 – 500 ug/l, measured).

C₂₀₋₃₀ liquid LCCPs

Fish (96-h): no effects at limit of solubility.

Daphnia magna (48h): no effects at limit of solubility.

C₂₀₋₃₀ solid LCCPs

Fish (96-h): no effects at limit of solubility

No study is available for C₂₀₋₃₀ solid LCCPs, but no effects are expected given no effects were seen with C₂₀₋₃₀ liquid LCCPs. No valid algal study exists for any of the LCCPs, but data from related chlorinated paraffins (SCCPs and MCCPs) suggest that LCCPs would show no effects on algae. The overall toxicity profile of these substances (SCCP, MCCP, LCCPs) suggest that filling this data gap is not critical for the environmental assessment.

Chronic studies in fish are available for C₂₀₋₃₀ liquid and solid LCCPs. No effects were seen in the tests (NOECs equating to the highest concentrations tested were reported: 4 mg/l nominal and 3.8 mg/l nominal). The results may be read across to C₁₈₋₂₀ LCCPs.

Daphnia magna has been identified as the most sensitive species for chlorinated paraffins as a substance class. Two studies are available which investigated chronic toxicity to *Daphnia magna* from C₁₈₋₂₀ LCCPs. One showed no effects at a saturation limit of 2 µg/L (measured) and the other, which followed a water-accommodated fraction technique, showed effects at 58-65 µg/L and no effects at 29 – 32 µg/L (measured). Based on these data, the worst case assumption is that the NOEC for C₁₈₋₂₀ LCCPs for *Daphnia magna* is 29 µg/L (which is above many estimates of water solubility for LCCPs). Available chronic studies with C₂₀₋₃₀ liquid LCCPs in *Daphnia magna* indicate no effects are observed below the limit of water solubility; the same conclusion can be read across to C₂₀₋₃₀ solid LCCPs.

Upon release into the environment, the substances are likely to partition to sediment in the aquatic compartment and bind to soil in the terrestrial environment; no data for sediment- or soil-dwelling organisms were available.

LCCPs generally show little acute aquatic toxicity at concentrations at or above water solubility. Given the complexity of the substances and their very low solubility interpretation of test results is not straight forward. C₁₈₋₂₀ liquid LCCPs possess properties indicating a hazard for the environment (chronic toxicity to invertebrates). Based on the available data C₂₀₋₃₀ liquid and solid LCCPs appear to present a low hazard for the environment. LCCPs are not readily biodegradable, and may have a potential for bioaccumulation.

Use/Exposure

The total EU usage of LCCPs was in the range of 5,000-10,000 tonnes/year from 1998-2004. The main areas of use for LCCPs are as a flame retardant in rubber and textiles, and as a plasticiser/flame retardant in sealants/adhesives and paints. LCCPs may also be used to a lesser extent as a secondary plasticiser in PVC, as an extreme pressure additive in metal cutting/working fluids (oil- and/or water-based) and as a component of leather fat liquoring treatments (leather is treated with a fat liquor as the last step in its preparation; the fat liquor improves the feel and suppleness of the leather).

Occupational exposure to LCCPs may occur during their manufacture, their incorporation into downstream products (PVC, metal working fluids, sealants, rubber, leather fat liquors, paints, textiles) and their processing, especially at high temperatures and during the use of these products. Occupational exposure may occur via dermal contact, though workers are generally advised to wear protective clothing and avoid skin contact. Exposure by inhalation is not expected to be a likely source of exposure due to the very low volatility of LCCPs, though there is the potential for aerosols to form during the use of liquid products such as metal-working fluids or by inhalation of dusts from applications using the solid grades. Consumer exposure may occur through use of the substance as a plasticiser or flame retardant in consumer goods. Exposure would primarily be via the dermal route given the substance's physico-chemical properties. No information on migration of the substance from articles containing it is available. The concentrations of the substance used in articles are typically <1 -6% in PVC, and most rubber and paints. In exceptional cases, up to 15% is used in cabling materials and in some rubbers. Coatings that contain LCCPs are typically only used in occupational settings (e.g., roadway paint). Releases to the environment could occur during production, the processing steps for the identified uses of the substance, use of articles containing the substance, and at end of life disposal. However, exposure is expected to be low from the majority of these releases. Depending on the waste disposal practices followed for water-based emulsions for metal working fluids that may contain the substance, release of the substance to the environment may occur. However, the use of LCCPs in metal working fluids is expected to be minor compared to other applications.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	Mixture of two isomers: 109-52-4 and 116-53-0
Chemical Name	Commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid commercial mixture of approximately 64% n-pentanoic acid, CAS No.109-52-4 and 36% 2-methyl-1-butyric acid, CAS No. 116-53-0
Structural Formula	CH ₃ -CH ₂ -CH ₂ -CH ₂ -COOH n-pentanoic acid CH ₃ -CH ₂ -CH(CH ₃)-COOH 2-methyl-1-butyric acid
SUMMARY CONCLUSIONS OF THE SIAR Analogue Rationale The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid contains two aliphatic acid isomers: n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%). 2-Methyl-1-butyric acid is not isolated and is not produced except as the minor component of the commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid. Data from chemicals with structures and carbon chain lengths similar to the components of the commercial mixture have been used to satisfy endpoints or augment available data for the mixture. Propionic acid's use as an analogue for n-pentanoic acid is based on the fact that propionic acid is a metabolite of n-pentanoic acid and 2-methyl-1-butyric acid and has similar irritative potential <i>in vivo</i> as n-pentanoic acid. Butyric acid data was also used as an analogue based on similar physical chemical properties and <i>in vivo</i> irritative potential. For the environment, Henry's Law constant, Log Kow, dissociation constant, photodegradation potential, and distribution in environmental compartments endpoints are addressed individually for each component, n-pentanoic acid and 2-methyl-1-butyric acid. For human health toxicity endpoints, data for propionic acid (CAS No. 79-09-4) are used as support for repeated-dose and reproductive toxicity endpoints. Propionic acid (a 3-carbon carboxylic acid) can be used as an analogue of n-pentanoic acid based on similarities in structure along with a common functional group. Both chemicals are corrosive, which is thought to contribute to the similar toxicities in repeated-dose studies. Finally, propionic acid is also a metabolic product of n-pentanoic acid and 2-methyl-1-butyric acid through intracellular oxidation pathways. Calcium propionate (CAS No. 4075-81-4), the calcium salt of propionic acid, is used as support for the developmental toxicity endpoint. Calcium propionate dissociates to propionate ions in water. In the stomach, both calcium propionate and propionic acid exist as the non-ionized acid. 2-Methyl-1-propionic acid (CAS No. 79-31-2), similar in structure to 2-methyl-1-butyric acid, is used to supplement the genetic toxicity endpoint. Due to similarities in metabolism (via beta-oxidation) and lower acute toxicity for the mixture compared with n-pentanoic acid, the straight chain (n-pentanoic acid) is an appropriate analogue for the mixture. n-Pentanoic acid is being presented at SIAM 29 as a separate case by the United States. Propionic acid has previously been assessed in the OECD HPV Chemicals Programme at SIAM 25. Physical-Chemical Properties The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid is a colourless liquid with a melting point of -44°C*, a boiling point of 183.1°C* and a vapour pressure of 0.1h Pa* at 20 °C. The calculated range for partition coefficients (log K_{ow}) for the commercial mixture is 1.18 to 1.39 at 25°C, and the water solubility is 32,000 mg/L* at 20°C. As the dissociation constant (pKa) for n-pentanoic acid is 4.83; the pKa for 2-methyl-1-butyric acid is 4.80. The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid has a pKa between 4.80 and 4.83, and is anticipated to exist in its dissociated forms at environmentally relevant pH values. * Reliability = 4, data provided by manufacturer; however, supported by the analogue data	

Human Health

n-Pentanoic acid and 2-methyl-1-butyric acid are metabolized by intracellular β -oxidation pathways in fatty acid metabolism at concentrations up to 67 mM and 1 M, respectively, with products being acetic acid and propionic acid. Both acetic and propionic acids are normal constituents of cells and are formed during oxidative degradation of isoleucine.

The oral LD₅₀ value for the commercial mixture n-pentanoic and 2-methyl-1-butyric acid, administered as a 40% solution in corn oil, is 4920 mg/kg bw for female rats and >4000 mg/kg bw for male rats. Signs of toxicity included hypoactivity, abnormal or uncoordinated gait, lacrimation, slow breathing, and prostration. Necropsy of animals dying on study revealed haemorrhages in the glandular portion of the stomach with multiple areas of ulceration. The dermal LD₅₀ in female rabbits is 1070 mg/kg bw; the commercial mixture was applied undiluted and produced oedema, necrosis, ulceration and desquamation at the application site. There was no mortality or signs of toxicity among male and female rats exposed for 6 hours to a substantially saturated vapour of the commercial mixture of n-pentanoic and 2-methyl-1-butyric acid. The commercial mixture of n-pentanoic and 2-methyl-1-butyric acid is corrosive and causes irreversible injury to the skin and eye. Severe irritation and ulceration, followed by necrosis, scabbing, alopecia, and desquamation were observed in a skin irritation assay performed in rabbits. The commercial mixture is a severe eye irritant. Severe corneal injury, iritis, and severe conjunctival irritation; haemorrhage, necrosis of the nictitating membrane, and corneal vascularization were observed in an eye irritation assay performed in rabbit. It is anticipated that high concentrations of the commercial mixture, produced as an aerosol or a vapour/aerosol mixture, will result in nasal and/or respiratory irritation. No experimental data are available for skin sensitisation in animals or humans for the commercial mixture or its components.

There are no repeated-dose toxicity studies for the commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid. Data are available for n-pentanoic acid and structural analogue propionic acid.

There are short-term repeated-dose data available for n-pentanoic acid for rabbits via the dermal route of exposure, and for rats via the oral route. In a repeated-dose dermal toxicity study in male and female rabbits, n-pentanoic acid in a mineral oil solution was applied to the skin at a dose of 500 mg/kg bw for a total of 10 applications over fourteen days. Death was observed in one female rabbit; all test animals displayed vocalization upon handling, decreased food consumption, decreased body weight, and severe signs of dermal irritation. In a repeated-dose oral toxicity study in female rats, n-pentanoic acid in corn oil was administered by gavage at doses of 0, 125, 250, 500, 750, and 1000 mg/kg bw/day for 10 consecutive days. Dyspnea or rales were observed in all treated groups. Decreased activity, lethargy, and immobilization were observed at 750 and 1000 mg/kg bw/day. Mortality occurred at doses of 250 mg/kg bw/day and greater and all animals died at 1000 mg/kg bw/day. In a third study, n-pentanoic acid was administered to 10 rats in a rice diet at doses up to 10% (w/w) of the diet; half were sacrificed at 115 days and the other half at 150 days. Stomachs were examined microscopically if gross lesions were observed. n-Pentanoic acid induced benign hyperplasia, hyperkeratosis, acanthosis and papillomas in the forestomach. No malignant changes were detected and there were no changes in the glandular portion of the stomach.

Repeated-dose oral toxicity data in dogs and rats are available for the analogue propionic acid. Dogs (4 to 8/sex/dose) were exposed to 0, 0.3, 1.0, or 3.0% propionic acid (approximately 0, 196, 660, and 1,848 mg/kg-bw/day for males and 0, 210, 696, and 1,832 mg/kg-bw/day for females) in the diet for 100 days. There was no mortality, no clinical signs of toxicity, and no haematological or clinical biochemistry changes. Microscopic examination of tissues revealed no lesions except point-of-contact diffuse epithelial hyperplasia of the mucosa of the esophagus in three dogs in the high-dose group. The incidence of lesions in the esophagus was similar in lower dose animals and controls. The incidence of lesions of the esophagus in the high-dose animals after a 6-week recovery interval was similar to controls. Based on the point-of-contact effect observed in the esophagus, the LOAEL for this study in dogs is 3% propionic acid (1,848 mg/kg-bw/day in male dogs, and 1,832 mg/kg-bw/day in female dogs) in the diet, and the NOAEL is 1% propionic acid or 660 mg/kg bw/day for males and 696 mg/kg bw/day for females. In a repeated dose oral toxicity study, rats (20/sex/dose) received 0, 0.62%, 1.25%, 2.5%, or 5% propionic acid in the diet for 91 days. There was no mortality. Males in the high dose group (5% in diet) exhibited decreased food consumption and decreased body weight gain, no other clinical signs of toxicity were observed. Point-of-contact effects observed were acanthosis, hyperkeratosis, and proliferation of the epithelium of the forestomach mucosa in rats in the high dose group; these changes were not observed after a 6-week recovery interval. Based on point-of-contact effects observed in the forestomach, the NOAEL for male and female rats in this study is 2.5% propionic acid in the diet, or approximately 1600 mg/kg bw/day.

Additional studies focused on the site-of-contact effect of the analogue propionic acid on the stomach; other tissues were not examined. Male rats (6 males/dose) were fed a control diet or a pellet diet containing 4%

propionic acid (approximately 2,700 mg/kg bw/day) for 24 weeks. Macroscopic and histopathological examination of the stomach revealed no adverse effects. Male rats (6/dose) were also given a control powdered diet, or a powdered diet containing 4% propionic acid for 12 weeks. Rats displayed severe hyperplastic changes and ulcerations in the forestomach but not in the glandular stomach.

In another study, groups of 30 male rats were fed 0, 0.4 or 4% propionic acid in ground rat feed for 20 weeks or lifetime. Of the rats fed 0.4% propionic acid (approximately 270 mg/kg bw/day), hyperplasia and hyperkeratosis were observed histologically in the forestomach. Among rats fed 4% propionic acid, forestomach epithelial changes such as hyperplasia and hyperkeratosis were noted at 20 weeks, and hyperplasia with ulceration, dyskeratosis and papillomatous elevations (one with unspecified “carcinomatous” changes) were noted after lifetime exposure. No histopathological changes were observed in the glandular stomach in these studies. The consistency of the diet appeared to influence the incidence of lesions observed. The point-of-contact effects observed in the rat forestomach in response to feeding high doses of short-chain fatty acids are likely to be the result of severe irritation and inflammation and the associated hyperplastic proliferative repair response.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium*, and in an *in vitro* HGPRT forward mutation assay using Chinese hamster ovary (CHO) cells, n-pentanoic acid was negative with and without metabolic activation. An *in vitro* chromosomal aberration test using CHO cells with n-pentanoic acid was positive with and without metabolic activation. An *in vitro* sister chromatid exchange assay in CHO cells, n-pentanoic acid was negative without metabolic activation and positive with metabolic activation. The effect of pH in these studies is uncertain because it was not measured. An *in vivo* micronucleus assay in mice, n-pentanoic acid was negative at doses of 25%, 50% and 80% of the LD50 via intraperitoneal injection, as determined in range-finding studies. Cytotoxicity (PCE/NCE ratios) was seen in females (but not males) in the range-finding test at 200 mg/mL, but was not observed in the definitive test at concentrations up to 266 mg/mL. Based on these data, the commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid is not expected to induce gene mutations but may induce chromosomal aberrations *in vitro*; it is not expected to induce micronuclei *in vivo*.

There are no valid carcinogenicity studies for the commercial mixture or its components. In an invalid (reliability score of 3) 80-week dermal toxicity assay in mice with significant methodological deficiencies, repeated dermal application of undiluted n-pentanoic acid (25 mg/mouse or approximately 950 mg/kg bw applied two times per week) induced mortality (66%), severe skin ulcerations, chronic inflammation, and regenerative repair with disproportionate cell proliferation which resulted in scar tissue formation and subsequent dysplasia, hyperplasia, and skin tumours. The controls also showed high mortality (48%). There is some uncertainty regarding the skin tumors observed in the repeated exposure dermal toxicity study and the positive *in vitro* genotoxicity results. However, these effects were likely due to the low pH of the test solutions.

There are no fertility studies available for the commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid or its components. Data are available regarding effects on reproductive organs for the structural analogue, propionic acid. In repeated-dose oral toxicity studies, there were no effects on reproductive organ weights, and reproductive organs and tissues were normal in male and female rats exposed to propionic acid at doses up to 5% in the diet (approximately 3300 mg/kg bw/day) for 91 days, with a NOAEL of 3300 mg/kg bw/day for reproductive organ toxicity. Similarly, there were no effects on reproductive organs in dogs fed propionic acid at doses up to 3% in the diet (1848 mg/kg bw/day for male dogs; 1832 mg/kg bw for female dogs) for up to 106 days, with a NOAEL of 1832 mg/kg bw/day for reproductive organ toxicity.

There are three developmental toxicity studies for n-pentanoic acid. Fetal malformations were not observed. However, significant maternal mortality limits the ability to make firm conclusions from these studies. In the most robust study, n-pentanoic acid in corn oil was administered by oral gavage to Sprague-Dawley rats on gestation days 6 through 15 at doses of 0, 50, 100, and 200 mg/kg bw/day. Rales and vocalization were reported during dosing in dams at all doses. Mortality of the dams occurred in all treated groups and was greater than 10% at 100 and 200 mg/kg bw/day. Necropsy of dams dying on study revealed respiratory tract congestion, distension of the gastrointestinal tract, and gastric irritation. Decreased fetal body weights were observed at 100 and 200 mg/kg. Developmental toxicity, as evidenced by an increased incidence of reduced ossification of the sternebrae, was observed at 50 and 100 mg/kg bw/day. Developmental effects may have been confounded by maternal toxicity.

The analogue, calcium propionate is the non-corrosive salt of propionic acid, and does not induce significant point-of-contact toxicity typical of the parent acid. Calcium propionate was administered to pregnant mice and rats via oral gavage during gestation days 6-15 at doses of 0, 3, 14, 65, and 300 mg/kg bw/day. Pregnant rabbits and hamsters were given calcium propionate via gavage at 0, 4, 19, 86, and 400 mg/kg bw/day during gestation days 6-18 (rabbits) or 6-10 (hamsters). In all species, there was no effect on maternal or fetal survival, or on fetal or litter size. No increases in fetal or skeletal abnormalities were observed. Both NOAELs for maternal toxicity

and developmental effects were the highest doses tested (300 mg/kg-bw/day mice and rats; 400 mg/kg-bw/day for rabbits and hamsters).

The commercial mixture of n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%) possesses properties indicating a hazard for human health (acute skin and eye irritation, repeated-dose toxicity associated with point of contact effects, and possible developmental toxicity in the presence of maternal toxicity). Adequate screening-level data are available to characterize the hazard for human health for the purposes of the OECD HPV Programme.

Environment

The commercial mixture of n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%) is not expected to undergo hydrolysis in the environment, due to the lack of hydrolyzable functional groups. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with an estimated half-life between 2.6 to 2.8 days (62.4-67.7 hours). For n-pentanoic acid, a half-life of 62.4 hours for atmospheric photo-oxidation was determined. For 2-methyl-1-butyric acid, a half-life of 67.7 hours for atmospheric photo-oxidation was determined. An OECD 301D Closed Bottle Test with the commercial mixture resulted in 72% biodegradation after 28 days. The commercial mixture is readily biodegradable under aerobic conditions.

Based on Level III fugacity modelling with equal and continuous distributions to air, water and soil compartments, it is estimated that the majority of n-pentanoic acid and 2-methyl-1-butyric acid will distribute mainly to the soil (61.8%, 57.2%) and water (33.8%, 36.8%) compartments with minor distribution to the air compartment (4.33, 5.84%) and negligible amount in the sediments compartment. When released to water, this commercial mixture will remain in the water compartment. The Henry's law constant for n-pentanoic acid is 4.48×10^{-7} atm-m³/mol (0.045 Pa-m³/mol) at 25 °C; the Henry's law constant for 2-methyl-1-butyric acid is 1.467×10^{-6} atm-m³/mol (0.149 Pa-m³/mol) at 25°C. These values suggest that volatilization of the components of the commercial mixture from the water phase is not expected to be high. The K_{oc} for n-pentanoic acid and 2-methyl-1-butyric acid were calculated to be 4.084 and 3.661 L/kg, respectively.

Bioaccumulation potential is low based on the preferred Log K_{ow} values of 1.39 and 1.18 for n-pentanoic acid and 2-methyl-1-butyric acid, respectively. The estimated BCF values with BCFWIN (v3.00) are 3.162 for both components of the commercial mixture.

The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid is comprised of two fatty acid isomers: n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%). The following acute toxicity test results* on the commercial mixture have been determined for aquatic species:

Fish	<i>Oncorhynchus mykiss</i>	OECD TG 203	96 h LC ₅₀ = 75.9 mg/L
Fish	<i>Pimephales promelas</i>	Static test system	96 h LC ₅₀ = 29 mg/L 96 h LC ₅₀ = 34 mg/L
Aquatic invertebrate	<i>Daphnia magna</i> Straus	OECD TG 202	48-hr EC ₅₀ = 88.1 mg/L
Algae	<i>Pseudokirchnerilla subcapitata</i>	OECD TG 201	96-hr E _b C ₅₀ = 51.8 mg/L (biomass) 96-hr E _r C ₅₀ = 66.2 mg/L (growth rate) 96-hr NOEC = 12.8 mg/L (biomass and rate)

*all results are based on measured test concentrations in unbuffered test solutions

The commercial mixture of n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%) possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L in unbuffered systems). However, the commercial mixture is readily biodegradable, has low bioaccumulation potential, and the observed aquatic toxicity is due to reductions in pH. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

Global production of n-pentanoic acid and 2-methyl-1-butyric acid was estimated to be approximately 30,000 tonnes in 2004. Consumption in 2004 was estimated to be 17,000 tonnes in the US, and 10,000 tonnes in Western Europe. The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid is produced in an

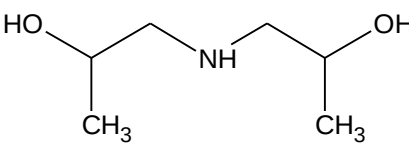
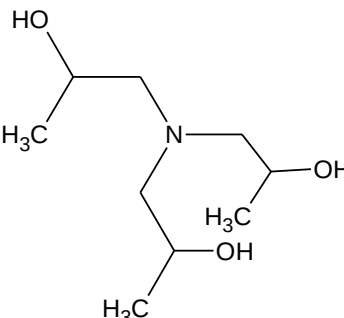
enclosed, continuous process by an air-oxidation reaction of a mixture of valeraldehyde and 2-methylbutyraldehyde.

The commercial mixture is used as an industrial intermediate in the manufacture of neopolyol esters for the production of industrial lubricants used in refrigeration applications, fire-resistant hydraulic fluids, and jet engines. Some specialty applications include its use as a pharmaceutical intermediate, and in the manufacture of isoamyl valerate (an ester solvent), metallic salts, and plasticizers. The two components, n-pentanoic acid and 2-methyl-1-butyric acid, have been identified as naturally-occurring volatiles in foods and both are food additives permitted for direct application to food. Both components are products of mammalian and microbial intercellular metabolism.

No monitoring data within production and processing plants in the United States are available. The commercial mixture is manufactured in an enclosed, continuous process. Engineering controls and vapour collection systems are used during production, transfer, and loading operations. These measures are used to limit workplace exposures and odour complaints.

Because of its objectionable odour, additional scrubbers and other emission controls are usually employed to minimize release of the commercial mixture of during manufacture and use. However, the commercial mixture may be released to the environment as a fugitive emission during production and use; its individual components may be found in the environment as naturally-occurring emissions from food products, microorganisms, animal wastes, and diesel exhaust.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Isopropanolamines category
Chemical Names and CAS Nos.	1,1'-Iminodipropan-2-ol (Diisopropanolamine, DIPA) (CAS No. 110-97-4) 1,1',1''-Nitrilotripropan-2-ol (Triisopropanolamine, TIPA) (CAS No. 122-20-3)
Structural Formulas	DIPA  TIPA 

SUMMARY CONCLUSIONS OF THE SIAR**Category Justification**

DIPA and TIPA are the secondary and tertiary amine analogues, respectively, of the isopropanol amines series of compounds differing by a single, common substituent, isopropanol.

These chemicals can be included in a single category for several reasons. Both have similar chemical structures and exhibit physico-chemical properties that are either very similar or that reflect incremental changes expected for an alcoholic amines series. Environmental fate characteristics are also similar, with the exception of biodegradation. DIPA is considered readily biodegradable but TIPA is not; however, TIPA will biodegrade to different extents under various conditions. Regarding mammalian toxicity, both compounds are skin and eye irritants, both target the kidney in repeated-dose studies (with the larger molecule showing greater toxicity), and both exhibit similarly low toxicity for other endpoints.

Physical-Chemical Properties

DIPA is a solid with a measured melting point of 42 °C, a measured boiling point of 249 °C at 1013 hPa, a measured vapour pressure of 0.00107 hPa at 25 °C, and a dissociation constant (pKa) of 9.1 at 25 °C. The octanol-water partition coefficient (log K_{ow}) is -0.79, and the measured solubility is 870 g/L at 25 °C. TIPA is also a solid with the measured melting points range from 45-50 °C. Its measured boiling point is 305 °C at 1013 hPa, a measured vapour pressure of 0.000013 hPa at 25 °C, and a dissociation constant (pKa) of 8.06 at 25 °C. The octanol-water partition coefficient (log K_{ow}) of TIPA is -0.15, and miscible with water at 25°C.

Human Health

The absorption, distribution, and excretion of DIPA have been studied in rats after dermal administration. A single dermal dose of 19 mg ¹⁴C-DIPA/ kg bw was applied to the shaved skin on the back of rats for up to 48 hrs. Only 16.2% of the ¹⁴C-DIPA was absorbed representing an absorption rate of less than 0.3% of the dose per hour. The main route of

elimination was via the urine with minor amounts in the feces and no accumulation in the tissues. DIPA was also administered at 19 mg/kg intravenously in rats where 96.8% of dose was excreted unchanged in the urine after 48 hrs.

Metabolism and excretion of TIPA was assessed in an OECD TG 417 oral study in male rats, in which single oral doses of 10.7 mg ¹⁴C-TIPA/kg bw were administered. Radioactivity peaked in the plasma at 0.25 hrs post-dosing and rapidly declined. Approximately 80% of the dose was excreted in 24 hours in the urine as unchanged TIPA. Minor amounts were eliminated in the feces and in the expired air with less than 1% remaining in the tissues or carcass.

The most reliable study for acute oral toxicity indicates LD₅₀ values between 2000 and 3980 mg/kg bw in rats for DIPA. For TIPA, two studies of acceptable quality indicate LD₅₀ values in rats of 5994 and 6500 mg/kg bw. Rats administered TIPA showed signs of lethargy, and at the highest TIPA dose, rats had pale watery eyes and diarrhea. The dermal 24-h LD₅₀ values in rabbits were 8000 mg/kg bw for DIPA and > 5000 mg/kg bw for TIPA.

In an OECD TG 404 study, no skin irritancy was reported in rabbits in which undiluted DIPA was in semi-occluded contact with the intact skin for at least 4 hours, but after prolonged occluded exposure using 10% or undiluted DIPA on intact or abraded skin, hyperemia and necrosis or denaturation were seen in rabbits. In an OECD TG 404 study, undiluted TIPA was also not irritating to rabbits after a 4-h exposure using semioclusive conditions. After prolonged covered contact of TIPA on rabbit skin, irritation (redness, swelling and scar formation) was observed. In separate OECD 405 guideline studies, undiluted DIPA and TIPA in the eyes of rabbits after exposure for 72 hours, resulted in irritation with severe effects in some animals.

No sensitisation potential was observed in screening tests involving repeated dermal applications of 50 % DIPA or 22% TIPA in guinea pigs.

Repeated dose studies have been conducted with DIPA in rats and TIPA in dogs and rats. In a repeat-dose oral toxicity study (OECD 408), rats (10/sex/dose) were administered DIPA at approximately 0, 100, 500 or 1000 mg/kg bw/day in their drinking water for 90 days. Another group (10/sex) was given untreated water for 28 days after the 90-day exposure to 1000 mg/kg-bw. Decreases in food and water consumption and body weight were observed at the highest dose and were associated with increased specific gravity and decreased volume of the urine. Serum cholesterol was increased and serum phosphorous was decreased at the highest dose, which were no longer seen at the end of the recovery period. Absolute and relative kidney weights were increased at 500 and 1000 mg/kg-bw without histopathological changes. The increased kidney weight was more pronounced in males than in females. The NOAELs were 100 mg/kg-bw/day for males and 500 mg/kg-bw/day for females. Rats (5/sex/dose) were also administered DIPA via drinking water at 100, 300, 600, 1200 and 3000 mg/kg bw/day for 14 days. At 1200 mg/kg bw/day, decreased body weights in males, slightly decreased food and water consumption, and increased relative kidney weights were observed. The NOAEL was 600 mg/kg-bw/day for male and female rats.

TIPA was administered to dogs (4/sex/dose) in their diet at 0, 500, 2000 or 7500 ppm (approximately 0, 16.8, 71.2 or 272 mg/kg bw/day in males or 0, 19.7, 78.3 or 288 mg/kg bw/day in females) for 100 days. Ophthalmology, hematology, serum chemistry, urinalysis, blood methemoglobin, macroscopic and microscopic examinations, and organ weight evaluations showed no treatment-related effects, resulting in a NOAEL of 272-288 mg/kg bw/day (the highest dose tested). Rats (5/sex/dose) were also administered TIPA via drinking water at 100, 300, 600, 1200 or 2000 mg/kg bw/day for 14 days. At 2000 mg/kg bw/day, decreased body weights, slightly decreased water consumption in females, and decreased protein and albumin were observed. At 1200 mg/kg bw/day, decreased protein and albumin were observed. Decreases in glucose were observed at 300 mg/kg bw/day and higher in males and 600 mg/kg bw/day and higher in females. Finally, increased relative kidney weights were observed at 300 mg/kg bw/day reaching statistical significance at 600 mg/kg bw/day in males. Increased relative kidney weights were observed in females starting at 300 mg/kg/day and became significant at 2000 mg/kg bw/day. The NOAEL was 100 mg/kg-bw/day for male and female rats.

Rats (5/sex/dose) were administered DIPA at 0, 100, 500 or 750 mg/kg-bw for 5 days/week for 28 days dermally. Moderate erythema, edema and scabs were noted at the application site but no systemic toxicity was observed, resulting in NOAELs for dermal irritation and systemic toxicity of 100 and 750 mg/kg bw/day, respectively. When TIPA was administered dermally at 0, 300, 1000 or 3000 mg/kg bw for 5 days/week for 28 days, rats exhibited minimal thickening of skin at the highest dose. Erythema and scabs were seen in one animal each at the mid- and high-doses. The NOAEL for systemic toxicity was 3000 mg/kg bw/day and the NOAEL for local effects was 300 mg/kg bw/day.

DIPA and TIPA did not cause gene mutations in a bacterial reverse mutation assay in several strains of *Salmonella typhimurium* or in Chinese hamster ovary cells. Neither substance resulted in chromosomal aberrations in rat lymphocytes. All the studies examined activity both in the presence and absence of metabolic activation. These chemicals are not

considered to be genotoxic *in vitro*.

The carcinogenic potential of DIPA and TIPA has been investigated in two oral studies. In one study, DIPA was administered via the diet to 20 males/dose at 0 or 1% DIPA (approximately 392 to 843 mg/kg bw/day) for 94 weeks. Sixteen of twenty animals survived. There were no significant differences between tumour incidence in controls or treated groups. A 104-week dietary study with 2% TIPA in the feed of male Wistar rats did not show any histological evidence of increased liver foci. Data from these studies combined with generally negative results from *in vitro* genotoxicity assays have indicated no evidence of a carcinogenic potential of these chemicals alone. However, the studies were limited in their ability to detect tumours because they used small numbers of males only and a single dose level.

The reproductive toxicity of TIPA was investigated in a one-generation study in rats in which the test substance was administered via the diet to 25 rats/sex/dose at approximately 0, 39.7, 160 or 609 mg/kg bw/day (males) or 0, 43.7, 182 or 700 mg/kg bw/day (females) for 5 weeks prior to mating, during mating, gestation and lactation. Twenty offspring/sex/dose were also given the same doses for 90 days post-weaning. No effects were reported and the reproductive NOAEL was 609/700 mg/kg bw/day (highest doses tested). In an OECD TG 414 developmental toxicity study, pregnant female rats were administered DIPA via oral gavage at 1000 mg/kg-bw/day on gestation days 6 to 20. The maternal and developmental NOAEL was 1000 mg/kg bw/day (highest dose tested). Based on these results, DIPA and TIPA are not expected to have the potential for reproductive or developmental toxicity.

DIPA and TIPA possess properties indicating a hazard for human health (skin and eye irritation). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

DIPA and TIPA do not possess a molecular structure that contains functional groups subject to hydrolysis under neutral ambient conditions. Based on the dissociation constants, these chemicals are expected to be largely in the protonated amine forms (conjugate acids) at pH 7. The compounds absorb light >290 nm, and therefore direct photolysis is possible. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals for DIPA is predicted to have a half-life of approximately 1.262 hours and for TIPA is predicted to be 1.035 hours when evaluated using the AOPWIN model. DIPA passed the test for ready biodegradation (OECD 301F assay). A 94% degradation of DIPA was observed within 28 days in the presence of activated sludge. TIPA, however, did not pass the test for ready biodegradation (OECD 301F assay), as it exhibited an average of 0% biodegradation based on oxygen consumption after 28 days. However, TIPA is susceptible to degradation in the environment. An aerobic metabolism study resulted in a half-life of 14.3 days with 39% mineralization in 30 days and 64% mineralization in 60 days. Another aerobic soil metabolism study resulted in a half-life of approximately 2 days with complete mineralization by 20 days.

A level III fugacity model with equal and continuous distribution to the air, water and soil compartments suggests that DIPA and TIPA will distribute mainly to the soil (62.2 and 69.4%) and water (37.8 and 30.6%) compartments, respectively, with negligible amount in the air (<0.1%) and sediment (<0.1%) compartments for both chemicals. When they are released only to water, they will distribute mainly to water (99.8%) with 0.2% to sediment and 0 % to air and soil.

Henry law's constant values for DIPA and TIPA of 6.91×10^{-11} atm-m³/mole (7.00×10^{-6} Pa-m³/mole) and 9.77×10^{-12} atm-m³/mole (9.90×10^{-7} Pa-m³/mole), respectively, at 25 °C suggests that volatilization of these chemicals from the water phase is expected to be low. The bioaccumulation potential of DIPA and TIPA is considered to be low based on log Kow values of -0.79 and -0.15, respectively, and supported by an estimated BCF value of 3 for both chemicals (BCFBAF Program (v3.00); USEPA, 2009).

The following acute toxicity test results have been determined for aquatic species:

DIPA

Fish [<i>Brachydanio rerio</i> (new name: <i>Danio rerio</i>)]	96 h LC ₅₀ ≥ 1000 - ≤ 2200 mg/L (nominal)
Invertebrate [<i>Daphnia magna</i>]	48 h LC ₅₀ = 277.7 mg/L (nominal)
Algae [<i>Scenedesmus subspicatus</i>]	72 h ErC ₅₀ = 270 mg/L (growth rate, nominal)

TIPA

Fish [<i>Cyprinus carpio</i>]	96 h LC ₅₀ > 1000 mg/L (nominal)
Invertebrate [<i>Daphnia magna</i>]	48 h LC ₅₀ = 857 mg/L (nominal)

Algae [*Scenedesmus subspicatus*]

72 h ErC₅₀ = 710 mg/L (growth rate, nominal)

72 h E_bC₅₀ = 50 mg/L (biomass, nominal)

72-h NOEC = 0.64 mg/L (biomass, nominal)

The chemicals in the isopropanolamines category possess properties indicating a hazard for the environment (acute aquatic toxicity to algae (biomass) between 0.1 and 100 mg/L for TIPA). DIPA is readily biodegradable but TIPA is not readily biodegradable. The bioaccumulation potential of DIPA and TIPA is considered to be low. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

DIPA had a production and/or import volume (aggregated across companies) in the United States between 4,540 to < 22,700 tonnes during 2005 as reported to the U.S. Environmental Protection Agency through Inventory Update Reporting (IUR). Four companies reported manufacturing or importing DIPA in quantities greater than 11.35 tonnes. The number of manufacturing, processing and use sites is between 100 and 999.

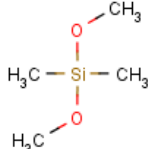
DIPA and TIPA are widely used as emulsifiers, stabilizers, surfactants and chemical intermediates. Major uses of DIPA include: 1) natural gas purification as a scavenger of carbon dioxide and hydrogen sulfide, 2) personal care products such as soaps and detergents as a pH adjuster or to form emulsifiers, foam stabilizers or viscosity modifiers, and 3) industrial metalworking as a corrosion inhibitor, and lubrication enhancer to reduce friction. The major applications of TIPA include: 1) coatings as a cross-linker, acid neutralizer to improve product stability and 2) pesticides as a neutralizer and to improve product stability.

The most likely routes of occupational exposure to DIPA and TIPA are the dermal route, or by inhalation exposure to aerosols. DIPA and TIPA are both manufactured in closed systems using engineering controls that prevent the escape of liquid or vapours and minimize release to the environment. Workers who produce DIPA or TIPA, and those using it as a chemical intermediate or in product formulations, could be exposed during maintenance, sampling, testing or other procedures. The potential for exposure is reduced by engineering controls and personal protective equipment.

Because DIPA and TIPA, or DIPA- and TIPA-derived fatty acid soaps and salts may be used in a wide variety of personal care products, the most likely route of consumer exposure to DIPA and TIPA in these products would be via the dermal route although some inhalation exposure may also be possible. These chemicals are also used in herbicide/pesticide formulations and coatings formulations, which may also introduce the possibility of dermal or inhalation exposure to DIPA and TIPA. There may also be low levels of DIPA and TIPA present in process waters from manufacturing and processing sites, which are discharged to a waste water treatment system.

The chemical is stored in closed tanks, and transported in bulk tank cars or trucks, intermediate bulk containers, as well as in drum quantities. Environmental release during transport is possible in the event of a transportation accident. Releases to water or as waste may occur as a result of consumer uses. At environmental pHs (typically pH 8) they are highly water soluble.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1112-39-6
Chemical Name	Dimethoxydimethylsilane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Reduced Testing Rationale**

Testing for water solubility, partition coefficient and biodegradation was not conducted because dimethoxydimethylsilane (DMDMS) undergoes rapid hydrolysis in the presence of water with the half life of <0.6 hours at pH 7 and 25°C. The hydrolysis products, methanol (CAS No. 67-56-1) and dimethylsilanediol (CAS 1066-42-8), are expected based on the chemical structure of DMDMS at an equal ratio of 2 moles methanol to 1 mole dimethylsilanediol. Nonetheless, modeled data are provided for the water solubility and partition coefficient endpoints for DMDMS; as it provides valuable information on substance behavior. Biodegradation data are available and provided for the hydrolysis products, methanol and dimethylsilanediol. In aqueous solutions, exposure to DMDMS is likely to be transient and observed aquatic toxicity is likely due primarily to the hydrolysis products, methanol and dimethylsilanediol. Dimethylsilanediol has been shown to be stable at environmentally relevant temperature and pH for 96 hours. As such, data from the hydrolysis products (methanol and dimethylsilanediol) are used to address the acute toxicity to fish and toxicity to aquatic plants for DMDMS. Data from the hydrolysis product methanol have been presented and agreed upon at SIAM 19 (sponsored by the United States; documents are available at http://www.oecd.org/document/63/0,3343,en_2649_34379_1897983_1_1_1_1,00.html).

Physical-Chemical Properties

The EPISuite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

Dimethoxydimethylsilane (DMDMS) is a liquid with a melting point of -80.2 °C, a boiling point of 81.5 °C at 1010.9 hPa and a measured vapour pressure of 113.68 hPa at 25°C. The calculated octanol-water partition coefficient (log K_{ow}) is 0.585, and the calculated water solubility is 6800 mg/L at 25 °C. The water solubility and log K_{ow} values are not applicable because the chemical is hydrolytically unstable.

Human Health

No toxicokinetics data are available on the parent substance; however, rapid hydrolysis of this material is expected to produce 2 moles of methanol and 1 mole of dimethylsilanediol. *In vitro* percutaneous penetration of ^{14}C -labeled dimethylsilanediol (^{14}C -DMSD) was evaluated when applied in aqueous solution to human skin for 24 hours [OECD TG 428]. At the end of the assay, 59.5% of ^{14}C -DMSD volatilized from the skin surface (captured in the charcoal baskets placed above the exposure site), 18.3% was on the skin surface, 2.5% remained in the skin after washing and tape stripping, and 13.9% of the applied dose was absorbed; 82.1% of the absorbed dose penetrated

through the skin.

The oral (gavage) LD₅₀ in male and female rats of DMDMS was 4235 mg/kg bw [OECD TG 401]. Central nervous system effects were the predominant clinical sign of toxicity. No experimental data are available for irritation or skin sensitization in animals.

In a combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], DMDMS was administered via gavage to 10 rats/sex/dose at 0 (corn oil), 50, 250 and 1000 mg/kg bw/day. Males were treated during pre-mating and mating periods. Males and toxicity group females were sacrificed after they had been treated for 29 or 28 days, respectively. Clinical signs included soiling of the chin and/or urogenital area in both sexes dosed at 1000 mg/kg bw/day; soiling of the muzzle was also noted in females at 1000 mg/kg bw/day. There were no statistically significant treatment-related differences between controls and treatment groups in mean body weight, body weight gain, food consumption, FOB tests and motor activity parameters, hematological, prothrombin and/or clinical chemistry parameters during the study. At 1000 mg/kg bw/day, statistically significantly decreased absolute and relative adrenal gland, thymus and testes weights and statistically significantly decreased absolute epididymides, prostate gland and seminal vesicle weights were observed in males; statistically significantly decreased absolute and relative spleen weight were observed in females. Statistically significantly increased absolute and relative liver weights were observed in males and females at 250 and 1000 mg/kg bw/day. Histopathological examination showed adverse changes at 1000 mg/kg bw/day in the liver of male rats (centrilobular hepatocyte hypertrophy, hepatocellular vacuolation and protoporphyria), adrenal glands (adrenal cortical atrophy), male kidneys, testes and epididymides of male rats (degeneration of spermatocytes, seminiferous tubular degeneration) and in the liver of female rats (centrilobular and panlobular hepatocyte hypertrophy). Follicular cell hypertrophy was observed in the thyroid gland of all males and females at 1000 mg/kg bw/day. This is considered as an adaptive secondary effect (related to up-regulation of hepatic microsomal enzymes) and adverse for the rat, but that the mechanism is generally not applicable to species with significant levels of thyroid binding globulin. The NOAEL for systemic toxicity was 250 mg/kg bw/day with a LOAEL of 1000 mg/kg bw/day.

DMDMS did not induce gene mutations in bacterial cells (*Salmonella typhimurium* TA98, TA100, TA102, TA1535 and TA1537) *in vitro* [OECD TG 471] or chromosomal aberrations in Chinese hamster ovary cells [OECD TG 473; tested at the limit dose of 10 mM]. Based on these results, DMDMS is not considered to be genotoxic *in vitro*.

No data are available for the carcinogenicity of DMDMS.

The reproductive toxicity of DMDMS has been investigated in a repeated-dose/reproductive/developmental toxicity screening test in rats [OECD TG 422]. DMDMS was administered via gavage to 10 rats/sex/dose at 0 (corn oil), 50, 250, and 1000 mg/kg bw/day. Males were treated for at least 29 days (14 days prior to mating and through the mating period) and females were treated for 14 days prior to mating, during mating and gestation periods and through post-partum day 3. There was a decrease in body weight gain for females at 1000 mg/kg bw/d (during gestational week 3 and during the 4 day post-partum period). Based on observations at 1000 mg/kg bw/day (an increase in days of gestation and a decrease in live pups), the NOAEL for effects on fertility was 250 mg/kg bw/day. No gross abnormalities were found for any of the pups. Based on observations at 1000 mg/kg bw/day (an increase in post-implantation loss, a significant decrease in the total number of viable pups and the ratio of number of viable pups/total, a decrease in final litter weight, a decrease in final average pup weight and an increase in the percentage of post-natal loss) the NOAEL for maternal and developmental toxicity was 250 mg/kg bw/day.

DMDMS may present a hazard for human health (repeated-dose (liver, adrenal gland, kidney, testes and epididymides), reproductive and developmental toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

Testing for water solubility, partition coefficient and biodegradation was not conducted because dimethoxydimethylsilane (DMDMS) undergoes rapid hydrolysis in the presence of water with the half life of <0.6 hours at pH 7 and 25°C.

The measured hydrolysis half-life for DMDMS at pH 7 and 25°C is <0.6 hrs. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 5.5 days with an overall OH rate constant of $1.96 \times 10^{-12} \text{ cm}^3/\text{molecule}\cdot\text{sec}$. The biodegradation of DMDMS has not been determined due to its

rapid hydrolysis. Based on the rapid hydrolysis of this material, any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only substances remaining in the test system will be methanol and dimethylsilanediol. Methanol is readily biodegradable based on the results of standard tests that show 76 – 82 % and 95 % removal in standard ready tests after 5 and 20 days, respectively. Dimethylsilanediol has been shown to biodegrade in soils at rates between 0.9 to 6.4% per month based on $^{14}\text{CO}_2$ production and is not expected to be readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that DMDMS will distribute mainly to the soil (58.3%), water (25.8%) and air (15.8%) compartments with minor distribution to the sediment compartment (<1%). However, DMDMS is unlikely to be found in the environment, as this material is hydrolytically unstable. A calculated Henry's Law constant of $1.20 \times 10^2 \text{ Pa-m}^3/\text{mole}$ ($1.18 \times 10^{-3} \text{ atm-m}^3/\text{mole}$) suggests that volatilization from the water phase for DMDMS is expected to be high.

(these two paragraph differ only slightly; one should be deleted; believe the first paragraph is correct)

Bioaccumulation is not anticipated since the parent compound, DMDMS, is hydrolytically unstable. The estimated BCF for the hydrolysis product dimethylsilanediol is low (3.16). However, as the model is not validated for this compound a final conclusion on bioaccumulation of dimethylsilanediol cannot be drawn with accuracy. Experimental BCFs of < 10 in fish species, including *Cyprinus carpio* and *Leuciscus idus*, have been measured for methanol.

Bioaccumulation is not anticipated since the parent substance DMDMS, is hydrolytically unstable. The estimated BCF for the hydrolysis product dimethylsilanediol is low (3.16). However, as the model is not validated for compounds containing silane in their structure a final conclusion on bioaccumulation of dimethylsilanediol cannot be drawn with accuracy. Experimental BCFs of < 10 in fish species, including *Cyprinus carpio* and *Leuciscus idus*, have been measured for methanol.

DMDMS reacts to form methanol and dimethylsilanediol through hydrolysis. The bioaccumulation potential for dimethylsilanediol cannot be predicted accurately, but is expected to be low (calculated BCF = 3.16). Methanol is not likely to bioaccumulate (measured BCF<10). Furthermore, due to these properties, current estimation models are not capable of calculating physicochemical or environmental fate values of dimethylsilanediol with a known degree of accuracy. The adsorption of dimethylsilanediol onto surfaces and its tendency to polymerize itself are important properties of this chemical. In the environment, dimethylsilanediol is expected to be found in water and air and to be adsorbed by soil and sediment, but is still subject to hydrolysis. Unbound dimethylsilanediol in air, water, and soil is expected to degrade photolytically to silica and carbon dioxide.

Due to the rapid hydrolysis of DMDMS, aquatic organisms are likely exposed to the parent and its hydrolysis products, methanol and dimethylsilanediol. Acute aquatic toxicity to invertebrates has been investigated for DMDMS. Data for the hydrolysis products, methanol and dimethylsilanediol, are provided for acute toxicity to fish, aquatic invertebrates and aquatic plants.

The following acute toxicity test results have been determined for aquatic species:

DMDMS

Fish: no data

Invertebrate [*Daphnia magna*]: 48 h $\text{EC}_{50} > 100 \text{ mg/L}$ (static; nominal)

Algae: no data

Methanol

Fish [*Lepomis macrochirus*]: 96 h $\text{LC}_{50} = 15,400 \text{ mg/L}$ (flow-through)

Fish [*Salmo gairdneri*]: 96 h $\text{LC}_{50} = 20,100 \text{ mg/L}$ (flow-through)

Fish [*Pimephales promelas*]: 96 h $\text{LC}_{50} = 28,100 \text{ mg/L}$ (flow-through)

Invertebrate [*Daphnia magna*]: 48 h $\text{EC}_{50} = 10,000 \text{ mg/L}$ (no details located)

Algae [*Scenedesmus quadricauda*]: 10-14 d $\text{EC}_{50} = 28,400$ (no details located)

Dimethylsilanediol

Fish [*Oncorhynchus mykiss*]: 96 h $\text{LC}_{50} > 126 \text{ mg/L}$ (static, measured)

Invertebrate [*Daphnia magna*]: 48 h $\text{EC}_{50} > 117 \text{ mg/L}$ (static; measured)

Algae [*Pseudokirchneriella subcapitata*]: 72 hr $\text{E}_{\text{v}}\text{C}_{50}$, $\text{EC}_{50} > 118$ (static; measured)

Algae [*Pseudokirchneriella subcapitata*] NOEC = 118 mg/L (static; measured)

DMDMS does not present a hazard for the environment based on its low hazard profile and the low hazard profile of its hydrolysis products. DMDMS is not expected to be readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

DMDMS was produced and/or imported in the United States at a volume between 454 and < 4,540 tonnes (1 million and < 10 million pounds) during 2005. This material is also produced in Japan (< 45 tonnes in 2005). The substance is used as a chemical intermediate, an intermediate for silicone polymer/oligomers, rubber additive, water repellent; and in automotive products. Percent use in the final product is 0.02-100% with no parent substance remaining after end use.

DMDMS is manufactured in closed systems. Engineering controls include ventilation devices and related equipment; closed sampling loops; grounding. Personal protective equipment includes safety glasses, respirator, gloves (impermeable chemical resistant), fire resistant clothing, safety shoes, and hard hat. No exposure is anticipated under routine operations. Potential routes of exposure during routine operations include dermal and inhalation.

The industrial consumers use DMDMS in closed systems; potential non-accidental exposure is not ruled out because additional information could not be obtained. Engineering controls include grounding and ventilation. Personal protective equipment includes gloves, safety glasses, and respirator. Potential routes of non-accidental exposure include inhalation and dermal.

DMDMS is used in consumer automotive products at <1%; dermal exposure is possible.

There are no intentional releases to the environment. The reactive nature of this material destroys the parent material in water, thus limiting environmental exposure to DMDMS.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1120-21-4
Chemical Name	<i>n</i> -Undecane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

n-Undecane is a colourless liquid with a water solubility of 0.004 mg/L to 0.044 mg/L at 25 °C. Melting point and boiling point are -25.5 °C and 195.9 °C respectively. A calculated partition coefficient between octanol and water (Log K_{ow}) is 5.74. Vapour pressure of *n*-undecane is 50 Pa at 25 °C. An estimated soil adsorption coefficient (Log K_{oc}) is 3.42.

Human Health

n-Undecane vapour was readily absorbed by inhalation and was distributed to various tissues, especially fat tissues in rats. *n*-Undecane was also preferentially distributed to brain and a long-lasting redistribution from fat to brain can occur. The amount of *n*-undecane that can be absorbed through the skin was very small *in vitro*. After a single topical dose of *n*-undecane, maximum concentration in blood (C max) occurred shortly after the end of exposure (t max, ca. 30 min) in two healthy human volunteers.

The 8-h inhalation LC₅₀ value was above 2.82 mg/L (saturated vapor) for male rats. No toxic effects were observed in clinical signs, body weights, necropsy and histological observations.

The oral LD₅₀ value was above 2000 mg/kg for male and female rats in the acute study following OECD TG401. No toxic effects were observed.

The incidences of mild irritancy to skin by *n*-Undecane were reported only from lower reliability studies (pigs and rabbits). Prolonged or repeated skin contact may cause defatting and dermatitis. No experimental data are available for eye irritation.

No experimental data are available for skin sensitization in animals and humans.

The repeat dose and reproductive/developmental toxicity screening toxicity of *n*-undecane has been investigated in one study. In a repeat dose and reproductive/developmental toxicity screening study in rats following OECD TG422, *n*-undecane was administered daily via gavage to 12 animals/sex/dose at 0, 100, 300, and 1000 mg/kg bw/day, for 46 days for males and from 14 days before mating to day 3 of lactation for females. Salivation was observed, and the body weight gain was suppressed in males given 1000 mg/kg bw/day, and body weights were increased in females given 1000 mg/kg bw/day during the lactation period. A decrease in hemoglobin concentration, an increase in white blood cells count, a decrease in albumin, and increases in α 2-globulin, glutamic-pyruvic transaminase, cholinesterase and total cholesterol were found in males given 1000 mg/kg bw/day. Liver and thymus weights were increased in males given 1000 mg/kg bw/day, and liver weights were elevated in females given 1000 mg/kg bw/day. No effects were detected at autopsy or after histopathological investigations. The NOAEL for repeat dose toxicity is considered to be 300 mg/kg bw/day for both sexes.

In a bacterial reverse mutation assay with *E.coli* WP2 *uvrA* and multiple strains of *Salmonella typhimurium* following OECD TG471 and 472, *n*-undecane was negative both with and without metabolic activation. An *in vitro* chromosomal aberration test using Chinese hamster lung (CHL/IU) cells was negative with and without metabolic activation following OECD TG473.

Undecane was shown to have tumour promoting activity in mice skin following dermal exposure three times per week with benzo[a]pyrene as an initiator for 440 days, although undecane alone did not induce tumours in mice skin. No other data are available on the carcinogenicity of *n*-undecane by other exposure routes.

The reproductive toxicity of *n*-undecane has been well investigated in a reproductive and developmental toxicity

screening test in rats following OECD TG422. In this study, *n*-undecane was administered daily via gavage to 12 animals/sex/dose at 0, 100, 300, and 1000 mg/kg bw/day, for 46 days for males and from 14 days before mating to day 3 of lactation for females. Reproductive toxicity in parental animals was not observed up to 1000 mg/kg bw/day. In offsprings of the 1000 mg/kg bw/day group, body weight gain was decreased. The NOAEL for reproductive toxicity is considered to be 1000 mg/kg bw/day, and the NOAEL for maternal and developmental toxicity is considered to be 300 mg/kg bw/day. However, the decreased body weight gain may be due to some general maternal toxicity.

***n*-Undecane may present a hazard for human health (repeated dose toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.**

Environment

In the atmosphere, *n*-undecane is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.854 days and a rate constant of 12.5×10^{-12} cm³/molecule-sec were obtained by AOPWIN for the indirect photo-oxidation by reaction with hydroxyl radicals in air. *n*-Undecane is not expected to directly photolyze due to a lack of absorption in the environment UV spectrum.

n-Undecane is not hydrolysed due to the lack of hydrolysable functional groups. *n*-Undecane is considered to be readily biodegradable. *n*-Undecane was degraded 100 % by BOD under aerobic conditions after 4 weeks cultivation period according to OECD Guideline 301C. No measured data of bio-accumulation of *n*-undecane is available. A bioconcentration factor of 120.9 was calculated with BCFWIN using a log K_{ow} of 5.74. A bioconcentration factor of 1420 was also calculated with the Arnot-Gobas method, which indicates that *n*-undecane has a moderate bioaccumulation potential.

Fugacity level III calculations show that *n*-undecane is mainly distributed to the water compartment (69.9 %) and air compartment (24.4 %) if equally and continuously released to the air, soil and water. A Henry's law constant of 7.04 atm.m³/mole at 25 °C suggests that volatilization from water surfaces may be an important fate process.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Oryzias latipes</i>]:	96 h LC ₅₀ >0.013 mg/L (measured)
Invertebrate [<i>Daphnia magna</i>]:	48 h EC ₅₀ = 0.011 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC ₅₀ >0.0059 (measured; growth rate)
	72 h EbC ₅₀ >0.0059 (measured; biomass)

The following chronic toxicity test results have been determined for aquatic species:

Invertebrate [<i>Daphnia magna</i>]:	21 d NOEC = 0.0057 mg/L (measured)
	21 d LOEC = 0.0083 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOEC >0.0059 mg/L (measured; growth rate)
	72 h NOEC >0.0059 mg/L (measured; biomass)

***n*-Undecane possesses properties indicating a hazard for the environment (acute aquatic toxicity values less than 1 mg/L for invertebrate, and chronic aquatic toxicity value less than 0.01 mg/L for invertebrate). However, the substance is readily biodegradable and has moderate bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.**

Exposure

The annual production volume of *n*-undecane in the sponsor country is expected to be 1,000-10,000 tonnes. The worldwide production volume of *n*-undecane is not available. In the Sponsor country *n*-Undecane is separated and purified by distillation from *n*-paraffins which is isolated from desulfurized kerosene by selective adsorption with molecular sieve.

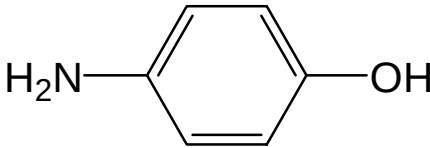
n-Undecane is used as feedstock for detergents and other industrial materials, reaction solvents and solvents for industrial cleaning in the sponsor country. *n*-Undecane is also used in consumer products like car wax, oil for lamp in the sponsor country. Uses for petroleum research, organic synthesis and distillation chaser are also known. It is reported that *n*-undecane is contained in gasoline. According to IUR information by US-EPA, *n*-undecane is used in consumer products like lubricants, greases and fuel additives. Therefore, consumer

exposure is expected through the use of these products.

n-Undecane is produced in continuous closed system where little potential exists for environmental exposure in the sponsor country. Vent gas from the system is burnt. Waste water, which may be released from the system through maintenance, is treated in the waste water treatment plant with activated sludge before it is released in the environment.

Occupational exposure to *n*-undecane through inhalation and dermal contact are possible. Swedish Permissible exposure limit for *n*-undecane is 350 mg/m³.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-30-8
Chemical Name	<i>p</i> -Aminophenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

p-Aminophenol is a white or reddish yellow crystalline solid with a water solubility of 15.7 g/L at 20 °C. The melting point and boiling point are 187.5 °C and 284 °C (decomposition point) respectively. A partition coefficient between octanol and water (Log Kow) is 0.04 at pH 7.4. A calculated vapour pressure of *p*-aminophenol is 0.00436 Pa at 25 °C.

p-Aminophenol is an amphoteric substance with both hydroxyl and amino functional groups. Dissociation constants of pKa1 = 5.48 and pKa2 = 10.30 show that *p*-aminophenol exists primarily as its neutral species in the environment at pH values between 6 and 9.

Human Health

Following oral administration to rabbits, 100 % of *p*-aminophenol is absorbed. In rabbits, the substance is excreted in the urine. Aminophenol conjugates and acetaminophenol and its conjugates were major urinary metabolites in rats subcutaneously administered with *p*-aminophenol. The dermal absorptions of *p*-aminophenol in rats and humans are 11% and 6-8% of the applied dose, respectively.

The oral LD₅₀ value was 671 mg/kg bw for male and female rats. *P*-Aminophenol caused lethargy, piloerection and oedematous swelling of the salivary glands. There are no reliable information for acute inhalation and dermal studies; however the inhalation LC₅₀ value is reported to be more than 5.91 mg/L and the dermal LD₅₀ value is reported to be more than 5000 mg/kg bw in the secondary literature.

The irritant effects on the skin were tested in accordance with standard guideline. *p*-Aminophenol was slightly irritating to rabbit skin. It led to slight edema of both the intact and abraded sites in one rabbit at 24hr after application and recovered within 72 hr (a primary irritation score of 0.2 out of 8). *p*-Aminophenol was slightly irritating to rabbit eyes, but caused no corneal opacity. All the lesions disappeared within 2 days of the instillation in rabbits. No experimental data were available for respiratory tract irritation in animals.

p-Aminophenol gave positive results for skin sensitization in a patch test in guinea pigs. Various human skin sensitisation studies showed positive reactions to *p*-aminophenol in hairdressers/barbers.

The repeated dose toxicity of *p*-aminophenol has been investigated in three studies. In a repeated dose oral toxicity study in rats following OECD TG No.407, the substance was administered via gavage to (6 animals/sex/dose) at 0, 4, 20, 100 or 500 mg/kg bw/day, for 28 days with a 14-day recovery period. Death was observed in one male due to renal damage at 500 mg/kg bw/day. Anemia-like findings were observed in males and females at 500 mg/kg bw/day. Brown urine was found in males and females at 100 and 500 mg/kg bw/day. There were increases in extramedullary hematopoiesis in 1 male and 5 females (2 females in the recovery group) and in hemosiderin pigment of the spleen in 5 females (6 females in the recovery group). Basophilic tubules in the kidney were observed in 1 male and 4 females at 100 mg/kg bw/day, and 4 males (3 males in the recovery group) and all females at 500 mg/kg bw/day. In addition, there were significantly increased absolute kidney

weights in females at 100 and 500 mg/kg bw/day and relative kidney weights in both sexes at 500 mg/kg bw/day. Significant increases in relative spleen weights in females at 500 mg/kg/day and in absolute and/or relative liver weights in both sexes at 500 mg/kg/day were also observed. Absolute brain weight was significantly decreased in the recovery group females at 100 and 500 mg/kg/day. Based on these results, the NOAEL for repeated dose oral toxicity was considered to be 20 mg/kg bw/day.

In a reproductive and developmental toxicity screening test in rats following OECD TG No.421, the substance was administered via gavage to (12 animals/sex/dose) at 0, 20, 100 and 500 mg/kg bw/day, for 40-60 days. Four males and 2 females died at 500 mg/kg/day. In these dead animals, renal pathological changes including tubular necrosis, basophilic tubules or protein cast etc. were observed. In the surviving animals, decreases in body weight gain and food consumption, and brown urine were observed. Histopathological changes in the kidney (basophilic tubules, protein cast, and granular cast) and spleen (deposits of hemosiderin in the red pulp and extramedullary hematopoiesis) were observed in both sexes. In males, testicular toxicities such as histopathological changes and decreased absolute and relative weights of the testes and epididymides were indicative of treatment related effects. These findings were observed in male and female groups at 500 mg/kg bw/day; brown urine in both sexes and decreased food consumption in females were also found at 100 mg/kg bw/day. Based on these effects, the NOAEL for repeated dose oral toxicity was considered to be 20 mg/kg bw/day.

In a repeated dose feeding study in rats, 40 male and 45 female rats per dose received concentrations of 0, 0.07, 0.2 or 0.7% p-aminophenol in the diet for up to 6 months (equivalent to ca. 0, 47, 133, or 467 mg/kg bw/day). A reduction of body weight gain was observed in both sexes at 467 mg/kg bw/day. Decreases in RBC and haemoglobin were observed in females of the 467 mg/kg bw/day group at 13 week. In the histopathological examination, nephrosis was observed in both sexes at 47 mg/kg bw/day at 13 weeks. Based on these results, the dose of 47 mg/kg bw/day was considered as the LOAEL for both sexes.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium* and *Escherichia coli* following OECD TG471 and TG 472, p-aminophenol was negative both with and without metabolic activation. An *in vitro* chromosomal aberration test using Chinese hamster lung (CHL/IU) cells following OECD TG473 was positive with and without metabolic activation. An *in vivo* micronucleus test using male mice following OECD TG474 was positive. An *in vivo* dominant lethal mutation test using male rats mated with untreated females was negative. Equivocal results exist concerning genotoxicity based on various *in vitro* and *in vivo* reports, but p-aminophenol is considered to be genotoxic (clastogenic) *in vitro* and *in vivo* based on positive results in the TG473 and TG 474 studies.

No reliable data were available for the carcinogenicity of p-aminophenol.

The reproductive toxicity of p-aminophenol has been well investigated in a reproductive and developmental toxicity screening test in rats [OECD TG 421]. In this study, p-aminophenol was administered via gavage to (12 animals/sex/dose) at 0, 20, 100, or 500 mg/kg bw/day, for 40-60 days. Death was observed in both sexes (4 males and 2 females) at 500 mg/kg bw/day. Histopathological examinations revealed decreased spermatocytes and spermatid levels, vacuolation of Sertoli cells, degeneration/necrosis of spermatocytes in the testis, and decreased sperm counts and debris of germ cells in the epididymis lumen at 500 mg/kg/day, but these changes did not affect male reproductive performance, as evidenced by no changes in the copulation index, fertility index or precoital interval. Terminated estrus, longer gestation period, decreased delivery index, increased number of stillborn pups, lowered pup weight, decreased viability of pup on PND4 were observed at 500 mg/kg/day. The NOAEL for reproductive toxicity was considered to be 100 mg/kg bw/day based on terminated estrus and longer gestation period at 500 mg/kg bw/day, and the NOAEL for developmental toxicity was considered to be 100 mg/kg bw/day based on decreased delivery index, increased number of stillborn pups, lowered pup weight and decreased viability of pup on PND4 at 500 mg/kg/day. However, these effects were observed at the high dose, at which significant systemic/maternal toxicity was observed.

In a feeding developmental toxicity study in rats, 25 female rats received concentrations of 0, 0.07, 0.2 or 0.7% p-aminophenol in the diet for 13 weeks (equivalent to ca. 0, 47, 133, or 467 mg/kg bw/day). They were then mated with untreated males. Pregnant females were once again fed with the p-aminophenol containing diet until day 20 of gestation, when they were killed. On day 0 of gestation, maternal body weights in the 133 and 467 mg/kg bw/day dose groups were lower than those of controls. From day 0 to day 20 of gestation, maternal weight gains in the 467 mg/kg bw/day dose group had decreased. Dose-related postimplantation loss was observed at 133 and 467 mg/kg bw/day in the presence of maternal toxicity. No toxicologically significant malformations were observed in the fetuses, but the number of variations (14th rudimentary ribs, unossified fifth or sixth sternbrae) was increased in the 133 and 467 mg/kg bw/day group as a consequence of maternal toxicity. The incidence of 14th rudimentary ribs is comparable with historical control, and increases of variations in the 14th ribs were only significant at the highest dose. Based on decreased maternal body weights at 133 mg/kg bw/day

and higher, the NOAEL for maternal toxicity was considered to be 47 mg/kg bw/day, but no adverse effects were observed on reproductive function. The NOAEL for developmental toxicity was considered to be 47 mg/kg bw/day based on postimplantation loss at 133 and 467 mg/kg bw /day, which is considered to be secondary effects of maternal toxicity.

p-Aminophenol may present a hazard for human health (skin irritation/sensitization, repeated dose toxicity and genotoxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

In the atmosphere, p-aminophenol is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.144 days and a rate constant of 74.2×10^{-12} cm³/molecule-sec are obtained by AOPWIN for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

p-Aminophenol is not stable to sunlight and turns violet on exposure to sunlight. As p-aminophenol has absorptions with λ_{max} of 294 nm in the environmental UV spectrum, direct photolysis by light may occur. p-Aminophenol is also expected to undergo rapid oxidation in the presence of air. p-Aminophenol is not hydrolysed due to the lack of hydrolysable functional groups. However, it is expected that p-aminophenol is not stable in water because of oxidation process in water. It is known that oxidation process of aminophenols leads to the formation of highly coloured polymeric quinoid structures. Half-life times in water are reported to be 7.67 days in purified water at 100 mg/L at pH 7 at 25 °C and 7.23 hours in de-chlorinated water at 1 mg/L at pH 7.3 – 7.6 at 24 °C. The latter value seems to be the most environmentally relevant one. However, there is some uncertainty on the reliability and relevance of both these half lives.

A test result with activated sludge showed 6 % degradation by BOD after four weeks cultivation according to the equivalent protocol with OECD Guideline 301C. After the cultivation period, no p-aminophenol was detected but polymerized substances were detected. BIOWIN estimation predicts that p-aminophenol is not readily biodegradable. According to these results, p-aminophenol is considered to be not readily biodegradable.

In a study performed according to OECD Guideline 305C with carp exposed to p-aminophenol at concentrations of 1.5 µg/L and 0.15 µg/L, bio-concentration factors of 10 – 46 were obtained over an eight-week exposure period. A bio-concentration factor of 3.2 was calculated by BCFBAFWIN using a log Kow of 0.04. These results demonstrate a low bioaccumulation potential of p-aminophenol in aquatic organisms. An estimated log Koc of 1.96 indicates a low potential for accumulation in soil.

Fugacity level III calculations show that p-aminophenol is mainly distributed to the water compartment (99.5 %) if released to the water. A Henry's law constant of 2.01×10^{-5} Pa.m³/mole at 25 °C suggests that the volatilisation potential of p-aminophenol from the water surface is expected to be low.

The following acute and chronic toxicity test results have been determined for aquatic species. In view of the half-life observed at 1 mg/L, it is possible that the species are exposed to both parent substance and degradation products.

Fish [Oryzias latipes]:	96 h LC50 = 0.93 mg/L (measured)
Invertebrate [Daphnia magna]:	48 h EC50 = 0.098 mg/L (measured)
Algae[Pseudokirchneriella subcapitata]:	72 h ErC50 = 0.15 mg/L (measured; growth rate)
	72 h EbC50 = 0.11 mg/L (measured; biomass)
Fish [Oryzias latipes]:	41 d NOEC = 0.064 mg/L(measured, growth)
Invertebrate [Daphnia magna]:	21 d NOEC = 0.055 mg/L (measured)
Algae[Pseudokirchneriella subcapitata]:	72 h NOEC = 0.036 mg/L (measured; growth rate)
	72 h NOEC = 0.036 mg/L (measured; biomass)

p-Aminophenol possesses properties indicating a hazard for the environment (acute aquatic toxicity values lower than 1 mg/L for fish, invertebrate and algae, chronic aquatic toxicity values lower than 0.1 mg/L for fish, invertebrate and algae and not readily biodegradable). However, the substance has low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

Production of p-aminophenol in Japan was about 400 tonnes in 2007. Production and import volume of aminophenols without distinction of ortho, meta and para isomers was reported to be 1,000 – 10,000 tonnes in Japan in fiscal year 2004. Production volume of p-aminophenol in the USA was between 500,000 to 1 million pounds in 2006 according to IUR information supplied by the US-EPA. Worldwide production volume of p-aminophenol was not available. p-Aminophenol is produced by electrolytic reduction of nitrobenzene in sulphuric acid or manufactured by reduction of p-nitrophenol with iron filings and hydrochloric acid.

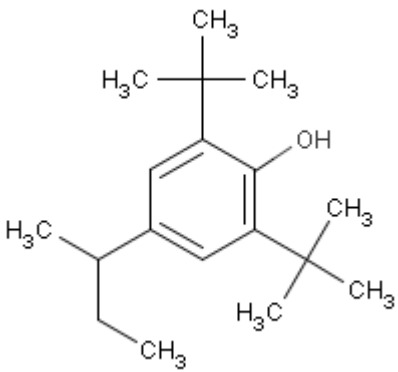
p-Aminophenol is used as an intermediate for sulfur dyes, rubber antioxidant, and photo-graphic developer in Japan. This substance is also used as an intermediate for pharmaceutical products, a wood stain, imparting a rose-like colour to timber and a dyeing agent for furs and feathers. p-Aminophenol is used as a developer in oxidation hair dyes.

As p-aminophenol has high water solubility with 15.7 g/L at 20 °C and low vapour pressure with 0.00436 Pa at 25 °C, it is thought that water compartment is the main target if p-aminophenol is released during the industrial processes. No detailed information was available as to what extent p-aminophenol is released during the manufacturing and processing processes in Japan. However, it is mentioned that most production of the technical grade aminophenols occurs on-site as they are chiefly used as intermediate reactants in continuous chemical syntheses. As p-aminophenol is not readily biodegraded, the possibility of environmental release may exist.

A nation-wide environmental survey of chemicals conducted by the Japanese Ministry of Environment in fiscal year 1986 showed that p-aminophenol was not detected in environmental surface water in nine different places with detection limit of 0.8 µg/L. This survey also showed no detection of p-aminophenol in sediment in nine different places (detection limit of 0.05 µg/dry-g). The same survey conducted in the fiscal year 2004, and p-aminophenol was detected in environmental surface water in one place at the level of 0.02 – 0.05 µg/L.

Occupational exposure through inhalation of dust and dermal contact is possible. As p-aminophenol is used as an ingredient in hair dyes, direct consumer exposure does occur.

INITIAL TARGETED ASSESSMENT PROFILE

CAS RN	17540-75-9
Chemical Name	Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)- (DTBSBP)
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address the following environment endpoints: stability in water and biodegradability, bioaccumulation potential, acute toxicity to aquatic organisms based on read across to close structural analogues and application of (Q)SAR model predictions. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment are included in the Canadian screening assessment but have not been agreed upon by OECD member countries, and thus are not included in this profile.

The final screening assessment has been published under the responsibility of the Government of Canada.

[<http://www.ec.gc.ca/eesees/default.asp?lang=En&n=AE29F426-1>]

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its *Canadian Environmental Protection Act, 1999* (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: **inherently toxic** to humans or to the environment and that might be **persistent** and/or **bioaccumulative**; and substances to which people might have **greatest potential for exposure**. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release.

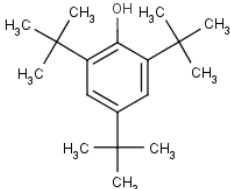
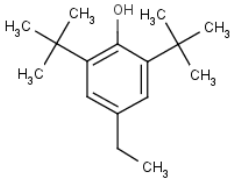
The substance, DTBSBP was identified as a high priority for assessment of ecological risk because it was found to meet the ecological categorization criteria for persistence, bioaccumulation potential and inherent toxicity to aquatic organisms, and was believed to be in commerce in Canada.

Analogue rationale

To fill data gaps for biodegradation, bioaccumulation and ecotoxicity endpoints, a literature search was performed

and the database ChemIDplus® was used to identify appropriate analogue substances of DTBSBP. The substances 2,4,6-tri-*tert*-butylphenol (CAS RN 732-26-3) and 2,6-di-*tert*-butyl-4-ethylphenol (CAS RN 4130-42-1) were found to be appropriate analogues for DTBSBP as they are similar in molecular mass and have similar structure and functional groups to DTBSBP. The molecular mass of DTBSBP is 262.44 g/mol. The structure and molecular mass of these analogue substances are presented in Table 1 below.

Table 1. Analogue substances of DTBSBP used in the assessment

Analogue	Structure	Molecular mass (g/mol)
2,4,6-tri- <i>tert</i> -butylphenol, CAS RN 732-26-3		262.4
2,6-di- <i>tert</i> -butyl-4-ethylphenol, CAS RN 4130-42-1		234.4

Physical-chemical properties

The substance DTBSBP is a liquid at room temperature. Physical-chemical property data for DTBSBP and analogue substances are presented in Table 2 below.

Table 2. Experimental and modelled physical-chemical properties of DTBSBP and analogue substances¹

CAS RN.	Log Kow	Water solubility (mg/L)	Melting Point (°C)	Boiling Point (°C)	Vapour Pressure (Pa)
17540-75-9 (DTBSBP)	6.43 (m) 6.1 (m)	0.25 (m) 2.5 (m)	102 (m) 18.9 (e)	330 (m) 275 (e)	0.0028 (m) 0.35 (m)
732-26-3	6.39 (m) 6.06 (e)	0.51 (m)	104 (m) 131 (u)	324 (m) 278 (u)	0.027 (m)
4130-42-1	5.52 (m)	2.1 (m)	92 (m) 44 (u)	310 (m) 272 (u)	0.29 (m)

(e= experimental data; m= modelled data; u= unknown: value is from a compilation volume)

- ¹. For a level comparison between all the substances, the first line of data for each substance shows data modelled using EPI Suite (2008) without the input of any available measured physical-chemical properties. The second line of data for each substance gives the measured values, where available, and in the case of DTBSBP, either measured values or values that were modelled using EPI Suite (2008) with some input of

measured or analogue physical-chemical property values. This second line of values in the table for DTBSBP are the values that were used for further modelling of the environmental fate, ecotoxicity and bioaccumulation of this substance. For some of the analogue values, the original source of the data is not actually known as the values were taken from compilation volumes.

Human Health

Not part of the targeted assessment.

Environment

The acid dissociation constant (pK_a) of DTBSBP was modelled using the ACD/ pK_a DB Prediction Module (2005, v.9.04). The relatively high value obtained ($pK_a = 11.85$) for the hydroxyl group of DTBSBP indicates that in water bodies at environmentally relevant pH (6–9), nearly 100% of the substance will be undissociated.

According to the results of Level III fugacity modelling (EQC model 2003, v.2.02), DTBSBP is expected to predominantly reside in sediment (54%) and in air (36%) if released only to air. It will primarily reside in sediment (96%) if released only to water, and in soil (99.9%) if released only to soil.

Based on its high estimated $\log K_{oc}$ value of 4.47 (PCKOCWIN, 2000, v.2.00), if released into water, DTBSBP is expected to adsorb strongly to suspended solids and sediment, and if released to soil, it will have high adsorptivity to soil particles (i.e., it is expected to be immobile). An estimated Henry's Law constant of $3.70 \text{ Pa}\cdot\text{m}^3/\text{mol}$ (HENRYWIN, 2000, v.3.20) suggests that volatilization from water surfaces and moist soils is not expected to be high.

Atmospheric degradation of DTBSBP was modelled using AOPWIN (2000, v.1.92). A predicted half-life of 0.52 days via reactions with hydroxyl radicals demonstrates that DTBSBP is likely to be rapidly oxidized. The substance is not expected to react with other photo-oxidative species in the atmosphere, such as O_3 .

Since only one experimental study on the biodegradation of DTBSBP was available, read-across analogue data and ultimate biodegradation predicted by models (BIOWIN 2000 v.4.10, TOPKAT 2004 v.6.2, Canadian POPs Model 2008) were also considered. All modelled results agree that DTBSBP will not biodegrade rapidly and is expected to have a long ultimate degradation half-life in water (months). These ultimate degradation results are consistent with the properties associated with the functional groups in the chemical structure of DTBSBP. The estimated results predicting an ultimate degradation half-life of ≥ 182 days in water are supported by the empirical data that indicate that DTBSBP and its analogue substances, 2,4,6-tri-*tert*-butylphenol and 2,6-di-*tert*-butyl-4-ethylphenol, do not readily biodegrade under aerobic conditions (OECD TG 301C; 0% BOD after 28 days; same result for all three substances). Also, DTBSBP does not contain functional groups expected to undergo hydrolysis in water, and this substance contains structural features associated with chemicals that are persistent (i.e., – *tert*-butyl branches, benzene ring with more than two substituents and $K_{ow} > 3$).

Since no experimental bioaccumulation data for DTBSBP were available, available analogue data and modelled $\log K_{ow}$, bioaccumulation factor (BAF) and bioconcentration factor (BCF) data were considered. The high modelled K_{ow} value of DTBSBP ($\log K_{ow} = 6.1$; KOWWIN v.1.67) indicates that uptake through the diet is expected to be an important route of bioaccumulation in fish. BAF and BCF values were predicted for DTBSBP and the two analogues using the Arnot-Gobas kinetic model corrected for metabolic rate for middle trophic level fish (BCFBAF, 2008, v.3.00). The BCF and BAF values predicted by this model for DTBSBP (BCF = 22 387 L/kg, BAF = 870 963 L/kg) and the two analogues (BCF = 3119 and 14 050 L/kg, BAF = 7534 and 324 700 L/kg for 2,6-di-*tert*-butyl-4-ethylphenol and 2,4,6-tri-*tert*-butylphenol respectively) indicate that DTBSBP is likely to be highly bioaccumulative. The Arnot-Gobas model was shown to be a good predictor of the empirical BCF data when compared with the available empirical fish BCF data for the analogue substances (highest BCF = 4870 to 5060 for 2,6-di-*tert*-butyl-4-ethylphenol, and BCF = 16 000 to 23 000 L/kg for 2,4,6-tri-*tert*-butylphenol). Therefore, more weight is given to the results of the Arnot-Gobas model than to the results of the other two BCF models employed (BCFBAF 2008 v.3.00 – without correction for metabolic rate, and Dimitrov model in the Canadian POPs Model suite 2008), which produced BCF values of less than 5000.

There are no experimental data available for the aquatic toxicity of DTBSBP, therefore modelled and analogue data were used to estimate the potential for aquatic toxicity. Toxicity values were predicted for DTBSBP in fish (96h $\text{LC}_{50} = 0.039\text{--}0.1 \text{ mg/L}$; 60-day $\text{EC}_{50} 0.007 \text{ mg/L}$), water flea (96h $\text{EC}_{50} 0.015\text{--}0.93 \text{ mg/L}$; 21-day $\text{EC}_{50} = 0.12 \text{ mg/L}$), and algae (96h $\text{EC}_{50} 0.20 \text{ mg/L}$; chronic $\text{EC}_{50} 0.09 \text{ mg/L}$) using the models ECOSAR 2008 v.1.00,

Canadian POPs Model 2008, AIEPS 2003-2007 v.2.05, and TOPKAT 2008 v.6.2. The lowest predicted aquatic toxicity value for DTBSBP is the 60-day chronic EC50 value of 0.007 for fish (ECOSAR, 2008, v.1.00). In ECOSAR, toxicity predictions for DTBSBP were modelled as a phenol rather than as a neutral organic. However, the predictions for DTBSBP modelled as a neutral organic are very similar to the ECOSAR values modelled as a phenol. All toxicity predictions appear to be within the applicability domains of the models as none of the maximum K_{ow} and molecular weight cut-off values specified in ECOSAR are exceeded. In addition, the predictions are below the estimated water solubility of the substance. The following empirical aquatic toxicity data for the analogue 2,4,6-tri-*tert*-butylphenol are available: fish (48-96 h LC50 0.06->10 mg/L), water flea (48h LC50 = 0.11 mg/L; 21-day reproduction NOEC 0.36 mg/L), and algae (72h NOEC = 0.32 mg/L). The lowest measured analogue read-across aquatic toxicity value for 2,4,6-tri-*tert*-butylphenol is a 96-h LC50 of 0.06 mg/L for fathead minnow. The measured toxicity values seem to generally support the modelled toxicity values for DTBSBP.

DTBSBP possesses properties indicating a hazard for the environment (acute and chronic aquatic toxicity below 1 mg/L, not readily biodegradable and has high bioaccumulation potential).

Exposure Summary Information

DTBSBP is an organic substance that is used in Canada and elsewhere as an antioxidant and liquid stabilizer in plastics such as polyvinyl chloride (PVC) and polyurethane, as well as in brake fluids, ink resins and mineral/vegetable oils used industrial applications. It is also used as an antioxidant in the petrochemical sector.

This substance is not naturally produced in the environment. Currently the only known global manufacturer of this substance is located in the United States. A quantity of 16 686 kg of DTBSBP was imported into Canada in 2006, for use mainly in plastics manufacturing. The quantity of DTBSBP imported into Canada, along with the potentially dispersive uses of this substance, indicates that it may be released into the Canadian environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2943-75-1
Chemical Name	Triethoxy(octyl)silane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Triethoxy(octyl)silane undergoes rapid hydrolysis (the half-life of 0.3 to 0.6 hours at a pH of 7 and 25°C), which occurs during testing; exposures to triethoxy(octyl)silane are likely to be transient depending on the test system, and observed intrinsic toxicity is likely due to a mixture of the parent molecule and the hydrolysis products ethanol and octylsilanetriol, and to a lesser degree any polymerization products. Based on the chemical structure of triethoxy(octyl)silane, the hydrolysis products, ethanol (CAS No. 64-17-5) and octylsilanetriol (CAS No. 31176-12-2) are expected, at a ratio of 3 moles ethanol to 1 mole octylsilanetriol. The water solubility of the octylsilanetriol cannot be measured because of the tendency to self-condense into highly cross-linked, high molecular weight polymers at concentrations greater than approximately 500 mg/L. It is known, however, that the octylsilanetriol and small condensation products will only precipitate out of water due to formation of larger, water insoluble polymeric resins. Data from the hydrolysis product ethanol have been presented and agreed upon at SIAM 19 (documents are available at <http://www.inchem.org/documents/sids/sids/64175.pdf>).

Physical-Chemical Properties

The EPISuite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has been used for estimating some environmental fate parameters. This model has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

Triethoxy(octyl)silane is a clear, colorless liquid with a melting point of -46 °C, a boiling point of 257 °C at 1020 hPa and a measured vapour pressure of 0.63 hPa at 25 °C. The octanol-water partition coefficient (log K_{ow}) is >3.7 (measured) at 23 °C. Water solubility is < 0.13 mg/L at 22.8 °C (measured). The water solubility and log K_{ow} values may not be accurate because the chemical is hydrolytically unstable.

Human Health

No toxicokinetics data are available on the parent substance; however, rapid hydrolysis of triethoxy(octyl)silane is expected to produce 3 moles of ethanol for each mole of octylsilanetriol. The toxicokinetics data for octylsilanetriol are not available. Following any route of intake resulting in an elevated blood ethanol level, metabolism proceeds in three basic steps: ethanol is oxidized within the cytosol of hepatocytes to acetaldehyde, which is rapidly converted to acetate, which is released into the blood and oxidized by peripheral tissues to acetic acid and ultimately carbon dioxide, and water. The main pathway for ethanol metabolism proceeds via alcohol dehydrogenase. The rate of hepatic metabolism of ethanol is concentration independent except at very low or very high concentrations. The

kidneys and lungs excrete only 5 – 10 % of an absorbed dose of ethanol unchanged. The major route of excretion of ethanol is in the urine. Ethanol is excreted in the un-metabolized form in urine, exhaled air and sweat. Its metabolic products are also excreted by exhalation and in the urine.

The 4-hr inhalation LC₅₀ value was greater than approximately 0.248 mg/L (the saturated vapor concentration) for vapor for male and female rats (similar to OECD TG 403). The substance caused hyperactivity in a single animal; there were no other clinical signs of toxicity. The dermal LD₅₀ values were 6730 mg/kg bw for male and > 8000 mg/kg bw for female rabbits (similar to OECD TG 402). The substance caused irritation and necrosis at the site of contact, central nervous system (CNS) effects (limb paresis or paralysis) as the predominant clinical sign of toxicity, labored breathing, iritis, and weight loss with some emaciation. Findings at necropsy showed dark or bright red lungs and enlarged spleen. The oral LD₅₀ values were 12,200 mg/kg bw for male and 11,500 mg/kg bw for female rats (11,800 mg/kg bw for combined sexes) (similar to OECD TG 401). The substance caused CNS effects as the predominant clinical sign of toxicity (sluggishness, aggressive behaviour, and unsteady gait with limb paresis or paralysis). Microscopic examination suggested effects on the renal system (nephritis, hydronephrosis, tubular dilation, renal mineralization, and hemorrhages of the urinary bladder). In a second study, the oral LD₅₀ value was > 5110 mg/kg bw for male and female rats (OECD TG 401). The substance caused CNS effects (uncoordination, stilted gait, labored breathing, sunken sides and vocalization on handling) as the predominant clinical sign of toxicity; there were no gross necropsy findings in surviving animals. The gastro-intestinal tract was severely autolytic in the single female that died on day 7.

Triethoxy(octyl)silane was moderately irritating to the skin (test similar to OECD TG 404). Moderate erythema and moderate edema were observed in a skin irritation assay performed in rabbits. The effects were reversible by day 7. In a second study, triethoxy(octyl)silane was highly irritating to the skin (OECD TG 404). Moderate erythema and moderate-to-severe edema were observed in a skin irritation assay performed in rabbits. All skin effects were reversible by day 10. Triethoxy(octyl)silane was slightly irritating to eyes (similar to OECD TG 405). Transient iritis and minor-to-moderate conjunctival irritation with ocular discharge were observed in an eye irritation assay performed in rabbits. All effects were reversible by day 7. In a second study, triethoxy(octyl)silane was slightly irritating to eyes (OECD TG 405). Diffuse redness and slight swelling of the conjunctivae were observed in an eye irritation assay performed in rabbits. All effects were reversible by 48 hours.

No experimental data were available for skin sensitization in animals.

In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422) triethoxy(octyl)silane was administered in dried (excess moisture content removed intentionally), deacidified peanut oil daily, seven days a week by oral gavage to 10 Sprague-Dawley rats/sex/group at 0, 100, 300 or 1000 mg/kg bw/day for 28 (males) or 29 (toxicity group females) days. Reproductive group females (10/group) were treated with the same dose levels for up to 45 days (prior to mating through post-partum day 4). Clinical signs included soiling of the head in 300 and 1000 mg/kg bw/day male and toxicity group females and 1000 mg/kg bw/day reproductive group females. Clinical observations consistent with neuromuscular toxicity (decreased activity, dragging of the hindlimbs and/or incoordinated gait) occurred only in the 1000 mg/kg bw/day reproductive group females, but were not observed in the males or toxicity group females. However, no changes were noted during Functional Observational Battery and Motor Activity evaluations in males and toxicity group females. Treatment-related decreases in group mean body weights and/or body weights gains occurred in all animals at 1000 mg/kg bw/day with associated decreases in food consumption (females). There was an increase in mean absolute and relative liver weights in males (relative: 11.7% and 17.3%) and toxicity group females (relative: 4.7% and 27.8%) at 1000 mg/kg bw/day. Histopathological findings were identified in the liver (dose-related centrilobular hypertrophy at 300 and 1000 mg/kg bw/day in toxicity and reproductive groups; not considered adverse as these changes are consistent with common adaptive changes that occur in the liver upon xenobiotic administration), bladder (diffuse epithelial hyperplasia in all animals at 1000 mg/kg bw/day) and kidneys, adrenal, thymus, spleen and brain, spinal cord, peripheral nerves and skeletal muscles (1000 mg/kg bw/day). CNS degeneration of white matter, predominantly the cerebellum and medulla, occurred in a large percentage of the toxicity and reproductive group females. In the brain, 40% and 80% of the 1000 mg/kg bw/day toxicity and reproductive group females exhibited white matter degeneration, respectively. Degeneration of the spinal cord occurred in 50% and 90% of the 1000 mg/kg bw/day toxicity and reproductive group females, respectively. The peripheral nerves (sciatic and tibial) also showed minimal to severe degeneration and demyelination in both 1000 mg/kg bw/day toxicity and reproductive group females, with less incidence and severity occurring in the toxicity group females. Based on the bladder epithelial hyperplasia in males and the neuromuscular findings in the toxicity and reproductive group females at 1000 mg/kg bw/day, the NOAEL for systemic toxicity was 300 mg/kg bw/day. In another study (similar to OECD TG 407), dietary administration of triethoxy(octyl)silane for 28

days to male and female Fisher 344 rats did not result in any treatment-related clinical signs or changes in food consumption, body and organ weights, hematology and clinical chemistry evaluations, or gross pathology and histopathology evaluations which were considered to reflect an adverse effect of the diet. The NOAELs were determined to be greater than 592.2 and 639.6 mg/kg bw/day (10,000 ppm) for male and female rats, respectively, the highest dose tested.

Triethoxy(octyl)silane did not induce gene mutations in bacterial cells (*Salmonella typhimurium* TA98, TA100, TA1535 and TA1537, and *Escherichia coli* WP2uvrA) *in vitro* (OECD TG 471 or similar to OECD TG 471) in two separate studies or induce chromosomal aberrations in Chinese hamster ovary cells (similar to OECD TG 473). Based on these results, triethoxy(octyl)silane is not considered to be genotoxic *in vitro*.

No data are available for the carcinogenicity of triethoxy(octyl)silane.

In the combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422) mentioned above, triethoxy(octyl)silane was administered in dried, deacidified peanut oil daily, seven days a week by oral gavage to 10 rats/sex/group at 0, 100, 300 or 1000 mg/kg/day for 28 days in males and up to 45 consecutive days in females. Reproductive parameters evaluated included evidence of mating, pregnancy, duration of gestation, mean number of implantation sites, mean number of corpora lutea, mean mating and fertility indices and evaluation of loss of offspring (pre-implantation and post-natal loss). Changes in reproductive parameters were limited to the 1000 mg/kg bw/day group. Mating and fertility were unaffected by treatment. The mean duration of gestation was increased (5.6%) compared to controls ($p < 0.01$). Of the seven dams that successfully initiated parturition, four of these dams exhibited dystocia (difficult/prolonged labor). Developmental parameters evaluated included total litter size, mean litter size, mean live litter size, mean litter weight, mean ratio of live births/litter size, sex ratio, pup viability, pup body weight and body weight gain. Changes in developmental parameters were limited to the 1000 mg/kg bw/day group. The mean number of live male and female pups/dam at first litter check (PND 0) in the 1000 mg/kg bw/day group was statistically decreased by 39.3% compared to controls. PND 0 mean litter weights, average pup body weights and body weight gains were similar to controls. By PND 4, several dams in the 1000 mg/kg bw/day group had been euthanized due to the severity of various clinical signs and/or difficulty during labor. Only four dams continued through PND 4. Of these litters, the total viable pups on PND 4 were decreased compared to controls, resulting in a 25.2% decrease in percent viability of pups/dam on PND 4 compared to controls. This significant decrease was due to a single dam that had a 14.3% post-natal loss of offspring. The remaining dams had no post-natal loss of pups between Days 0-4. PND 4 mean litter weights, average pup body weights and body weight gains in the 1000 mg/kg bw/day group were also decreased compared to control weights. External gross lesions were not observed for treated dams or pups. The reproductive effects only occurred at the 1000 mg/kg bw/day dose level in association with marked maternal toxicity. As such it is not possible to determine with confidence if the 1000 mg/kg bw/day dose level represents the NOAEL. Therefore, the reproductive toxicity NOAEL is considered to be > 300 mg/kg bw/day. The developmental effects only occurred at the 1000 mg/kg bw/day dose level in association with marked maternal toxicity. As such it is not possible to determine with confidence if the 1000 mg/kg bw/day dose level represents the NOAEL. Therefore, the developmental toxicity NOAEL is considered to be > 300 mg/kg bw/day.

Triethoxy(octyl)silane may present hazard for human health (skin irritation; repeated-dose toxicity-urinary tract; neuromuscular system-at high doses). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The measured hydrolysis half-life for triethoxy(octyl)silane is 0.3-0.6 hours at 25 °C and pH 7. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 4.5 hours with an overall OH rate constant of 2.8×10^{-11} cm³/molecule-sec. Triethoxy(octyl)silane is considered not readily biodegradable (5-6%, 28 d) following OECD TGs 301 B, 301 C and 301 D for ready biodegradability; based on the rapid hydrolysis of this material any potential for biodegradation is likely to be due to the hydrolysis product ethanol. The other hydrolysis products, octylsilanetriols and condensed octylsilanetriols are expected to be not readily biodegradable.

A level III fugacity model calculation with equal and continuous release to air, water and soil compartments suggests that triethoxy(octyl)silane will distribute mainly to the sediment (69.8%) and water (19.9%) compartments with minor distribution to the soil and air compartments (7.2 and 3%, respectively). However, triethoxy(octyl)silane is unlikely to be found in the environment, as this material is hydrolytically unstable. Henry's Law constant of 1.49×10^2 Pa-m³/mole (1.47×10^{-3} atm-m³/mole) suggests that volatilization from the water phase for triethoxy(octyl)silane is

expected to be high.

A dynamic 70-day study (OECD TG 305C) was conducted to evaluate the bioconcentration of ^{14}C -test substance by the common carp. A flow-through system was used to maintain a mean measured water concentration of 0.166 mg/L (high) or 0.0141 mg/L (low) for a 56-day exposure period. Test fish were then placed in clean water for a 14-day depuration period. Radioanalysis of the fish was performed throughout the exposure and depuration periods. BCFs in this study were estimated to be 1670 for the high treatment level and 1980 for the low treatment level with a geometric mean average of 1818. While the fish in this test significantly accumulated the test material from water, the majority of ^{14}C -test substance was cleared (depuration) within 14 days when the fish were placed in uncontaminated water. Results are based on total radioactivity (the test substance was radiolabelled on the octyl chain). The results represent the bioaccumulation of the parent compound and its hydrolysis/degradation products. Ethanol is not likely to bioaccumulate (calculated BCF=3.16).

Triethoxy(octyl)silane reacts to form ethanol and octylsilanetriol through hydrolysis. Furthermore, due to these properties, current estimation models are not capable of calculating physicochemical or environmental fate values with a known degree of accuracy. No information on the environmental fate of octylsilanetriol was found. However, based on studies on related monomeric silanols, it is expected that the adsorption of octylsilanetriol onto surfaces and condensation to disiloxanes in dilute aqueous solution may be important properties of this chemical. Octylsilanetriol is expected to partition primarily to soil and water due to its high water solubility and potential to bind to mineral surfaces. In water and air, octylsilanetriol may degrade photolytically. Slow biodegradation in water and soil might also occur.

Due to the rapid hydrolysis of triethoxy(octyl)silane in ecotoxicity studies, aquatic organisms are likely exposed to the parent and its hydrolysis products, ethanol, octylsilanetriol, and condensed octylsilanetriol materials. No toxicity data specifically relating to the silanol hydrolysis products are available.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Oncorhynchus mykiss*]: 96 h $\text{LC}_{50} > 0.055$ mg/L (OECD TG 203; flow-through; measured; tested at the water solubility limit)

Invertebrate [*Daphnia magna*]: 48 h $\text{EC}_{50} > 0.049$ mg/L (OECD TG 202; flow-through; measured; tested at the water solubility limit)

Algae [*Pseudokirchneriella subcapitata*]: 72-hour E_yC_{50} , E_rC_{50} , $\text{E}_b\text{C}_{50} > 0.13$ mg/L (OECD TG 201; nominal; tested at the water solubility limit)

Algae [*Pseudokirchneriella subcapitata*] $\text{NOEC} = 0.13$ mg/L (nominal; tested at the water solubility limit)

Triethoxy(octyl)silane does not present an acute hazard for the environment based on its low hazard profile at the limit of water solubility. However, this chemical is not readily biodegradable. The parent chemical and/or some of its hydrolysis products have a moderate bioaccumulation potential. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

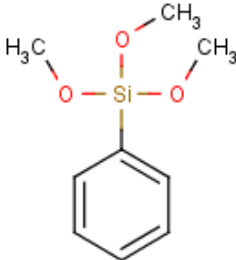
Triethoxy(octyl)silane was produced and/or imported in the United States at a volume between 454 and < 4,540 tonnes (1 million and < 10 million pounds) during 2005. This material is also imported into Europe (91 to 272 tonnes). The substance is used as a hydrophobation agent (building protection), manufacturing intermediate, water repellent, and pigment treatment. Percent use in final product <5 - 100% with no parent substance remaining after end use.

During manufacturing, occupational exposure through dermal and inhalation routes is possible, although worker exposures due to non-accidental releases are expected to be low, and are expected to occur only during transfer and sampling. These exposures are minimized by use of personal protective equipment (PPE) and engineering controls. PPE includes hard hat, glasses, chemical and fire resistant clothes, safety shoes, chemical resistant gloves, and respirator. Use of engineering controls includes pressure and temperature controls; location ventilation; closed sample loops, kettle house ventilation and local vent drops. The industrial consumer may use the substance in open applications to walls (building water-proofing) and closed systems with proper materials of construction. Engineering controls include ventilation systems, automatic feed systems with interlocks, grounded equipment, and splash guards at appropriate locations.

There are no consumer uses of the substance.

There are no intentional releases to the environment. The reactive nature of this material destroys the parent material in water, thus limiting environmental exposure to triethoxy(octyl)silane.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2996-92-1
Chemical Name	Trimethoxyphenylsilane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties****Reduced Testing Rationale**

Trimethoxyphenylsilane (TMPS) undergoes rapid hydrolysis in the presence of water; the half life at pH 7 and 25°C is 24 minutes (RCC, 2008a). Based on the chemical structure of TMPS, this hydrolysis is expected to produce 3 moles of methanol (CAS No. 67-56-1) for each mole of phenylsilanetriol (CAS No. 3047-74-3). Methanol was previously assessed in the OECD HPV Chemicals Programme. Because TMPS is hydrolytically unstable, water solubility and partition coefficient were not measured; modeled values are provided. Due to the rapid hydrolysis of TMPS in aqueous solutions, aquatic organisms are likely exposed to the parent and its hydrolysis products, methanol, phenylsilanetriol, and condensed silanetriol materials.

The EPI Suite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

Trimethoxyphenylsilane (TMPS) is a liquid with a melting point of <-20.2 °C, a boiling point of 225.9 °C at 1021.4 hPa and a measured vapour pressure of 0.182 hPa at 25 °C. The calculated octanol-water partition coefficient (log K_{ow}) is 0.55, and the calculated water solubility is 69,000 mg/L at 25 °C. The water solubility and log K_{ow} values may not be accurate because the chemical is hydrolytically unstable.

Human Health

No toxicokinetics data are available on the parent substance; however, rapid hydrolysis of this material is expected to produce 3 moles of methanol for each mole of phenylsilanetriol. Based on reported toxicity following repeated oral exposure (gavage), TMPS is systemically absorbed and then distributed to and excreted at least in part, from the urinary tract. The toxicokinetics of phenylsilanetriol are not available. Data from the hydrolysis product methanol have been presented and agreed upon at SIAM 19 (sponsored by the United States; documents are

available at http://www.oecd.org/document/63/0,3343,en_2649_34379_1897983_1_1_1_1,00.html).

Methanol is readily absorbed by inhalation, ingestion and dermal contact and distributes rapidly throughout the body. Metabolism in humans, rodents, and monkeys contributes up to 98 percent of the clearance, with more than 90 percent of the administered dose exhaled as carbon dioxide. Renal and pulmonary excretion contributes only about 2 – 3 percent. The metabolism and toxicokinetics of methanol varies by species and dose. In humans, the half-life is approximately 2.5 – 3 hours at doses lower than 100 mg/kg bw. At higher doses, the half life can be 24 hours or more.

There are no reliable data for acute toxicity via either the inhalation or dermal routes. In an acute toxicity study conducted according to OECD TG 425, a total of 7 female rats were administered TMPS by oral gavage including 4 animals at 2000 and 3 animals at 550 mg/kg bw in polyethylene glycol 300. When the single animal dosed at 2000 mg/kg bw in a limit-test died spontaneously on study day 2, a main test with 6 animals was conducted. In the main test, all three animals dosed at 2000 mg/kg bw had to be killed *in extremis* on study days 4, 5 or 6 and all animals dosed at 550 mg/kg bw survived. Animals at 2000 mg/kg bw appeared unhealthy; effects on respiration, coordination and body weight loss were noted. Slight ruffled fur and slight sedation were observed in two of three animals dosed at 550 mg/kg; no clinical signs were observed in the third animal dosed at 550 mg/kg bw. There was no effect on body weight at 550 mg/kg bw. Three animals dosed at 2000 mg/kg bw showed a greater than 20% loss of body weight prior to being killed *in extremis*; no body weight was recorded at the spontaneous death of the first animal dosed at 2000 mg/kg bw that was found dead on test day 2. Macroscopic findings at 2000 mg/kg bw included light red congested lungs, black brown stomach distended with gas, tan discoloration of kidneys, and spleen reduced in size; there were no macroscopic findings at 550 mg/kg bw. The estimated LD₅₀ was 1049 mg/kg bw.

No experimental data are available for irritation or skin sensitization in animals.

In a combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], TMPS was administered to four groups of 10 rats/sex/dose level by gavage daily at 0 (dried and deacidified corn oil), 100, 250 and 500 mg/kg bw/day. Males were exposed for 28 days (including 14 days prior to pairing) and females were exposed for 14 days prior to pairing, through the pairing and gestation periods until the F1 generation reached day 4 postpartum. Administration of TMPS at 500 mg/kg bw/day caused a reduction of food consumption in males during the first week of treatment and in females during the pre-pairing period up to day 14 of the gestation period. Reduced body weight was noted in males throughout the study and in females throughout the gestation period. Kidney weight was increased in males and thickened urinary bladder in males and females was seen at this dose. An increase of concentration of urea, bile acids and cholesterol was also noted in males at 500 mg/kg bw/day. Multifocal tubular degeneration/regeneration and transitional cell hyperplasia of kidney were noted in males and females. At 250 mg/kg bw/day, an increase in the urea and bile acid concentrations was observed. Multifocal tubular degeneration/regeneration and transitional cell hyperplasia of kidney were noted in males and females at this dose. The urinary bladder was observed to be thickened in males and females at all dose levels. This finding correlated with the histopathology examination showing perivascular lymphoid cell infiltration and transitional cell hyperplasia of the urinary bladder. Based on the findings in urinary bladder, a NOAEL (No Observed Adverse Effect Level) for systemic toxicity of TMPS could not be established. The LOAEL was 100 mg/kg bw/day. In a 4-week whole-body vapour inhalation (7 hr/day, 5 days/week) study conducted similar to OECD TG 412, there were no adverse treatment-related effects noted at any of the vapour concentrations administered. The NOAEC was determined to be 649 mg/m³ (highest concentration tested).

TMPS did not induce gene mutations in bacterial cells (*Salmonella typhimurium* TA-1535, TA-1537, TA-98 and TA-100 and *Escherichia coli* WP2 uvrA), but did induce chromosomal aberrations in Chinese hamster V79 cells *in vitro* [OECD TG 473]. Based on these results, TMPS is considered to be genotoxic *in vitro*.

No data are available for the carcinogenicity of TMPS.

In the combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422] with TMPS, the NOAEL for reproductive/developmental toxicity was 500 mg/kg bw/day (highest dose tested). The LOAEL for maternal toxicity was 100 mg/kg bw/day. Overall, TMPS did not show evidence of reproductive/developmental toxicity.

TMPS may present hazard for human health (repeated-dose toxicity; genotoxicity). Adequate screening-level data

are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

Testing for water solubility, partition coefficient and biodegradation was not conducted because TMPS undergoes rapid hydrolysis in the presence of water with a measured hydrolysis half life of 24 minutes at pH 7 and 25°C.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 2.4 days with an overall OH rate constant of $4.4 \times 10^{-12} \text{ cm}^3/\text{molecule-sec}$. The biodegradation of TMPS has not been determined due to its rapid hydrolysis. Based on the rapid hydrolysis of this material, any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only substances remaining in the test system will be methanol and phenylsilanetriol. Methanol is readily biodegradable based on the results of standard tests that show 76 – 82 % and 95 % removal in standard ready tests after 5 and 20 days, respectively. However, phenylsilanetriols and its condensed silanol oligomers are expected to be not readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that TMPS will distribute mainly to the soil (69.7%) and water (22.3%) compartments with minor distribution to the sediment and air compartments (5 and 2.9%, respectively). However, TMPS is unlikely to be found in the environment, as this material is hydrolytically unstable. A calculated Henry's Law constant of $5.41 \times 10^{-1} \text{ Pa-m}^3/\text{mole}$ ($5.34 \times 10^{-6} \text{ atm-m}^3/\text{mole}$) suggests that volatilization from the water phase for TMPS is not expected to be high.

Bioaccumulation is not anticipated since the parent substance, tmps, is hydrolytically unstable. The estimated bcf for the hydrolysis product phenylsilanetriol is low (3.16). However, as the model is not validated for substances containing silane in their structure a final conclusion on bioaccumulation of phenylsilanetriol cannot be drawn with accuracy. Experimental bcfs of < 10 in fish species, including *cyprinus carpio* and *leuciscus idus*, have been measured for methanol.

TMPS reacts to form methanol and phenylsilanetriol through hydrolysis. The bioaccumulation potential for phenylsilanetriol cannot be predicted accurately, but is expected to be low (calculated BCF= 3.16). Methanol is not likely to bioaccumulate (measured BCF<10). Furthermore, due to these properties, current estimation models are not capable of calculating physicochemical or environmental fate values with a known degree of accuracy. No information on the environmental fate of phenylsilanetriol was found. However, based on studies on related monomeric silanols, it is expected that the adsorption of phenylsilanetriol onto surfaces and condensation to disiloxanes in dilute aqueous solution may be important properties of this chemical. Phenylsilanetriol is expected to partition primarily to soil and water due to its high water solubility. In water and air, phenylsilanetriol may degrade photolytically. Slow biodegradation in water and soil might also occur.

Due to the rapid hydrolysis of TMPS, aquatic organisms are likely exposed to the parent and its hydrolysis products, methanol, silanetriol, and condensed silanetriol materials. No toxicity data specifically relating to the silanol hydrolysis products are available.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Oncorhynchus mykiss*] 96-h $\text{LC}_{50} > 0.074 \text{ mg/L}$ (OECD TG 203, flow-through)*

Invertebrate [*Daphnia magna*] 48-h $\text{EC}_{50} > 0.0029 \text{ mg/L}$ (OECD TG 202, flow-through)*

Algae [*Pseudokirchneriella subcapitata*] 72-h E_yC_{50} , E_rC_{50} , $\text{E}_b\text{C}_{50} > 0.2 \text{ mg/L}$ (OECD TG 201, nominal)

Algae [*Pseudokirchneriella subcapitata*] $\text{NOEC} \geq 0.2 \text{ mg/L}$ (OECD TG 201, nominal)

*The functional water solubility of TMPS (in the test media) was observed to be 0.2 mg/L (nominal). Testing was done using limit of solubility 0.2 mg/L (nominal); measured concentrations are reported.

TMPS does not present an acute hazard for the environment based on its low hazard profile at the limit of water

solubility. This substance is expected to be not readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

In the Sponsor Country, production volume in 2005 was ca. 454 – 2268 tonnes in the United States of America. This material is also produced in Japan (45 tonnes in 2005). TMPS is used in automotive, water repellent, paint additive, chemical intermediate, primer and adhesion promotion, silicone elastomer catalyst production (polycondensation system), and as an intermediate for silicone polymers/oligomers. Percent use in final product <5 - 100%, with no parent substance remaining after end use.

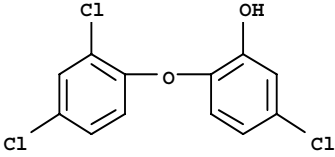
The substance is manufactured in closed systems. Only during sampling or product transferring, the open system conditions are encountered; however; these operations are conducted in the presence of inert systems (nitrogen) which reduce safety concerns. Use of engineering controls includes grounding, local exhaust ventilation, and closed sampling loops. Personal protective equipment (PPE) includes gloves, safety glasses, respirator, fire resistant clothing, safety shoes, and hard hat. No exposure is anticipated under routine operations. Potential routes of exposure during routine operations include dermal and inhalation.

The substance is used as a crosslinker for two-part mold making applications by industrial consumers. The substance is handled in both closed and open systems (only during sampling/transferring). Engineering controls include grounding and ventilation. PPE includes gloves, safety glasses, and a respirator if the Threshold Limit Value is expected to be exceeded during sampling or product transferring. When standard operating procedures are followed, exposures are not anticipated. In the event of a non-routine work event, exposures are possible via the oral, dermal and inhalation route.

The substance is used in consumer adhesives at less than 1%. Dermal is a potential route of exposure.

There are no intentional releases to the environment. The reactive nature of this material destroys the parent material in water, thus limiting environmental exposure to TMPS.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3380-34-5
Chemical Name	Triclosan; Phenol, 5 chloro-2-(2,4-dichlorophenoxy)-
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

Triclosan is a white to off-white crystalline powder with a faint aromatic odour, a melting point of 54° to 57.3°C, decomposition temperature of 280-290°C, and a measured vapour pressure of 5.33×10^{-4} Pa at 20°C. The measured octanol-water partition coefficient ($\log K_{ow}$) is 4.76, and the water solubility is 10 mg/L at 20°C with a pKa of 8.1. K_{oc} values estimated from the $\log K_{ow}$ are 8417-9740 L/kg.

Human Health

In humans, triclosan is well absorbed from the gastrointestinal tract with peak plasma concentrations occurring after 1.6–5 hours and absorption ranging between 57-91%. Dermal absorption in humans from products containing triclosan varies between 3-14%, depending on the formulation. The observation of clinical signs of toxicity in repeat dose inhalation toxicity studies in rats (2 hours/day for 21 days, nose-only, doses up to 1.3 mg/L) indicates that absorption can occur via the inhalation route. Bioavailability of triclosan is likely to be substantially greater by inhalation compared to oral or dermal routes due to the absence of first pass metabolism. Triclosan is widely distributed to organs and tissues with the highest levels generally seen in well-perfused and excretory organs such as the liver, lung, kidney, gastrointestinal tract and gall bladder. Triclosan is rapidly removed from the blood, and extensive first pass metabolism occurs following oral or dermal administration. The half life elimination from plasma in human adults following oral administration ranged between 15-29 hours. Following dermal exposure, the half life elimination from plasma ranged between 34-374 hours. Enterohepatic circulation has been demonstrated clearly in rats in dedicated studies, while comparatively limited evidence (eg. residual gastrointestinal radioactivity) is available for mice and hamsters. The major metabolic pathways in humans and animals involve glucuronide and sulphate conjugation, and metabolism to these conjugates has also been observed in the skin. Evidence of phase-1 metabolism found in rodent studies has not been reported in humans. In humans, excretion is relatively rapid; the major route of excretion being via urine (up to 87%), while excretion via faeces, the major route in rodents, is of secondary importance. Based on this, enterohepatic circulation appears to be a minor route of elimination compared to rodents. Triclosan has been detected in human breast milk samples indicating potential excretion in breast milk. The human oral and dermal data provide no evidence of a bioaccumulation potential.

Triclosan has low acute oral and dermal toxicity but considerable inhalation toxicity. The triclosan oral LD_{50} was greater than 5000 mg/kg bw in rats (males and females combined). An acute dermal toxicity study with a slurry of triclosan in propylene glycol reported the LD_{50} to be equal to or greater than 9300 mg/kg bw in rabbits. The only acute (4 hour) inhalation toxicity study available in rats indicated an LC_{50} greater than 0.15 mg/L (the highest dose tested). Acute inhalation toxicity was also determined from a repeat dose inhalation toxicity study in rats in which more than 50% of the rats died after the initial single 2-h exposure to 10% ethanol aerosol containing 1300 mg triclosan/m³ air, indicating an LC_{50} less than 1.3 mg/L. At necropsy, acute

purulent inflammation with focal ulceration of mucous membranes in the nasal cavity and trachea was seen along with haemorrhage and severe acute congestion and oedema in the lung of dead rats.

Triclosan is a moderate skin irritant in rabbits; erythema and oedema were observed in a skin irritation assay performed in rabbits with both intact and abraded skin. Responses were comparable or slightly more severe with abraded skin. Human patch test results with various formulations of triclosan also indicate the chemical to be a skin irritant. No significant phototoxicity was observed in human or animal studies. Triclosan is considered to be an eye irritant in rabbits; erythema and oedema of the conjunctiva and reversible corneal effects (severe on day 1) were observed in an eye irritation assay performed in rabbits; however, the experimental data available do not provide conclusive evidence to show that the chemical causes severe or irreversible eye damage. Triclosan is considered to be a respiratory tract irritant. Inflammation of the nasal cavity and trachea were observed at necropsy in animals that died in a repeat dose inhalation toxicity study performed in rats.

Skin sensitisation studies conducted with triclosan formulations in well conducted guinea pig studies were all negative. Human volunteer studies conducted with formulations up to 25% triclosan did not show skin sensitisation potential; however, up to about 0.3% of patients with dermatitis or eczema have shown positive skin reactions to triclosan.

The repeated dose toxicity of triclosan has been investigated in several animal studies; no reliable human data were available. In a 13-week oral study in mice, a LOAEL of 25 mg/kg bw/day was identified based on effects on haematology parameters, relative liver weights and total cholesterol. No NOAEL was identified. The relevance of this study is limited by particular sensitivity in the mouse to peroxisome proliferation, an effect not regarded as relevant to humans. In a repeat dose oral toxicity study in rats (OECD TG No. 453), the substance was administered via the diet to 60 rats per sex per group at 0, 12, 40, or 127 mg/kg bw/day in males and 0, 17, 56, or 190 mg/kg bw/day in females for 2 years, in addition 10 rats per sex per group received a dose equivalent to 247 mg/kg bw/day in males and 422 mg/kg bw/day in females for one year. No significant difference in survival was observed between triclosan treated and control animals of either sex. Treatment related effects included reduction in body weight gain of males at 247 mg/kg bw/day (10%), and of females at 190 (6%) and 422 mg/kg bw/day (23%) treated for one year. The reduction in body weight gain observed at these higher doses in both males and females suggested that the maximum tolerated dose was reached in this study. However, no significant difference in body weight was seen in treated and control animals at the end of two years. A statistically significant increase in ovary weights was seen in females at 190 mg/kg bw/day after 2 years of treatment (75% absolute, 69% relative weight). However, this was not associated with any histopathological changes in the ovaries. At 2 years, decreases in absolute spleen weights (approximately 22.5% irrespective of dose) and relative spleen weights (17, 25 and 28% at 17, 56 and 190 mg/kg bw/day respectively) were seen in females, but these showed no dose response, were not accompanied by histopathological changes and were not regarded as sufficient evidence of an adverse effect. Histopathological changes including hepatocyte hypertrophy and hepatocyte vacuolisation in cells, were only seen in the liver of males (at 127 mg/kg bw/day after 13 and 78 weeks and at 247 mg/kg bw/day after 1 year of treatment), indicating the liver as the target organ following oral administration of triclosan. Changes in haematology and/or biochemical parameters included a decrease in serum aspartic aminotransferase in males at 40 mg/kg bw/day and above and an increase in corpuscular haemoglobin concentration in females at 17 mg/kg bw/day after 1 year of treatment; however, these changes were not considered adverse. Based on the histopathological effects observed in the liver in males at 127 mg/kg bw/day and the trend for reduction in body weight gain observed for females at 190 mg/kg bw/day, the NOAEL for repeat dose oral toxicity was determined to be 40 mg/kg bw/day in males and 56 mg/kg bw/day in females. Studies in other species including mice, hamster and baboon also suggest the liver as a target organ.

In a 90 day repeat dose dermal toxicity study in rats (OECD TG No. 411), triclosan was administered in propylene glycol as an occlusive topical application to 10 rats per sex per group at 0, 10, 40 or 80 mg/kg bw/day for at least 6 hours per day. The only treatment related effect observed was erythema and/or oedema at 10 mg/kg bw/day and above, with severity increasing with dose. No mortality or clinical signs of toxicity were seen. At necropsy, hyperplasia, hyperkeratosis, inflammation and focal necrosis were seen at the application site. With the exception of one animal, dermal findings were observed to return to normal in the recovery group. As there were no significant clinical chemistry or haematological or histopathological changes to indicate reliable evidence of systemic toxicity, the NOAEL for repeated dose dermal toxicity was considered

to be 80 mg/kg bw/day, the highest dose tested. For local irritant effects, no NOAEL could be identified.

A number of *in vitro* and *in vivo* genotoxicity studies were available. In all the Ames tests with multiple strains of *Salmonella typhimurium* (some conducted according to OECD Guidelines), triclosan gave negative results with and without metabolic activation. In all studies, cytotoxicity was reported at high doses and controls behaved predictably. A weak positive result was observed in a bacterial reverse mutation assay (*Bacillus subtilis*) (5 mg/disc) with and without metabolic activation. An *in vitro* chromosomal aberration test with Chinese hamster ovary cells exposed to concentrations up to 1 µg/mL was negative with and without metabolic activation. However, another chromosomal aberration test with Chinese hamster V79 cells exposed to 3 µg/mL produced a significant increase in the incidence of chromosome aberrations in the absence of cytotoxicity with and without metabolic activation. Negative results were observed in two unscheduled DNA synthesis assays. Gene mutation tests in mouse lymphoma L5178Y cells with and without metabolic activation at concentrations of 15 µg/ml and 20 µg/ml did not demonstrate mutagenic potential. *In vivo* micronucleus assays in mice, and a chromosome aberration test in rats were negative up to the maximum tolerated doses. Although there were some positive results *in vitro*, overall, triclosan is not considered to be genotoxic *in vivo*.

The carcinogenic potential of triclosan has been investigated. In an oral study in rats (OECD TG 453), triclosan was administered via the diet to 60 rats per sex per dose at 0, 12, 40 or 127 mg/kg bw/day in males and 0, 17, 56 or 190 mg/kg bw/day in females for 2 years. In addition, 10 rats per sex per group were administered doses equivalent to 247 mg/kg bw/day in males and 422 mg/kg bw/day in females. There was no significant difference in survival observed between the control and treatment groups. No treatment related tumours were observed at any dose in either sex.

In an oral carcinogenicity study in hamsters (OECD TG 451), triclosan was administered via the diet to 60 hamsters per sex per dose at 0, 12.25, 75 or 250 mg/kg bw/day for 90 to 95 weeks. At the highest dose, systemic toxicity was clearly evident in both sexes, and a deterioration in the clinical condition and increase in mortality were observed in males after week 80, suggesting that the maximum tolerated dose was exceeded. No treatment related tumours were observed at any dose in either sex. Based on these results, triclosan is considered to have no carcinogenic potential.

The reproductive toxicity of triclosan has been well investigated in a two generation study in rats (OECD TG 416, with some exceptions). In this study, triclosan was administered via the diet to 25 rats per sex per dose at 0, 17, 56 or 176 mg/kg bw/day in males and 0, 23, 73 or 229 mg/kg bw/day in females, during a pre-mating period of at least 10 weeks and a mating period of up to 3 weeks. Females were also administered the test material throughout gestation and lactation. No deaths or clinical signs of toxicity were seen in F0 and F1 parental animals. In F1 pups, postnatal survival from day 0 to 4 was slightly reduced at the top dose (82% survival compared to 90-96% in the other groups). No effect was seen on fertility at any dose tested. There was some evidence of systemic toxicity in parental animals with reductions in body weight gain of 10% or greater seen in F1 males and females at the top dose of 176 and 229 mg/kg bw day respectively, during the growth and development stage. In F2 pups, a slight decrease in postnatal survival from day 0 to 4 and day 4 to 21 and a slight decrease in mean body weights (< 10%) were observed at the top dose. No treatment related changes were seen in F2 animals maintained up to postnatal day 21 for body weight gain, food consumption or at necropsy. The NOAEL for reproductive toxicity was determined to be 176 and 229 mg/kg bw/day and to be 56 and 73 mg/kg bw/day for systemic toxicity, in males and females, respectively. Based on these results, triclosan is not considered to be a reproductive toxicant.

The developmental toxicity of triclosan has been investigated in rats and rabbits in two gavage studies [OECD TG 414 (Teratogenicity) and ICH (Embryo-foetal development, Stage C guidelines, with the exception that the placenta was not grossly examined)] at doses of 0, 15, 50 or 150 mg/kg bw/day triclosan (with 1% carboxymethylcellulose in a 20% glycerine in water suspension). In the rat study, no effect was seen on the number of implantations, resorptions, live foetuses or foetal body weight and no treatment related visceral changes or skeletal malformations in foetuses were seen at any of the doses tested up to 150 mg/kg bw/day. Compared to controls, slight increased incidences (not statistically significant) in foetuses with one or more variations in retarded ossification were seen in triclosan treated groups (91.2%, 92.4%, 92.9% and 95.3% at 0, 15, 50 and 150 mg/kg bw/day, respectively). Triclosan was not a developmental toxicant in the rat in this study. Decreased food consumption, also observed at 150 mg/kg bw/day, may suggest maternal toxicity. No treatment related changes in dam body weight were reported at this dose. Based on these effects, the NOAEL for maternal toxicity was considered to be 50 mg/kg bw/day and the NOAEL for developmental toxicity was

150 mg/kg bw/day.

No evidence of developmental toxicity was observed in rabbits at doses up to 150 mg/kg bw/day. At this highest dose, slight but statistically significant decreases in mean body weights (<10%) were seen on gestation days 14 and 16 and statistically significant decreases in maternal body weight gain were seen on days 16-19. Decreases in food consumption were also observed during the dosing period. No effects were seen in pregnancy rates, sex ratios or foetal weights. A slight decrease in the number of implantations and number of live foetuses per litter, and a decrease in % resorptions per litter were seen at 150 mg/kg bw/day, but these were not statistically significant and within historical control ranges. Increased incidences (per foetus and per litter) of additional subclavian arteries were seen that were outside historical control ranges. However, these effects were neither dose related nor statistically significant at the highest dose (150 mg/kg bw/day), and therefore, not regarded as treatment related. No treatment related skeletal variations were observed. The NOAEL for developmental toxicity was considered to be 150 mg/kg bw/day and the NOAEL for maternal toxicity 50 mg/kg bw/day.

In another study in mice, the only treatment related developmental finding of delayed ossification of forelimb phalanges at 350 mg/kg bw/day was considered to be a consequence of maternal toxicity. The NOAEL for maternal toxicity was 75 mg/kg bw/day. The NOAEL for developmental toxicity was 350 mg/kg bw/day as the effect seen was secondary to maternal toxicity. Overall, triclosan is not considered a developmental toxicant.

Several recent studies of thyroid effects of triclosan have been published. However, the alterations in thyroid hormone levels in these animal studies did not lead to physiological changes in the short term. Differences in thyroid hormone physiology and regulation exist between rats and humans to the extent that extrapolation between rats (a very sensitive model for chemically induced changes in the thyroid hormone axis) and humans may not be straight forward.

Triclosan possesses properties indicating a hazard for human health (acute inhalation toxicity, skin, eye and respiratory irritation, liver toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

At environmental pH below ~8, the undissociated form of triclosan is expected to be the dominant form. Triclosan is hydrolytically stable in water at pH 4, pH 7 and pH 9 at 50°C, and it has an estimated half-life longer than 1 year at 25°C in waters of pH 4, 7 and 9. Aqueous photolysis is potentially a significant means of dissipation of triclosan in the environment, depending on water pH, as well as latitude and seasonal effects. The aqueous photolysis half-life of triclosan in water at pH 7 under irradiated conditions was ~41 minutes with a rate constant of 1.68×10^{-2} /minute. However, other laboratory experiments showed that triclosan (phenolic or molecular form) is relatively photostable, with the deprotonated phenolate (anionic) form of triclosan relatively more photodegradable and able to rapidly degrade (orders of magnitude faster) when exposed to sunlight. When irradiated by UV light in the solid state or in aqueous solution, some triclosan is converted to the dioxin 2,8-DCDD. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 7.96 hours, but little triclosan is expected to partition to the atmosphere and photo-oxidation is not expected to be a significant dissipation route.

Based upon results from tests using the standard method OECD 301B (CO₂ Evolution, Modified Sturm Test - % degradation over 28 days was 37%, at 10 mg/L and 18% at 20 mg/L) and 301F (manometric respirometry test – 52% degradation over 28 days at 10 µg/L), triclosan is not considered readily biodegradable. However, these and other studies with activated sludge under aerobic conditions suggest that triclosan may be inherently biodegradable, with substantial mineralisation to CO₂ occurring. A high degree of mineralisation (>70%) was demonstrated in laboratory-scale continuous activated sludge systems. Potentially influencing factors in these tests include the concentration (potentially exceeding toxic levels) and extent of habituation of the microorganisms present to triclosan.

Laboratory experiments with European soils at 20°C (OECD TG 307) showed that triclosan was degraded in three aerobic soils with a DT50 of 2.5-3.3 days, but degradation slowed significantly over time, with a DT90 of 19.1-231 days. In an Australian soil incubated at 22°C, a half-life of 18 days was observed under aerobic

conditions, but triclosan persisted under anaerobic conditions over the 70 day experimental period. In sewage sludge-amended American soils under laboratory conditions reported half-lives for triclosan were 17.4-35.2 days. In a study with two US soils with and without biosolids amendment, triclosan half-lives were 20-58 days. Biosolids amendment did not statistically significantly change the degradation rates. Degradation under aerobic conditions proceeds primarily via the formation of methyl triclosan, which is slower to degrade. Some mineralization of the residues is observed. In aerobic aquatic systems, triclosan dissipates rapidly from the water phase by degradation and adsorption to the sediment. In both compartments, it degrades to numerous minor metabolites, bound residues and carbon dioxide. In contrast to its degradation in aerobic environments, triclosan degrades very slowly and is persistent under anaerobic conditions, for example in soil and sediment. Triclosan has been shown to be persistent in sediments from natural waterways from several North American and European countries, with occurrences tracking the time course of usage and wastewater treatment strategies employed as far back as the 1960s.

A predicted Henry's law constant of 5×10^{-9} atm/m³ mole at 25°C suggests that volatilization of triclosan from the water phase is not expected to be high. A K_{oc} of 47454 L/kg was estimated in suspended solids obtained from deactivated sewage sludge (total organic carbon content 45.5%). Based on the log K_{ow} of 4.76, K_{oc} values of 9740 L/kg and 8417 L/kg were estimated by a QSAR model for predominantly hydrophobic substances and KOCWIN (v 2.0) respectively. Values determined in two soils with and without biosolids amendment ranged from 11397 to 15892. The adsorption coefficients indicate a high potential for strong adsorption to soils and sediments.

A fugacity model calculation using the EPI Suite[®] program (EPIWEB 4.0), with the model estimates for K_{OC} and degradation rates, and with equal and continuous distributions to air, water and soil compartments suggests that triclosan will distribute mainly to the soil (74.2%) and sediment (16.4%) compartments, with a minor amount to the water compartment (9.2%) and a negligible amount in the air compartment (0.2%). If released equally to the water and soil compartments, triclosan again partitions predominantly to the soil and sediment compartments (70.6% and 18.8%, respectively), with a minor amount to the water compartment (10.6%) and negligible amount to air (<0.01%).

Triclosan is expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor of 1000 to >5000, and bioaccumulation is pH dependent (greater accumulation at lower pH).

The following acute toxicity test results have been determined for aquatic species:

Fish

Fathead minnow (<i>Pimephales promelas</i>)	96 h LC ₅₀ = 260 µg/L (nominal)
Bluegill sunfish (<i>Lepomis macrochirus</i>)	96 h LC ₅₀ = 370 µg/L (nominal)
Zebra fish (<i>Brachydanio rerio</i>)	96 h LC ₅₀ = 540 µg/L
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96 h LC ₅₀ = 350 µg/L
Golden orfe (<i>Leuciscus idus</i>)	96 h LC ₅₀ = 560 µg/L
Medaka (<i>Oryzias latipes</i>)	96 h LC ₅₀ = 602 µg/L (nominal)

Invertebrates

<i>Daphnia magna</i>	48 h EC ₅₀ = 550 µg/L (nominal)
<i>Ceriodaphnia dubia</i>	48 h EC ₅₀ = ~130 µg/L at pH 6.8-7.0, ~180 µg/L at pH 7.4-7.6, ~240 µg/L at pH 8.0-8.2, ~420 µg/L at pH 8.5 (measured)

Algae

Green algae (<i>Scenedesmus subspicatus</i>)	72 h ErC ₅₀ = 2.8 µg/L (measured)
Green algae (<i>Scenedesmus subspicatus</i>)	72 h EbC ₅₀ = 0.7 µg/L (measured)
Green algae (<i>Pseudokirchneriella subcapitata</i>)	96 h EbC ₅₀ = 4.46 µg/L (nominal)
Cyanobacteria (<i>Anabaena flosaquae</i>)	96 h ErC ₅₀ = 1.6 µg/L (measured)
Cyanobacteria (<i>Anabaena flosaquae</i>)	96 h EbC ₅₀ = 0.97 µg/L (measured)
Diatom (<i>Navicula pelliculosa</i>)	96 h EbC ₅₀ = 19.1 µg/L (nominal)
Duckweed (<i>Lemna gibba</i>)	7 d ErC ₅₀ > 62.5 µg/L (nominal)

Microorganisms

Triclosan is an antimicrobial compound to many bacteria, fungi, moulds and yeasts. Some species are resistant to triclosan and others are able to use it as a sole carbon source. Effects occur in sensitive micro-organisms at

concentrations of ≥ 0.01 ppm. Limited available data indicate that effect levels of triclosan on activated sewage sludge micro-organisms vary depending on the level of acclimation. The release of triclosan into the environment has the potential to change microbial communities and their genetics through selection of resistant individuals and promoting a negative effect on important ecosystem bacteria (through death or inhibition).

Minimum Inhibitory Concentration (MIC) in laboratory agar cultures:

Gram-positive bacteria MIC 1 to >1000 ppm

Gram-negative bacteria MIC 0.01 to >1000 ppm

Moulds and yeasts MIC 1 to >1000 ppm

The following chronic toxicity test results have been determined.

Fish

Zebra fish 10 d NOEC = 200 $\mu\text{g/L}$

Rainbow trout 96 d NOEC = 34.1 $\mu\text{g/L}$

Invertebrates

Daphnia magna 21 d NOEC = 132 $\mu\text{g/L}$ (measured)

C. dubia 7 days NOEC = 4 - 6 $\mu\text{g/L}$ (measured)

Algae

Green algae (*Scenedesmus subspicatus*) 72 h NOEC = 0.5 $\mu\text{g/L}$ (measured)

Green algae (*Scenedesmus subspicatus*) 96 h NOEC = 0.69 – 2.38 $\mu\text{g/L}$ (measured)

Cyanobacteria (*Anabaena flosaquae*) 96 h NOEC = 0.81 $\mu\text{g/L}$ (measured)

The following toxicity test results have been determined for terrestrial species:

Birds

Mallard 14 d single oral LD_{50} >2150 mg/kg bw (nominal)

Bobwhite quail 14 d single oral dose LD_{50} = 862 mg/kg bw (nominal)

Bobwhite quail 8 day LC_{50} >864 mg/kg bw (measured) and NOEC = 179 ppm (measured)

Terrestrial invertebrates

Earthworms (*Eisenia foetida*) 14 d LC_{50} >1026 mg/kg dry weight and NOEC = 1026 mg/kg dry weight (nominal)

Terrestrial plants

Cucumber (time weighted average for shoot length over a 21 day exposure period) NOEC = 65 $\mu\text{g/kg}$ when grown in sandy soil (measured)

Endocrine activity

Studies with Japanese medaka indicate that triclosan and/or its metabolite methyl-triclosan may potentially have weak androgenic and/or anti-estrogenic action in fish. There is also evidence for potential endocrine-disrupting activity in amphibians; in one study with tadpoles of *Rana catesbeiana* it was concluded that exposure to low levels of triclosan (as low as 0.15 $\mu\text{g/L}$ for 4 days) disrupted thyroid hormone-associated gene expression and can alter the rate of thyroid hormone-mediated postembryonic anuran development.

Triclosan possesses properties indicating a hazard for the environment (acute toxicity for algae, aquatic invertebrates, and fish below 1 mg/L, chronic toxicity to algae and aquatic invertebrates below 10 $\mu\text{g/L}$, and evidence for potential endocrine modulating activity). The substance is not readily biodegradable [and persistent under anaerobic conditions in soil and sediment] and has potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

Triclosan is not manufactured in Australia. It is imported into Australia as a raw chemical or as an ingredient in various products. The total amount of triclosan imported annually has decreased from 31 tonnes in 2002 to 21 tonnes in 2005. Worldwide production volume is not available. Triclosan is mainly produced by treatment of 2,4,4'-trichloro-2'-methoxydiphenyl ether with aluminium chloride in benzene under reflux.

In Australia, triclosan is used as an ingredient in cosmetics and personal care products, therapeutic and

veterinary products, pesticides, household and industrial cleaning products, grouting material, and in some oil-based paints. It is incorporated into some plastics and textile products during manufacture. It is also imported into Australia as an ingredient in a large number of end products intended for consumer use, including cosmetic and personal care products and is probably present in some imported finished plastic and textile articles. Triclosan is used in these products for its broad-spectrum anti-microbial activity.

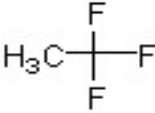
Although not a SIDS endpoint, studies on possible development of cross-resistant bacteria following triclosan exposure show that bacterial resistance can be generated under laboratory conditions.

Triclosan has been reported in natural waters from Australia and several North American (United States and Canada) and European countries (Germany, Norway, Switzerland, The Netherlands and United Kingdom), and in sediments of natural waterways from several North American (United States) and European countries (Germany, Spain, Sweden, Switzerland). Monitoring of the levels of triclosan in sewage effluent and receiving freshwaters is being conducted in Australia (sponsor country).

No occupational or effluent monitoring data are available from processing/formulation sites in Australia. Occupational exposure through dermal and inhalation routes is possible. Considering the types of triclosan containing products available to public, consumer exposure may occur mainly through the dermal route. However, oral exposure through accidental or incidental ingestion of lip balm, toothpaste or mouthwash formulations, and inhalation exposure through breathing aerosols generated from cosmetics and personal care products may also occur.

Release of triclosan to the environment occurs during washing and bathing after use of triclosan containing cosmetics and personal care products, from disposal of products and through discharges from formulating facilities. Environmental exposure is possible through wastewater discharge of triclosan in raw untreated sewage, treated effluent or surface waters in effluent receiving environments.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	420-46-2
Chemical Name	1,1,1-Trifluoroethane (HFC-143a)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Supporting Chemical Justification**

For the environment part, an analog, 1,1-Dichloro-1-fluoroethane (HCFC 141b; CAS No. 1717-00-6) was used as a surrogate for the algal toxicity and biodegradation endpoints. This approach is acceptable because HCFC 141b is also a halocarbon structurally similar to HFC 143a. HCFC 141b is more water soluble and less volatile than HFC-143a. HCFC 141b has been previously assessed in the OECD HPV Chemicals Program (documents are available at <http://www.inchem.org/documents/sids/sids/1717006.pdf>).

Physical-chemical properties

1,1,1-trifluoroethane (HFC-143a) is a colorless and odorless gas at room temperature with a melting point of -111.3 °C, a boiling point of -47.4 °C at 1013hPa and a measured vapour pressure of 1262-1272 kPa at 25 °C. The calculated octanol-water partition coefficient (log K_{ow}) is 1.74 and the measured water solubility is 761 mg/L at 25 °C. The flammability limits of HFC-143a at 20 – 25°C are 7.1 – 16.1%.

Human Health

Data on toxicokinetics of 1,1,1-trifluoroethane are available from studies in rats and human volunteers. Studies in male rats (conducted via inhalation) indicate that the major metabolite found in urine after inhalation exposure to a concentration of 40,000 ppm 1,1,1-trifluoroethane for 4 hours (at saturation) is trifluoroethanol. Minor metabolites included the glucuronide conjugate of trifluoroethanol, trifluoroacetic acid, trifluoroacetaldehyde and the urea conjugate of trifluoroacetaldehyde. No metabolites were identified following exposure to air concentrations of 4800 ppm or lower. In another study, a significant decrease in liver glutathione was seen in rats exposed to concentrations greater than 10,000 ppm for 4 hours. In vitro studies using microsomes from rats or humans confirm low levels of metabolism. Less than 2.6 % of parent compound was metabolized when microsomes were exposed to 20000 or 60000 ppm, no metabolism was detected at 200 ppm. The major metabolite was trifluoroethanol and the minor metabolites were not identified.

Nine (occupationally exposed) male human volunteers were exposed to 500 ppm of 1,1,1-trifluoroethane for two hours during light physical exercise in an exposure chamber. A plateau blood concentration of $4.8 \pm 2.0 \mu\text{M}$ 1,1,1-trifluoroethane was reached within 30 minutes of exposure. The concentration in plasma and inhaled air decreased quickly and in parallel when exposure was stopped. The urinary excretion of 1,1,1-trifluoroethane after exposure was 0.0007% of the inhaled amount. The half-time in urine was 53 minutes. The kinetic behaviour was in agreement with a very low blood:air partition coefficient and zero metabolism.

Acute inhalation exposure of rats (male and female) to concentrations up to 591,000 ppm (approximately 2030 mg/L) 1,1,1-trifluoroethane for four hours (nose only) did not cause lethality [OECD 403]. Body weight loss was the only clinical sign of toxicity. The LC_{50} was greater than 591,000 ppm. 1,1,1-Trifluoroethane induced cardiac sensitization in dogs at concentrations of 300,000 ppm. No effects of exposure at 500 ppm for 2 hours were seen

in humans either in the electrocardiographic monitoring or as rating for irritation and CNS symptoms. No reliable data on irritation were available for 1,1,1-trifluoroethane.

The repeated-dose toxicity of 1,1,1-trifluoroethane has been investigated in two studies. In a 4-week repeated-exposure inhalation toxicity study in male rats, the substance was administered via inhalation (whole body) at 0, 2000, 10,000 or 40,000 ppm (0, approximately 6.9, 34.4, 137.5 mg/L respectively) for 6 h/day, 5 days/week. The high exposure level was chosen as it approximated 50% of the lower flammability limit (7.0 to 7.5%). No treatment-related mortality, clinical signs, body weight changes or macroscopic or microscopic changes in the testes or epididymides were observed. The NOAEC was 40,000 ppm. In a second study [OECD TG 413], rats (20/sex/concentration) were similarly exposed via inhalation (whole body) for 13 weeks. The recovery groups of 10 animals/sex/concentration were included in the study which continued for four additional weeks without exposure. No mortality or treatment-related changes were observed. In addition to the guideline histopathological evaluations, liver samples were collected from 5 rats/group for determination of β -oxidation activity as a measure of peroxisomes proliferation. There was no proliferation of hepatic peroxisomes. The NOAEC was 40,000 ppm.

In two bacterial reverse mutation assays/Ames tests with multiple strains of *Salmonella typhimurium* [OECD TG 471] 1,1,1-trifluoroethane was negative both with and without metabolic activation. An *in vitro* chromosomal aberration test [OECD TG 473] was negative with and without metabolic activation when human lymphocytes were exposed to 5000, 15,000, 25,000 or 35,000 ppm 1,1,1-trifluoroethane for 3 hours at 37 °C. An *in vivo* micronucleus assay [OECD TG 474] was negative, in which mice were exposed whole body for 6 hours/day for two consecutive days to 2000, 10,000 or 40,000 ppm 1,1,1-trifluoroethane. Based on these results, 1,1,1-trifluoroethane is considered to be non genotoxic *in vitro* and *in vivo*.

In a limited oral carcinogenicity study, HFC143a was administered in corn oil, by gavage to male and female rats at a dose of 300 mg/kg, 5 days/week for 52 weeks. The rats were then observed for an additional 72 weeks. No chemical related carcinogenic or chronic toxic effects were seen.

No reproductive toxicity study is available for 1,1,1-trifluoroethane. No treatment-related effects were seen following histological examination of the reproductive organs (testes, epididymides, prostate, ovaries and uterus) in the 13-week whole body inhalation repeated-dose toxicity study when animals were exposed (whole body) to 1,1,1-trifluoroethane up to 40,000 ppm. The developmental toxicity of 1,1,1-trifluoroethane has been investigated in rats and rabbits in studies conducted according to OECD TG 414. The pregnant rats were exposed (whole body) from day 7 through day 16 of gestation and the pregnant rabbits were exposed from day 6 through day 18 of gestation. In both studies the exposure levels were 0 (control), 2000, 10,000 or 40,000 ppm. No evidence of developmental toxicity was observed in rats or rabbits. The NOAEC for maternal and developmental toxicity in both studies was 40,000ppm.

This chemical does not present hazard for human health based on its low hazard profile. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Chemicals Programme.

Environment

1,1,1-Trifluoroethane does not contain any hydrolysable groups and does not undergo hydrolysis. For the photodegradation, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 9,600 days. The 100-year global warming potential has been estimated as 3800 (compared with 1 for CO₂) and the atmospheric lifetime has been estimated as 48.3 years. These estimations are based on information presented by the Intergovernmental Panel on Climate Change (IPCC). The global warming potential of this chemical is acknowledged and being addressed by other programs. Based on the analog data for HCFC-141b, 1,1,1-trifluoroethane is considered to be not readily biodegradable. In general, low molecular weight halocarbons are not readily degradable. A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that 1,1,1-trifluoroethane will distribute mainly to the air (52.1 %) and water (47.2 %) compartments with minor distribution to the soil (0.47 %) and sediment (0.19%) compartment. If released only to the air compartment, this chemical stays in the air compartment (> 99.9 %) with negligible amounts in other compartments. As this chemical is a gas, it will be released almost exclusively into the air.

The estimated Henry's Law constant of 7.80×10^4 Pa·m³/mole suggests that volatilization of 1,1,1-trifluoroethane from the water phase is expected to be high. The bioaccumulation potential is expected to be low based on the estimated log K_{ow} of 1.74 and estimated BCF value of 0.81.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Oncorhynchus mykiss</i>]:	96 h LC ₅₀ > 40 mg/L (measured, highest concentration tested); 109 mg/l (modelled)
Invertebrate [<i>Daphnia magna</i>]	48 h EC ₅₀ = 300 mg/L (measured)
Aquatic plants:.	96-h EC ₅₀ = 71 mg/L mg/L.(modelled)
Aquatic plants (analog HCFC-141b)	72 h NOEC > 44 mg/L (measured; highest concentration tested)

This chemical does not present hazard for the environment based on its low hazard profile. This chemical is considered not readily biodegradable and the bioaccumulation potential is expected to be low. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

Annual global production for 2006 is estimated to be between 10,000 and 50,000 tons. There are two identified production sites, one in the U.S. and one in France. It is produced at a purity of >99.9% and sold as a liquified gas. It is flammable. It is used in stationary air conditioning systems and commercial refrigeration.

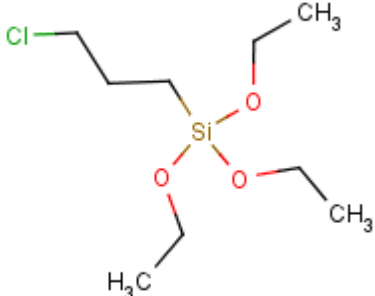
Since 1,1,1-trifluoroethane is a gas with a low boiling point (-47.4°C), it is produced in sealed systems. There is no monitoring data for 1,1,1-trifluoroethane (from effluents, surface water in occupational settings) available from the production and processing sites in the US or France. However, the American Industrial Hygiene Association's Workplace Environmental Exposure Level committee recommends an OEL (occupational exposure limit) of 1000 ppm as an 8-hr TWA.

It is a gas with a boiling point of -47.4°C and therefore must be used in sealed systems. During the past 6 years a total of 19 samples were collected at Honeywell's production site. Most samples were below the limit of detection (approximately 0.1 ppm) and the highest level reported was 0.65 ppm.

When released into the environment, it will partition almost exclusively into the air. It has an atmospheric life time of 3 years. It is not an ozone depleting substance. Based on a 100 year time horizon, it has a global warming potential of 3800 relative to CO₂ which is 1.

Occupational exposure through inhalation is possible. Consumer exposure is considered to be negligible. Environmental exposure through air is possible but will be very low/considered negligible.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	5089-70-3
Chemical Name	(3-Chloropropyl)triethoxysilane (CPTES)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

The sponsored substance, (3-Chloropropyl)triethoxysilane (**CPTES**) is structurally analogous to (3-chloropropyl)trimethoxysilane (**CPTMO**, CAS No. 2530-87-2). Both **CPTES** and **CPTMO** hydrolyze to form 3 moles of ethanol or methanol, respectively, for each mole of chloropropylsilanetriol. **CPTMO** has previously been assessed in the OECD HPV Programme and the SIDS dossier can be viewed at <http://www.chem.unep.ch/irptc/sids/OECD/SIDS/2530872.pdf>. Similar structures, hydrolysis rates and available toxicological profiles for acute toxicity, irritation and sensitization support the use of **CPTMO** data for the genetic, repeated-dose and reproductive/developmental toxicity endpoints. The hydrolysis half-lives for **CPTES** and **CPTMO** at acidic pH (representative of the mammalian gut) are similarly rapid with half-lives of < 24 minutes (**CPTES**; pH 4) and 14.6 minutes (**CPTMO**; pH 5) at 25°C and therefore significant systemic exposure to unhydrolyzed (**CPTES/CPTMO**) parent is unlikely. The analogue approach was not used for ecotoxicity. The hydrolysis product, ethanol (CAS No. 64-17-5), has previously been assessed in the OECD HPV Programme and the SIDS dossier can be viewed at <http://www.chem.unep.ch/irptc/sids/OECD/SIDS/64175.pdf>. **CPTMO** represents a worst case as an analogue for **CPTES**, as methanol is more toxic than ethanol. The contribution of three moles of corresponding alcohol (methanol or ethanol) to the toxicity of the parent silane is expected to be negligible in rodents. However, the possibility of effects in humans that are not expressed in rats cannot be excluded. Methanol exhibits potential hazardous properties for human health (neurological effects, CNS depression, ocular effects, reproductive and developmental effects, and other organ toxicity). Rapid metabolism and excretion is noted depending on the dose. The assessment [of ethanol] is focused on its use as industrial chemical. Ethanol possesses properties that indicate a hazard for human health but these are manifest only at doses associated with consumption of alcoholic beverages.

Physical-Chemical Properties

The EPI Suite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

CPTES is a liquid with a measured melting point of less than -20.2 °C, a measured boiling point of 494 °C at

1017.1 hPa and a measured vapour pressure of 0.309 hPa at 25 °C. The measured octanol-water partition coefficient ($\log K_{ow}$) is 3.13 at 21°C, and the measured water solubility is greater than 113 mg/L at room temperature. The water solubility and $\log K_{ow}$ values may not be applicable because the substance is hydrolytically unstable.

Human Health

No toxicokinetics data are available for **CPTES**; however, hydrolysis of this substance is expected to produce 3 moles of ethanol for each mole of chloropropylsilanetriol.

Acute inhalation toxicity data are not available. The dermal LD_{50} of **CPTES** in male and female rats was greater than 2000 mg/kg bw. Erythema was noted at the site of contact. The oral (gavage) LD_{50} of **CPTES** in male and female rats was greater than 5000 mg/kg bw. Clinical signs included urogenital or ventral abdominal staining, soft stool, mucoid feces and piloerection. The dermal LD_{50} in rats of **CPTMO** is greater than 2000 mg/kg bw. Additional dermal LD_{50} values in rabbits include 2.83 mL/kg (male), 3.36 mL/kg (male) and 3.73 mL/kg (female). The oral (gavage) LD_{50} in rats of **CPTMO** is greater than 2000 mg/kg bw. Additional oral LD_{50} values in rats include 6.17 mL/kg (female) and 9.51 mL/kg to 10 g/kg (male).

CPTES is considered non-irritating to slightly to the rabbit skin and rabbit eyes. **CPTES** is not a skin sensitizer. **CPTMO** has been shown to have none to moderate irritation to the skin and eyes. **CPTMO** is not a skin sensitizer when tested under the conditions of OECD TG 406.

No data are available for the repeated-dose toxicity of **CPTES**. Repeated-dose toxicity data via the inhalation route are available for the analogue substance, **CPTMO**. In a 90-day inhalation repeated-dose toxicity study [OECD TG 413], rats were exposed to 0, 4, 41, 814 and 1627 mg/m³ (reported as 0, 0.5, 5, 100 and 200 ppm) **CPTMO** vapor six hours/day, five days/week. [Note that the animals from the 200 ppm group were evaluated only in the micronucleus assay.] Treatment-related histopathologic changes were observed in the urinary bladder in both sexes at 100 ppm (814 mg/m³), whereas histopathological changes in the kidneys (increased incidence and severity of alpha 2μ-globulin inclusions; hyaline droplet nephropathy) were observed only in males exposed to 100 ppm (814 mg/m³). Based on these effects the lowest-observed-adverse-effect-concentration (LOAEC) in the rat was established at 100 ppm (814 mg/m³). The no-observed-adverse-effect-concentration (NOAEC) for male and female rats was reported to be 5 ppm (41 mg/m³). In a 28-day inhalation repeated-dose toxicity study [OECD TG 412], rats were exposed whole-body to mean concentrations of **CPTMO** at 0, 81, 407, 798 or 1563 mg/m³ (reported as 0, 10, 50, 100 or 200 ppm) for six hours/day, five days/week. Histopathological changes included effects on adrenal glands (in males at 798 mg/m³ and in both sexes at 1563 mg/m³), kidneys (in males at 407, 798 and 1563 mg/m³), liver (in males at 1563 mg/m³) and, at 81 mg/m³ on the urinary bladder of females (also at 407, 798 and 1563 mg/m³ in both sexes). A NOAEC was not established in this study. In a combined repeated-dose/reproductive/development toxicity screening test [OECD TG 422], male rats were exposed whole body to **CPTMO** concentrations at 0, 41, 203 or 814 mg/m³ (target concentrations of 0, 5, 25 or 100 ppm) for six hours/day for 28 days and female rats were exposed to the same concentrations throughout the 14-day pre-pairing, pairing and gestation periods until day 19 post coitum. **CPTMO** exposure up to and including the high concentration of 100 ppm (814 mg/m³) did not result in any signs of general toxicity of the test substance, including effects in the urinary bladder and kidney. Based on these results, the NOAEC in the rat was established at 100 ppm (814 mg/m³). Although the effect on the urinary bladder and kidney was not observed in all repeated inhalation exposure studies with **CPTMO**, the NOAEC for this effect across all studies is considered to be 5 ppm (41 mg/m³). The conclusion has been reached that it is plausible the biological variation is often seen among tests and possibly, between testing laboratories; and, the 90-day study should be considered as carrying the most weight as it is the study with the longest duration and provides the most conservative NOAEL. The estimated overall NOAEC for **CPTES** is 100 ppm (814 mg/m³).

One bacterial reverse mutation test with **CPTES** was positive, and one was negative. **CPTMO** was not considered to be an inducer of micronuclei *in vivo* in two studies, but was mutagenic *in vitro* (positive in all bacterial mutation assays conducted in the presence and absence of metabolic activation, and in an *in vitro* mouse lymphoma mutagenesis assay). The balance of evidence is that ethanol is not genotoxic. Negative results from a number of bacterial mutation assays appear to be reliable. Of the mammalian cell mutation assays a weak mutagenic effect in mouse lymphoma cells occurred only at very high ethanol concentrations. *In vivo* tests for chromosome aberrations in both rats and Chinese hamsters have given negative results [with ethanol]. There is very little evidence to suggest that ethanol is genotoxic in somatic cells and it may have a very limited capacity to induce genetic changes

in vivo but under very specific circumstances and at very high doses achievable in humans only by deliberate oral ingestion [of ethanol]. **CPTES** may be expected to be mutagenic in *in vitro* systems.

No data are available for the carcinogenicity of **CPTES** or the analogue substance, **CPTMO**. Evidence of the carcinogenicity of ethanol is confined to epidemiological studies assessing the impact of alcoholic beverage consumption. These do not indicate any such hazard exists from potential exposure to ethanol in the work place or from the use of ethanol in consumer products.

No data are available for the reproductive and developmental toxicity of **CPTES**. The analogue substance, **CPTMO** has been assessed for reproduction and developmental toxicity following inhalation exposure in the combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422] in rats, described above. Exposure to **CPTMO** up to and including the highest concentration of 100 ppm (814 mg/m³) did not result in any signs of systemic, reproductive or developmental toxicity. Based on these results the NOAEC for reproductive and developmental toxicity in the rat was 100 ppm (814 mg/m³). **CPTES** is not expected to be a reproductive or developmental toxicant. Methanol exhibits potential hazardous properties including reproductive and developmental effects. The assessment of [ethanol] is focused on its use as industrial chemical. Ethanol possesses properties that indicate a hazard for human health but these are manifest only at doses associated with consumption of alcoholic beverages.

(3-Chloropropyl) triethoxysilane may possess properties indicating hazard for human health (based on slight skin and eye irritation and *in vitro* genotoxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The hydrolysis half-life for **CPTES** is 35 hours at 25 °C and pH 7 resulting in the formation of ethanol and chloropropylsilanetriol. In the atmosphere, indirect photo-oxidation by reaction of **CPTES** with hydroxyl radicals is predicted to occur with a half-life of 6.2 hours with an overall OH rate constant of $2.06 \times 10^{-11} \text{ cm}^3/\text{molecule}\cdot\text{sec}$. **CPTES** was biodegraded by 46% in 28 days, indicating the test substance is not readily biodegradable; based on the hydrolysis of this substance, some potential for biodegradation of the hydrolysis product ethanol is likely. In aerobic conditions using adapted wastewater from domestic sewage, degradation of ethanol was 74% after 5 days rising to 95% by day 15 and in similar conditions in synthetic seawater, ethanol was degraded by 45% after 5 days rising to 75% by day 20. Neither chloropropylsilanetriol nor condensed silanetriol materials are expected to be readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that **CPTES** will distribute mainly to soil (83.3%) compartment with minor distribution to water and sediment compartment (9.1 and 6.8%, respectively) and negligible amount in the air compartment. However, **CPTES** is unlikely to be found in the environment, as this substance is hydrolytically unstable. Henry's Law constant of 12.8 Pa-m³/mole ($1.26 \times 10^{-4} \text{ atm}\cdot\text{m}^3/\text{mole}$) suggests that volatilization from the water phase for **CPTES** is expected to be moderate.

Bioaccumulation is not anticipated since the parent substance **CPTES** is hydrolytically unstable. The estimated BCF for **CPTES** is low (1.73). However, as the model is not validated for compounds containing silane in their structure, a final conclusion cannot be drawn with accuracy for **CPTES** and its hydrolysis product chloropropylsilanetriol. Ethanol is not likely to bioaccumulate (calculated BCF=3.16).

Due to the hydrolysis of **CPTES**, aquatic organisms are likely exposed to a mixture of the parent and its hydrolysis products, ethanol, chloropropylsilanetriol, and condensed silanetriol materials.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Brachydanio rerio</i>] 96 h LC ₅₀ :	80 mg/L (semi-static; measured)
Invertebrate [<i>Daphnia magna</i>] 48 h EC ₅₀ :	140 mg/L (static; nominal)
Algae [<i>Scenedesmus subspicatus</i>] 72 h EC ₅₀ :	> 819 mg/L (biomass and growth rate) (static; nominal)

(3-Chloropropyl) triethoxysilane possesses properties indicating a hazard for the environment (acute aquatic toxicity values for fish between 1 and 100 mg/L). The substance is not readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purposes of

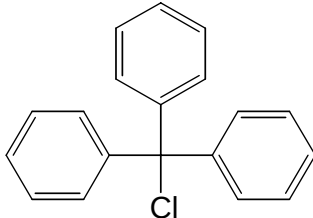
the OECD HPV Chemicals Programme.**Exposure**

CPTES was produced and/or imported in the United States at a volume of 4,540 – < 22,680 tonnes (10 - < 50 million pounds) during 2005. The only use of **CPTES** is as a chemical reactant; it is used as an intermediate for synthesis of organofunctional silane coupling agents. It is used in formulations at 100% or up to 50 mole-% (up to 80 weight %); no parent substance is expected to remain after end use. Uses are the same in the US, Europe and Japan.

At the manufacturing site, **CPTES** is manufactured and consumed in closed systems. Ventilation devices and other related equipment such as closed sampling loops and special measuring and control equipment are used. Personal protective equipment (PPE) includes safety glasses, respirator, gloves (impermeable chemical resistant), fire resistant clothing, safety shoes, and hard hat. Worker exposure to **CPTES** due to non-accidental releases at the facility level is not expected; PPE minimizing the potential for exposure via the dermal and inhalation routes. No environmental exposure is expected.

There are no consumer uses of **CPTES**.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	76-83-5
Chemical Name	Triphenylmethyl chloride
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address only the following endpoint(s): Human Health: acute toxicity, repeated dose toxicity and mutagenicity. It cannot be considered as a full SIDS Initial Assessment. Nevertheless, the conclusions for the endpoints addressed have been agreed by member countries and may be used for hazard and risk assessment. Results on other endpoints may be relevant for hazard and risk assessment but have not been addressed in the assessment.

As the following results demonstrate, triphenylmethyl chloride was designated as a Type II monitoring chemical substance under the Japanese Chemical Substances Control Law; such chemicals may have potential of long- term toxicity for human health, and their production volume should be monitored.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law, hazard assessment of existing chemical substances has been conducted. If a chemical substance is evaluated as “not biodegradable (persistent)” and “not highly bioaccumulative”, at least a 28-days repeated dose toxicity study and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long- term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

Triphenylmethyl chloride was evaluated as “not biodegradable (persistent)” and “moderately bioaccumulative” by METI (Ministry of Economy, Trade and Industry). Biodegradation and bioaccumulation are not parts of the targeted assessment and therefore not presented in ITAP. The initial hazard assessment of triphenylmethyl chloride was conducted in order to determine whether the chemical is classified as a Type II monitoring chemical substance in Japan.

This assessment document was originally based on the material from the chemical assessment council of MHLW (Ministry of Health, Labour and Welfare), and we reassessed the toxicological profile and re-established NOAELs for the OECD HPV chemical programme.

Physical-chemical properties (neither assessed, nor part of the targeted assessment, provided for information only)

Triphenylmethyl chloride is a white to slight yellow powder with a melting point of 113.5 °C, a boiling point of 310 °C and a calculated vapour pressure of 0.000516 Pa at 25 °C. A measured octanol-water partition coefficient (log K_{ow}) is 5.25, and estimated water solubility is 0.535 mg/L at 25 °C.

Human Health

The oral LD₅₀ value in rats for triphenylmethyl chloride was greater than 2000 mg/kg bw in both sexes (OECD TG 401). Triphenylmethyl chloride administered orally caused no effects at a dose of 2000 mg/kg bw in rats.

In a repeated dose oral toxicity study in rats following standard guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species in compliance with GLP, the substance was administered via gavage at 0 (vehicle control: corn oil), 12, 60, 300 mg/kg bw/day for 28 days. No death was observed in either sex. Increased relative liver weight and hypertrophy of the centrilobular hepatocytes were evident in both sexes given 60 and 300 mg/kg bw/day. A decrease in serum glucose level was observed in females at 60 and 300 mg/kg bw/day and in males at 300 mg/kg bw/day. Mucosal thickening of the cecum was observed in females given 60 mg/kg bw/day and both sexes given 300 mg/kg bw/day. Based on these results, the NOAEL of repeated dose oral toxicity was considered to be 12 mg/kg bw/day in both sexes.

In a bacterial mutation study using four strains of *Salmonella typhimurium* and an *Escherichia coli* WP2 *uvrA* strain (OECD TG 471), triphenylmethyl chloride was negative with and without metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells gave also negative results in either the presence or absence of metabolic activation (OECD TG 473). All positive controls responded appropriately for gene mutations and chromosomal aberration assays. Based on these results, triphenylmethyl chloride is considered to be non genotoxic *in vitro*.

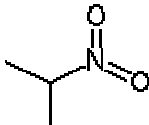
Agreed hazard conclusions

The chemical possesses properties indicating a hazard for human health endpoints targeted in this assessment (repeated dose toxicity) .

Available Exposure information (not part of the targeted assessment, provided for use information only)

In Japan, triphenylmethyl chloride is mainly used as an intermediate in medicines.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	79-46-9
Chemical Name	Propane, 2-nitro- (2-Nitropropane)
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address the following human health endpoints: carcinogenicity and genotoxicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment are included in the Canadian screening assessment but have not been agreed upon by OECD member countries, and thus are not included in this profile.

The final screening assessment has been published under the responsibility of the Government of Canada.
 [<http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=3FDF4576-1>]

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its *Canadian Environmental Protection Act, 1999* (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: **inherently toxic** to humans or to the environment and that might be **persistent** and/or **bioaccumulative**; and substances to which people might have **greatest potential for exposure**. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release.

The substance, 2-nitropropane was identified as a high priority for assessment of human health risk because it was considered to present intermediate potential for exposure and had been classified by other agencies on the basis of carcinogenicity.

Physical-chemical properties

The substance, 2-nitropropane, is a liquid at room temperature with a melting point of -93°C, boiling point of 120°C and vapour pressure of 2290 Pa at 25°C (all measured values). The measured octanol-water partition coefficient (log K_{ow}) is 0.93, and the measured water solubility is 17 000 mg/L at 25°C.

Human Health Targeted Endpoints

A sufficient genotoxicity database was available. The chemical tested positive in bacterial mutation assays with and without metabolic activation. It induced gene mutations in Chinese hamster cells and rat hepatoma cells. In cultured human peripheral lymphocytes with metabolic activation, it showed clear evidence of chromosomal aberration and induction of sister chromatid exchanges (SCEs) although negative results were found in Chinese hamster ovary cells in SCEs (with and without metabolic activation). 2-Nitropropane induced unscheduled DNA synthesis in

human, rat and mouse hepatocytes. It also induced micronuclei in three rat hepatoma cell lines but not in Chinese hamster lung V79 cells (all without metabolic activation).

The genotoxic effects of 2-nitropropane were corroborated in a series of *in vivo* studies. In mice exposed by intraperitoneal injection, an increased frequency of mutations in the LacI gene and an increased expression of the tumour suppressor gene, p53, were observed in the liver. 2-Nitropropane induced micronuclei in the hepatocytes and bone marrow of rats treated orally, but not in the peripheral blood of mice treated via intraperitoneal injection. Unscheduled DNA synthesis occurred in the hepatocytes of orally treated rats. Furthermore, DNA strand breaks were reported in the bone marrow of rats, and in the stomach, colon and liver of mice after administration of 2-nitropropane via intraperitoneal injection; however, no effect on the kidney, urinary bladder, lung, brain and bone marrow of mice were observed. It also induced DNA base modifications in the liver of rats treated orally and intraperitoneally. Significant increases in 8-hydroxydeoxy-guanosine levels, an indication of oxidative stress induced DNA damage, were observed in the liver of rats and mice treated with 2-nitropropane orally or intraperitoneally, but no effect was observed on the kidney of rats. In summary, 2-NP was mutagenic *in vitro* and *in vivo* and clearly genotoxic.

Carcinogenicity potential was determined on the basis of oral toxicity (subchronic exposure but assessed after a lifetime) and subchronic to long-term inhalation studies. There were no human cancer data available. Liver tumours were observed in rats treated with 2-nitropropane via different routes of exposure. In one carcinogenicity study, male rats were orally administered 2-nitropropane at 0 or 40 mg/kg-bw, 3 times a week for 16 weeks, at which time dosing was discontinued due to high mortality. Animals were observed for the following 61 weeks (total duration of the test 77 weeks). All of the animals treated with 2-nitropropane developed benign or malignant liver tumours. Metastases were also observed in the lungs of some of these rats. In another study, male rats were administered 2-nitropropane via inhalation (whole body) at 0, 98 or 755 mg/m³ for 1 to 6 months. All of the rats exposed to 755 mg/m³ for 6 months developed multiple hepatocellular carcinomas. Although there were no tumours seen in the rats exposed to 755 mg/m³ for 3 months, hyperplastic changes in the liver were observed. No tumours were noted in the rats exposed to 98 mg/m³. In addition to these cancer studies, it was reported that inhalation or intraperitoneal exposure to 2-nitropropane had been shown to have an initiating action in rats treated also with established promoters.

Exposure to 2-nitropropane has also induced non-cancer effects, mainly on the liver, in experimental animals. In rats exposed by inhalation to 78 mg/m³ 2-nitropropane for 22 months, slightly increased focal vacuolization of the cytoplasm of hepatocytes and focal areas of hepatocellular nodules were observed in males. 78 mg/m³ was determined to be the lowest LOAEC amongst the chronic toxicity studies; a NOAEC was not determined. In a sub-chronic oral study in male rats exposed to 2-nitropropane at 89 mg/kg-bw, 3 times a week (equivalent to 38 mg/kg-bw per day), for 4 months, no consistent effect on numbers of preneoplastic or neoplastic renal lesions, or neoplasms in the liver was observed. However, in a sub-chronic inhalation study, liver cellular damage, which was considered to be preneoplastic, was observed at 755 mg/m³ in rats exposed via inhalation for 3 to 6 month. The lung was also a target for non-cancer effects in rodents exposed to 2-nitropropane. Pulmonary lesions in male rats exposed to 2-nitropropane via inhalation for 1 to 6 months was observed at 755 mg/m³. However, no adverse effects were observed in rabbits subjected to the same treatment conditions.

2-Nitropropane possesses properties indicating a hazard for the human health endpoints, carcinogenicity and genotoxicity (increased incidence of liver tumours and lung metastases, clear evidence of genotoxicity).

Exposure Summary Information

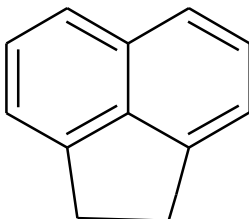
2-Nitropropane is used as a solvent and chemical intermediate. As a solvent, it may be used in vinyl inks, electrostatic paints, adhesives, varnishes, polymers, and synthetic materials. 2-Nitropropane may be used to dissolve a large number of resins; these solvent-resin mixtures have reportedly found use as coatings in the lining of beverage cans.

2-Nitropropane is also reportedly used as a component of explosives and propellants, and in fuels for internal combustion engines. The information available suggests that use of 2-nitropropane in paints and coatings is limited to a few specific industrial applications, thus no consumer scenarios for use of paints and coatings were generated. The exposure of the general population as a result of industrial use of 2-nitropropane within Canada is likely to be negligible. It is acknowledged that the information that has been presented in published reviews to characterize the uses of this substance may be somewhat dated, and may not reflect the current exposure

conditions for the Canadian population.

No companies in Canada reported manufacturing 2-nitropropane in a quantity greater than or equal to the 100 kg reporting threshold, but 100 to 1000 kg of the substance was reported to be imported in 2006. No domestic releases were reported to Canada's National Pollutant Release Inventory between 1997 and 2007 (most recent data available). Additionally, no releases to the environment were reported for 2006 under a survey conducted in Canada. In the United States, the Toxic Release Inventory database indicates on-site releases from 8 facilities totalling 11,725 kg (25,850 lbs) in 2007.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	83-32-9
Chemical Name	1,2-Dihydroacenaphthylene
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address only the following endpoint(s): [Human Health: acute toxicity, repeated dose toxicity and *in vitro* mutagenicity]. It cannot be considered as a full SIDS Initial Assessment. Nevertheless, the conclusions for the endpoints addressed have been agreed by OECD member countries and may be used for hazard and risk assessment. Results on other endpoints may be relevant for hazard and risk assessment but have not been addressed in the assessment.

As the following results demonstrate, 1,2-dihydroacenaphthylene was designated as a Type II monitoring chemical substance under the Japanese Chemical Substances Control Law; such chemical substances may have potential of long- term toxicity for human health, and their production volume should be monitored.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law, hazard assessment of existing chemical substances has been conducted. If a chemical substance is evaluated as “not biodegradable (persistent)” and “not highly bioaccumulative”, at least a 28-day repeated dose toxicity study and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long- term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

1,2-Dihydroacenaphthylene was evaluated as “not biodegradable (persistent)” and “moderately bioaccumulative” by METI (Ministry of Economy, Trade and Industry). Biodegradation and bioaccumulation are not part of the targeted assessment and therefore not presented in this ITAP. The initial hazard assessment of 1,2-dihydroacenaphthylene was conducted in order to determine whether the chemical is classified as a Type II monitoring chemical substance in Japan.

This assessment document was originally based on the material from the chemical assessment council of MHLW (Ministry of Health, Labour and Welfare), and we reassessed the toxicological profile and re-established NOAELs for the OECD HPV chemical programme.

Physical-chemical properties (neither assessed, nor part of the targeted assessment, provided for information only)

1,2-Dihydroacenaphthylene is a white to yellow powder with a relative density of 1.189 g/cm³, a melting point of 95 °C, a boiling point of 279 °C and a vapour pressure of 0.36 Pa at 20 °C. A measured octanol-water partition coefficient (log K_{ow}) is 3.92, and water solubility is 3.8 mg/L at 25 °C.

Human Health

The oral LD₅₀ value in rats for 1,2-dihydroacenaphthylene was greater than 2000 mg/kg bw in both sexes (OECD TG 401). 1,2-Dihydroacenaphthylene administered orally caused no effects at a dose of 2000 mg/kg bw in rats.

In a repeated dose oral toxicity study in rats following standard guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species in compliance with GLP, the substance was administered via gavage at 0 (vehicle control: 0.5% CMC), 12, 60, 300 mg/kg bw/day for 28 days. Neither death nor clinical sign was observed in both sexes. Serum phospholipid was increased in 60 mg/kg bw/day females and both sexes given 300 mg/kg bw/day. In the 300 mg/kg bw/day group, there were also increases in total cholesterol in both sexes and in total bilirubin in males. In the histopathological examination, centrilobular hypertrophy of the hepatocytes was found in the liver in both sexes of the 300 mg/kg bw/day group, and erosion of glandular stomach was observed in female given 60 or 300 mg/kg bw/day. Based on these results, the NOAEL of repeated dose oral toxicity was considered to be 12 mg/kg bw/day in both sexes.

Bacterial reverse mutation assay of 1,2 -dihydroacenaphthylene was conducted using four *Salmonella typhimurium* strains, TA98, TA100, TA1535 and TA1537, and an *Escherichia coli* WP2 uvrA (OECD TG 471 and 472). In *Salmonella typhimurium* TA1537, the number of revertants was slightly increased in the absence of metabolic activation, but dose-dependency was not found. This finding was not observed in an additional study using TA1537 and TA97 obtained from another source. There was no increase in the number of revertants in the TA1537 strain under the presence of metabolic activation and in the other strain with and without the metabolic activation. In an *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473), structural chromosomal aberrations were dose-dependently induced at the cytotoxic doses in the short-term treatment with an exogenous metabolic activation system. Therefore, 1,2-dihydroacenaphthylene is considered to be genotoxic *in vitro* although the toxicological significance is equivocal due to the lack of data at non-cytotoxic doses under this test condition.

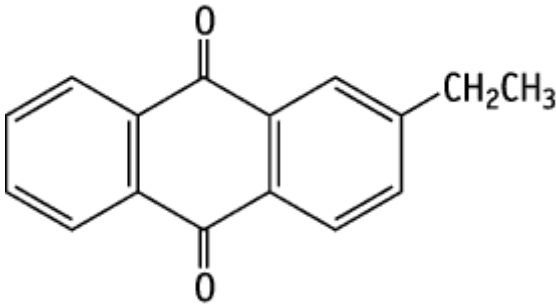
Agreed hazard conclusions

The chemical possesses properties indicating a hazard for human health endpoints targeted in this assessment (repeated dose toxicity and genotoxicity *in vitro*).

Available Exposure information (not part of the targeted assessment, provided for use information only)

In Japan, 1,2-dihydroacenaphthylene is mainly used as an intermediate in dyes, and as a raw materials in synthetic resins, pesticides or disinfectants.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	84-51-5
Chemical Name	2-Ethylanthracene-9,10-dione
Structural Formula	
SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT NOTE: The present assessment is targeted to address only the following endpoint(s): [Human Health: acute toxicity, repeated dose toxicity and in vitro mutagenicity]. It cannot be considered as a full SIDS Initial Assessment. Nevertheless, the conclusions for the endpoints addressed have been agreed by member countries and may be used for hazard and risk assessment. Results on other endpoints may be relevant for hazard and risk assessment but have not been addressed in the assessment. As the following results demonstrate, 2-ethylanthracene-9,10-dione was designated as a Type II monitoring chemical substance under the Japanese Chemical Substances Control Law; such chemical substances may have potential of long- term toxicity for human health, and their production volume should be monitored. Rationale for targeting the assessment Under the Japanese Chemical Substances Control Law, hazard assessment of existing chemical substances has been conducted. If a chemical substance is evaluated as “not biodegradable (persistent)” and “not highly bioaccumulative”, at least a 28-day repeated dose toxicity study and two <i>in vitro</i> mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long- term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored. 2-Ethylanthracene-9,10-dione was evaluated as “not biodegradable (persistent)” and “moderately bioaccumulative” by METI (Ministry of Economy, Trade and Industry). Biodegradation and bioaccumulation are not part of the targeted assessment and therefore not presented in ITAP. The initial hazard assessment of 2-ethylanthracene-9,10-dione was conducted in order to determine whether the chemical is classified as a Type II monitoring chemical substance in Japan. This assessment document was originally based on the material from the chemical assessment council of MHLW (Ministry of Health, Labour and Welfare), and we reassessed the toxicological profile and re-established NOAELs for the OECD HPV chemical programme. Physical-chemical properties (neither assessed, nor part of the targeted assessment, provided for information only) 2-Ethylanthracene-9,10-dione is a yellow microcrystalline powder with a melting point of 108.8 °C and a calculated vapour pressure of 0.00013 Pa at 25 °C. A measured octanol-water partition coefficient (log K_{ow}) is 4.37,	

and an estimated water solubility is 0.405 mg/L at 25 °C.

Human Health

2-Ethylanthracene-9,10-dione administered orally caused no effects at a dose of 2000 mg/kg bw in rats and the oral LD₅₀ was greater than 2000 mg/kg bw in both sexes (OECD TG 401).

In a repeated dose oral toxicity study in rats following standard guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species in compliance with GLP, the substance was administered via gavage at 0 (vehicle control, 0.5% CMC Na with 0.1% Tween80), 10, 50, 250 mg/kg bw/day for 28 days. No death was observed in either sex. Increases in absolute and relative weights of liver in both sexes, and spleen in females, and relative weight of kidney in males were observed in the 250 mg/kg bw/day group. On histopathological examination, centrilobular hypertrophy of hepatocytes was found in both sexes given 50 mg/kg bw/day and more, and the degree of this change tended to be dose-dependent. Moreover, the hepatocytes showed anisonucleosis in both sexes in the 250 mg/kg bw/day group. In the spleen, hemosiderosis and hemostasis were found in females given 50 mg/kg bw/day and more, and males given 250 mg/kg bw/day, and extramedullary hematopoiesis was found in males given 50 mg/kg bw/day and more, and females given 250 mg/kg bw/day. The LOAEL was 10 mg/kg bw/day and the NOAEL was not established in this study based on the decrease in the density of erythrocytes in males given 10 mg/kg bw/day and more, and in females given 250 mg/kg bw/day.

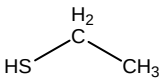
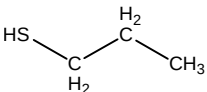
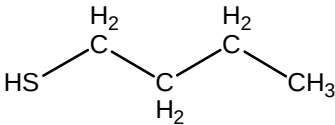
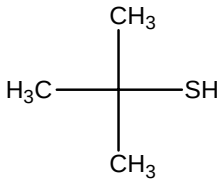
In a bacterial mutation study using four strains of *Salmonella typhimurium* and an *Escherichia coli* WP2 *uvrA* strain (OECD TG 471), 2-ethylanthracene-9,10-dione was negative with and without metabolic activation. In *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473), 2-ethylanthracene-9,10-dione was positive based on increase in the number of cases of polyploidy with the short-term treatment. Some indications of structural aberration were also observed. Some predictions on *in vivo* genotoxicity and carcinogenicity are available in the initial targeted assessment report (ITAR).

Agreed hazard conclusions

The chemical possesses properties indicating a hazard for human health endpoints targeted in this assessment (repeated dose toxicity and mutagenicity/genotoxicity *in vitro*).

Available Exposure information (not part of the targeted assessment, provided for use information only)

In Japan, 2-ethylanthracene-9,10-dione is mainly used as a sensitizer for photo-resists or a catalyst for manufacturing hydrogen peroxide.

Category Name	C2-C4 Aliphatic Thiols Category	
Chemical Names and CAS Nos.	1-Ethanethiol (CAS No. 75-08-1) 1-Propanethiol (CAS No.107-03-9) 1-Butanethiol (CAS No.109-79-5) 2-Propanethiol, 2-Methyl (CAS No. 75-66-1)	
Structural Formulae	 1-Ethanethiol (Ethyl Mercaptan)	 1-Propanethiol (n-Propyl Mercaptan)
	 1-Butanethiol (n-Butyl Mercaptan)	 2-Propanethiol, 2-Methyl (t-Butyl Mercaptan)

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The C2-C4 Aliphatic Thiols contain a sulfhydryl (SH) functional group with a straight or branched aliphatic carbon chain that characterizes the category. The four aliphatic thiols are soluble in water and have reasonably comparable melting points, initial boiling points and vapor pressures, as well as very low and objectionable odor thresholds. The water solubility and narrow range of octanol-water partition coefficients (log Kow) for the three linear C2-C4 Aliphatic Thiols indicate that they will have similar environmental fate and are not expected to bioaccumulate in aquatic organisms. Ecotoxicity is similar for the three linear C2-C4 Aliphatic Thiols with data for fish, invertebrate and algae toxicity indicating a similar order of acute toxicity across the chemicals tested (ecotoxicity is less for t-butyl-mercaptan). ECOSAR has been used to address and support the data gaps for the linear category members. Environmental fate and toxicity data are available for the branched t-butyl mercaptan. The available toxicology data show that the C2-C4 Aliphatic Thiols also have a similar order of toxicity under a variety of experimental conditions. In the WHO document (<http://www.inchem.org/documents/jecfa/jecmono/v44jec09.htm>), the applicability domain for the alkyl and aromatic thiols evaluated is much wider for simple, alkyl thiols and the “category” is based on the presumed common metabolism of these thiols. Simple thiols are metabolized via several different pathways in mammalian systems that include: S-methylation, resulting in a methyl thioether that would undergo S-oxidation; reaction with glutathione to form mixed disulfides (the likely form in circulation); and, especially for the low molecular weight thiols [methanethiol was presented as the example], oxidative desulfuration to yield CO and SO₄. From this information and available toxicity data, it can be concluded that the category members show a similar order of toxicity. Although the data for **n-butyl mercaptan** cannot be used for read-across purposes quantitatively, data can be used qualitatively to determine the hazard for these chemicals based on their common metabolic pathways. Therefore, although the specific test substance as described and discussed is referenced, the data satisfy the SIDS requirements for all four category members.

Physicochemical Properties

The C2-C4 mercaptans (ethyl, n-propyl, n-butyl, and t-butyl) are liquids at room temperature. The respective measured melting points are -147.8, -113.3, -115.9, and -0.5°C; the measured boiling points are 35.1, 67.8, 98.5, and 64°C; the measured vapor pressures are 705, 205, 60.6, 240 hPa (all at 25°C); the measured water solubility values are 15600, 1900, 595, 1470 mg/L (at 25°C, n-butyl at 20°C); the octanol log K_{ow} values are 1.27 (predicted), 1.81 (measured), 2.28 (measured), 2.14 (predicted). The

pKa for all four mercaptans is 10.7.

Human Health

No toxicokinetic, metabolism or distribution studies were identified for any of the C2-C4 Aliphatic Thiols. A description of the likely metabolism of the C2-C4 Aliphatic Thiols is summarized above in Category Rationale.

In rats, 4-hour LC₅₀ values for the C2-C4 Aliphatic Thiols via inhalation ranged from > 2.52 mg/L (for **ethyl mercaptan**) to 98.3 mg/L (for **t-butyl mercaptan**) in rats and mice. Clinical signs included lacrimation, hunched posture, tremors, staggering gait, muscular weakness, cyanosis, sedation. Irritation of the mucous membrane evidenced by rubbing of the eyes and nose, eye closure, watering of the eyes, corneal opacities and retracting of the head were also observed for **t-butyl mercaptan**. Respiratory tract irritation may occur following high exposures to the C2-C4 Aliphatic Thiols. The dermal LD₅₀ values for all category chemicals ranged from 1682 mg/kg bw (for n-propyl mercaptan) to > 2000 mg/kg-bw for the other category mercaptans. Initial skin contact evoked a severe pain reaction with a slight darkening in the skin color. Erythema and thickened skin were the most common findings after dermal application of the C2-C4 Aliphatic Thiols. The oral LD₅₀ for the C2-C4 Aliphatic Thiols in rats ranged from 682 mg/kg bw (for **ethyl mercaptan**) to 4729 mg/kg bw (for **t-butyl mercaptan**). In the oral studies, rats exhibited ruffled fur, docility, lacrimation, staggering, and blood stains around the nose and sedation at the higher doses.

Ethyl and n-propyl mercaptans were moderately irritating following 4-hour occluded exposure in rabbits; the irritation resolved within 24 hours. **n-Butyl and t-butyl mercaptans** were non-irritating in the same study design. In a second study, **n-propyl mercaptan** was minimally irritating to 3 of 6 rabbits following application for 4 hours under occlusive conditions (similar conditions to OECD TG 404). **n-Propyl mercaptan** was moderately irritating to the eyes of rabbits (similar conditions to OECD TG 405). All eyes were normal following a 7-day observation period. Based on the available data, the C2-C4 Aliphatic Thiols group chemicals are mild to moderate skin irritants to the rabbit skin and at most moderately irritating to rabbit eyes.

In the Buehler test under the EPA OPPTS 870.2600 test guideline, **t-butyl mercaptan** resulted in dermal scores (Grade 1-3) in guinea pigs at 24 and 48 hours following induction with a 100% solution and a challenge using a 75% solution. **t-Butyl mercaptan** was a skin sensitizer in guinea pigs. No skin sensitization data were available for ethyl, n-propyl, and n-butyl mercaptans. Based on the available data, the C2-C4 Aliphatic Thiols group chemicals are considered as skin sensitizers.

Repeated-dose toxicity has been investigated in 13-week inhalation toxicity studies with **n-butyl and t-butyl mercaptan** and an oral combined repeated-dose/reproductive/developmental toxicity study with **t-butyl mercaptan**. In the 13-week inhalation study (similar to OECD TG 413), rats (15/sex/concentration) were exposed (whole body) to **n-butyl mercaptan** vapor concentrations of 0, 9, 70, or 150 ppm (0, 0.033, 0.26 or 0.55 mg/L) for six hours per day, five days per week. Decreased red blood cells were observed for females at week 12 for the 70 ppm group and at weeks 6 and 12 for the 150 ppm group. A statistically significant elevation of neutrophils and a corresponding decrease of lymphocytes were noted for the 150 ppm group of females at week 12. None of these changes were out of the normal range for rats and therefore were not considered to be biologically significant. No effects on hematology parameters were observed in males. Lung weights were statistically significantly elevated for males at 70 and 150 ppm. The only histopathological finding attributable to the test material was the presence of increased macrophages of trace severity in the lungs of male and female rats in the 150 ppm group. The NOAEC and the LOAEC were 9 ppm (0.033 mg/L/day) and 70 ppm (0.26 mg/L/day), respectively. In the 13-week inhalation study (similar to OECD TG 413), rats (15/sex/concentration) were exposed to **t-butyl mercaptan** vapor concentrations of 0, 9, 97 or 196 ppm (0, 0.033, 0.36 or 0.72 mg/L) for six hours per day, five days per week. There were no deaths, clinical signs of toxicity or body weight changes observed. Differences in blood urea nitrogen and erythrocyte count observed at 6 and/or 12 weeks were within historical control ranges and were not considered toxicologically significant. No compound-related macroscopic lesions were observed in any of the rats that were sacrificed at the termination of the study or those that died during the course of the study. Toxicologically significant increases in the mean absolute and relative weight of the kidneys occurred in male rats exposed to 97 and 196 ppm. There was a compound- and concentration-related increase in chronic nephrosis (varying degrees of multifocal degeneration of the proximal convoluted tubules, tubular regeneration, and inflammatory cell infiltration of the interstitium) in 14 of 15 animals at the high concentration (196 ppm), 13 of 15 at the mid concentration (97 ppm) and 7 of 15 animals at the low concentration (9 ppm). Even though presence of α -2u-globulin was not assessed by appropriate staining in this study, it was done for the oral combined repeated-dose/reproductive/developmental toxicity screening test (42 – 53 days). Taking into account similar pathological findings on male rat kidney in both studies, it is assumed that effects found are indicative of α -2u-globulin nephropathy, which has no relevance to human health. The NOAEC was established at 196 ppm (0.72 mg/L). Based on an increase of alveolar macrophages in male and female rats exposed to 97 and 196 ppm, the NOAEC for pulmonary irritation was established at 9 ppm (0.033 mg/L).

In the combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), rats (12/sex/group in the main study and 5 males and 5 non-mated females in the recovery groups) were administered **t-butyl mercaptan** in corn oil by gavage at 0, 10, 50 or 200 mg/kg bw/day for 42-53 days. The recovery groups of control and high dose were monitored without

dosing for 2 weeks for recovery. Decreased body weight was observed in both sexes at 200 mg/kg bw/day throughout the administration period. During the recovery period, a lower body weight was observed in females, but body weight gains throughout the recovery period were similar to those of the control group. Decreased food consumption was observed in males at 200 mg/kg bw/day on days 4 and 15 of administration and in females at 200 mg/kg bw/day throughout the administration period. During the recovery period, females exhibited lower food consumption on day 1 of the recovery period, but food consumption after day 4 of the recovery period was similar to the control group. There was no effect on urinalysis measurements. For both sexes, changes in hematological and clinical chemistry parameters (either increases or decreases depending on the parameter) were observed at 50 and 200 mg/kg bw/day during dosing but only at 200 mg/kg bw/day during the recovery period. At necropsy, enlargement and discoloration of the kidneys were observed in 1, 3, and 4 males at 10, 50, and 200 mg/kg bw/day, respectively and liver enlargement was observed in 2 males at 200 mg/kg bw/day; after the recovery period, kidney enlargement was observed in 1 male at 200 mg/kg bw/day. No gross findings were recorded for females. Increases in absolute and relative liver weights were observed in males (50 and 200 mg/kg bw/day) and females (200 mg/kg bw/day). Kidney weight in males at 50 and 200 mg/kg bw/day and relative weight at all doses were significantly increased. A decrease in absolute thymus weight was observed in males at 200 mg/kg bw/day. Following the recovery period, increased relative liver weight was observed in both sexes and increases in absolute and relative weights of the kidneys were observed in males at 200 mg/kg bw/day. Histopathological changes were observed in the liver and spleen of both sexes and in the kidneys of males including: hepatocellular centrilobular hypertrophy in males at 50 and 200 mg/kg bw/day and in females at 200 mg/kg bw/day; hemosiderin deposits in the red pulp in the spleen of both sexes at 200 mg/kg bw/day; periportal fatty degeneration of hepatocytes in males at 50 and 200 mg/kg bw/day; basophilic renal tubules and hyaline deposits in proximal tubular epithelial cells in the kidneys in males at all doses which were considered to be indicative of α -2u-globulin nephropathy, which has no relevance to human health. Following the recovery period, hemosiderin deposits were observed in the red pulp of the spleen of both sexes, basophilic renal tubules were observed in the kidneys in males, and periportal fatty degeneration of hepatocytes was observed in 1 male and 1 female at 200 mg/kg bw/day. The NOAEL was 10 mg/kg/day for males and 50 mg/kg/day for females.

No reliable oral repeated-dose toxicity studies were identified for **ethyl, n-propyl, or n-butyl mercaptans**. Data for acute toxicity indicate that there are differences in potency between the shorter (C2) and longer chain (C4) aliphatic thiols. However, 13-week repeated-dose inhalation toxicity data show similar toxicity profiles for methyl mercaptan and butyl mercaptans (**n-butyl- and t-butyl-mercaptans**). The NOAEC value for these chemicals was 0.033 mg/L. Therefore, **n- and t-butyl mercaptans** data are used to read across to **ethyl- and n-propyl-mercaptans**. Methyl mercaptan was assessed at SIAM 27 and is not a member of this category.

Ethyl, n-butyl, and t-butyl mercaptans were not mutagenic in *in vitro* bacterial reverse mutation assays (OECD TG 471) with or without metabolic activation. In *in vitro* mammalian cell gene mutation (mouse lymphoma) assays (OECD TG 476), neither **n-butyl nor t-butyl mercaptan** induced mutagenic responses while **ethyl mercaptan**, at one intermediate dose (90.5 μ g/ml), without activation, increased induction of mutations that was 2-fold greater than the negative control. Because only one dose level, in the absence of S9, elicited a 2-fold response, the results were considered to be equivocal. In an *in vitro* sister chromatid exchange assay (OECD TG 473), **n-butyl mercaptan** did not induce a statistically significant genotoxic effect. **Ethyl mercaptan** showed a positive response in this assay at the highest concentration; however, excessive cytotoxicity, as represented by limited numbers of cells to evaluate, may have caused the increase in sister chromatid exchanges (SCEs). No reliable *in vitro* genotoxicity studies were identified for n-propyl mercaptan. In an *in vivo* mouse micronucleus assay (OECD TG 474), **t-butyl mercaptan** did not induce chromosomal mutations. No *in vivo* genotoxicity studies were identified for **ethyl, n-butyl, and n-propyl mercaptan**. Overall, based on the weight of evidence, it is concluded that these compounds do not induce gene mutations in bacteria or chromosomal aberrations *in vivo* or *in vitro*.

No carcinogenicity studies were identified for any of the four compounds in the C2-C4 Aliphatic Thiols category.

t-Butyl mercaptan did not result in toxicity to the embryo or fetus or show developmental toxicity via gavage dosing to rats at doses as high as 200 mg/kg bw/day in the previously described combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422). Neonatal toxicity was evident at 200 mg/kg bw/day based on reduced body weights of the pups on PND4. For **n-butyl mercaptan**, the NOAEC for both maternal and fetal toxicity was 152 ppm (0.58 mg/L) in rats. In pregnant mice, mortality was observed at concentrations of 68 and 152 ppm (0.26 and 0.58 mg/L); however, no fetal toxicity was observed in surviving animals. The NOAEC for maternal toxicity was 10 ppm (0.038 mg/L) and 68 ppm (0.26 mg/L) for developmental toxicity. For **t-butyl mercaptan**, no exposure-related maternal or fetal toxicity occurred in rats or mice at exposures up to 195 ppm (0.72 mg/L). No reliable fertility/developmental toxicity studies were identified for ethyl or n-propyl mercaptans. Based on these screening-level results, the C2-C4 Aliphatic Thiols are not likely to result in reproductive or developmental toxicity.

Limited reports from human volunteer studies and reports of accidental exposure suggest that 3-hour exposure to 10 mg/m³ (4 ppm) **ethyl mercaptan** gave rise to nausea, headaches, fatigue and irritation of mucous membranes of the lips, mouth and nose.

Exposure at 1 mg/m³ (0.5 ppm) produced no unpleasant symptoms. Human volunteers exposed to ethyl mercaptan at 10 mg/m³ (4 ppm) 3 hr daily during 5-10 days, showed minimal effects such as rise in olfactory threshold and altered taste reaction to bitter and sweet substances. Volunteers also reported periodic nausea, irritation of mucous membranes of lips, mouth, and nose and sensation of fatigue.

These chemicals possess properties indicating a hazard for human health (mild to moderate skin and eye irritation, potential skin sensitization, and repeated-dose toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The C2-C4 Aliphatic Thiols do not react with water; the only functionality other than carbon-hydrogen bonds is the sulfhydryl group. Predicted atmospheric oxidation half lives (AOP v. 1.92) for these chemicals are 3.2 hours (**ethyl mercaptan**), 3.0 hours (**n-propyl mercaptan**), 2.9 hours (**n-butyl mercaptan**), and 3.9 hours (**t-butyl mercaptan**). There are no photoreactive groups in these molecules and, therefore, direct photolysis is not expected.

The level III fugacity model (EpiSuite 4.00) calculation for **ethyl mercaptan** with equal and continuous release (1000 kg/hr) to air, water, and soil, is 6.9% to air, 75% to water, 17% to soil, and 0.2% to sediment; for **n-propyl mercaptan** it is 6.0% to air, 68% to water, 25% to soil, and 0.2% to sediment; for **n-butyl mercaptan** it is 5.7% to air, 58% to water, 36% to soil, and 0.2% to sediment; and for **t-butyl mercaptan** it is 9.0% to air, 71% to water, 20% to soil, and 0.3% to sediment.

Three of the four C2-C4 Aliphatic Thiols have been evaluated in biodegradation studies conducted according to OECD TG 301D. **n-Propyl and n-butyl mercaptans** are readily biodegradable based on the Guideline criteria with 84.7% and 91.8% degradation after 28 and 14 days, respectively, with both meeting the 10-day window. For **ethyl mercaptan**, biodegradation reached 27.1% after 28 days and, therefore, it was not readily biodegradable. Due to tertiary branching, it is expected that t-butyl mercaptan is not readily biodegradable. A study evaluating the biodegradability of t-butyl mercaptan is in progress. Calculated Henry's law constants (HENRYWIN v. 3.0) for these chemicals are, for **ethyl mercaptan**: 3.5 x 10² Pa-m³/mole (3.5 x 10⁻³ atm-m³/mole), for **n-propyl mercaptan**: 4.7 x 10² Pa-m³/mole (4.6 x 10⁻³ atm-m³/mole), for **n-butyl mercaptan**: 6.2 x 10² Pa-m³/mole (6.1 x 10⁻³ atm-m³/mole), and for **t-butyl mercaptan**: 6.2 x 10² Pa-m³/mole (6.1 x 10⁻³ atm-m³/mole). These values suggest that volatilization of these chemicals from the water phase is expected to be high. Based on the estimated log Kow values of these chemicals (1.27 – 2.28) and water solubility (595 – 15,600 mg/L), their bioaccumulation potential is expected (BCFBFAF v. 3.00) to be low (estimated BCF = 3.2, 7.3, 15 and 12 for **ethyl, n-propyl, n-butyl** and **t-butyl mercaptans**, respectively).

The following aquatic acute toxicity results have been determined for the members of this category:

Endpoint CAS No.	Ethyl Mercaptan 75-08-1	n-Propyl Mercaptan 107-03-9	n-Butyl Mercaptan 109-79-5	t-Butyl Mercaptan 75-66-1
Fish 96-h LC ₅₀ (mg/L)	2.4 (m) ^a 4.8 (e)	1.3 (m) ^a 2.9 (e)	No data 1.7 (e)	34 (m) ^a 2.0 (e)
Aquatic Invertebrates 48-h EC ₅₀ (mg/L)	< 0.1 (LOQ) (m) ^b 0.38 (m; 24 h) ^b 0.65 (e)	0.07 (m) ^b 0.50 (e)	No data 0.38 (e)	6.7 (m) ^b 0.42 (e)
Algae 72-h EC ₅₀ (mg/L) 72-h NOEC (mg/L) 96 h EC ₅₀	0.76 (m; biomass) 3.0 (m; growth rate) ^c 0.1 (m; biomass) 0.83 (m; growth rate) ^c 0.35 (e)	No data 0.29 (e)	No data 0.22 (e)	12(m; biomass) ^c 24 (m; growth rate) ^c <6.41(m; biomass) ^c 6.41(m; growth rate) ^c 0.25 (e)

m= measured; e = ECOSAR predicted value; a: *Oncorhynchus mykiss* - (OECD TG 203); b: *Daphnia magna* - (OECD TG 202);

c: *Pseudokirchneriella subcapitata* - (OECD TG 201)

These chemicals possess properties indicating a hazard for the environment (acute toxicity to fish, invertebrates and algae from <1 to 100 mg/L). n-Propyl and n-butyl mercaptans are readily biodegradable. Ethyl mercaptan is not readily biodegradable and t-butyl mercaptan is expected to be not readily biodegradable. However, bioaccumulation potential for these chemicals is expected to be low. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

As reported to the U.S. Environmental Protection Agency (U.S. EPA) for the year 2005, companies produced or imported between 450-4500 metric tons (1 million to < 10 million pounds) each of n-propyl and n-butyl mercaptan, and between 4500-22,500 metric tons (10 million to < 50 million pounds) each of ethyl and t-butyl mercaptan.

All of the C2-C4 Aliphatic Thiols are produced by the reaction of hydrogen sulfide with ethylene, isobutylene, propylene, or butane-1, to produce **ethyl, n-propyl, n-butyl, or t-butyl mercaptan**, respectively, followed by purification by distillation.

Thiols possess a sulfhydryl group (-SH) that is instrumental in introducing a sulfur group into various biologically active molecules in the pharmaceutical and agrochemical industries. Thiols are used as closely-controlled intermediates in the production of pesticides; for example, thiols are used in the production of thiocarbamates for herbicides and thiophosphates for insecticides. Thiols also have antioxidant properties that render them useful as polymer additives. The odor detection characteristics of the lower molecular weight thiols and the low order of mammalian toxicity makes them ideally suited for use as odorants in commercial applications, including addition to propane and natural gas as detailed for ethyl mercaptan and t-butyl mercaptan below. Odor thresholds for **ethyl, n-propyl, n-butyl and t-butyl mercaptans** are estimated to be 0.1 – 1.0 ppb, 1.6 ppb, 0.1 – 1.0 ppb and 0.08 ppb, respectively.

Thiols comprise the family of organic sulfur compounds. In general, these compounds exist naturally (water, plants, soil) and are required for survival of all higher organisms. **Ethyl mercaptan** is generated from vegetables (e.g. cabbage), natural gas wells, coal tar and mammalian excretory products. **n-Propyl mercaptan** is released from freshly crushed onions and related plant bulbs and **butyl mercaptans** are components of skunk secretions. Some bacterial systems have been shown to utilize thiols as their direct source of sulfur, specifically degrading the materials by selective cleavage of the C-S linkage. Other microorganisms are capable of releasing lower thiols from larger sulfur compounds.

When they are used in closely-controlled reactions as intermediates in agrochemical and other industrial production, exposure to the C2-C4 Aliphatic Thiols is expected to be low. Residual mercaptans in finished products, except where used for odorants, are not expected because of the high reactivity and the need to remove the thiols due to odor. When used as odorants, due to very low odor thresholds (as noted above), even low concentrations of the C2-C4 Aliphatic Thiols can be detected. Thus, as an example, the low ppm level of ethyl mercaptan in propane is sufficient to alert people of a propane leak well before 20% of the lower explosive limit (LEL) of propane in air is reached (the LEL for propane is approximately 4-5%, so 1% propane in air is insufficient to present an explosive hazard and the ethyl mercaptan is present at <1ppm which is a sufficient concentration to allow a leak to be detected). For t-butyl mercaptan, it is added to natural gas by natural gas delivery companies in closely-controlled conditions. The target amount is approximately 0.5-1.0 lb odorant blend per 1 million standard cubic feet of gas.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	C ₇ -C ₉ Aliphatic Hydrocarbon Solvents Category	
Chemical Names and CAS Registry Numbers	Substance Name	CAS Number
	<u><i>n-Paraffins Subcategory</i></u>	
	n-Heptane	142-82-5
	n-Octane	111-65-9
	n-Nonane	111-84-2
	<u><i>Iso-Paraffins Subcategory</i></u>	
	Pentane, 2,2,4-trimethyl-	540-84-1
	Alkanes, C ₇₋₈ , iso-	70024-92-9
	Alkanes, C ₇₋₁₀ , iso-	90622-56-3
	<u><i>Multi-Constituent Subcategory</i></u>	
	Ligroine; petroleum ether	8032-32-4
	Naphtha, (petroleum), light catalytic reformed	64741-63-5
	Naphtha, (petroleum), solvent-refined light	64741-84-0
	Naphtha, (petroleum), hydrotreated heavy	64742-48-9
	Naphtha, (petroleum), hydrotreated light	64742-49-0
	Solvent naphtha, (petroleum), light aliphatic	64742-89-8
	Naphtha (petroleum), hydrosulfurized light, dearomatized	92045-53-9
Structural Formula and CAS Registry Numbers	Structural Formula	CAS Number
	<u><i>n-Paraffins Subcategory</i></u>	
	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	142-82-5
	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	111-65-9
	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃	111-84-2
	<u><i>Iso-Paraffins Subcategory</i></u>	
	$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ \text{CH}_3-\text{C}-\text{CH}_2-\text{C}-\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	540-84-1
	UVCB substances containing aliphatic (linear and branched paraffins) molecules of carbon and hydrogen, predominantly in the C ₇ to C ₉ range	70024-92-9
		90622-56-3
	<u><i>Multi-constituent Subcategory</i></u>	
	UVCB substances containing aliphatic (linear, branched, and cyclic paraffins) molecules of carbon and hydrogen, predominantly in the C ₇ to C ₉ range. The category only includes substances that have boiling ranges falling within approximately 90 to 151 degrees Celsius.*	8032-32-4
		64741-63-5
		64741-84-0
		64742-48-9
		64742-49-0
		64742-89-8
		92045-53-9
	* It should be noted that other substances defined by the same CAS RNs may have boiling ranges outside the range of 90-151degrees Celsius and that these substances are not covered by the category.	

SUMMARY CONCLUSIONS OF THE SIAR

Category Definition/Justification

The C₇-C₉ Aliphatic Hydrocarbon Solvents Category is comprised of 13 CAS registry numbers (CAS RNs) that are associated with pure and multi-constituent aliphatic hydrocarbon solvent commercial chemicals, which typically contain <1% aromatics with a few members containing up to approximately 3% aromatics and n-hexane content typically <0.1%, with a few members containing up to approximately 5%. The multi-constituent chemicals are further defined by boiling range [90 to 151 degrees Celsius] and predominant carbon number range, which is primarily from C₇ to C₉. This category contains 4 single chemicals and 9 multi-constituent substances that include straight chain (n-), branched (iso-), and/or cyclic aliphatic hydrocarbons. In the European Union REACH (Registration, Evaluation, and Authorization of Chemicals) legislation, these multi-constituent category members are organized in a group described as “unknown or variable composition, complex reaction products or biological materials (UVCBs).

In this category, the 13 CAS RNs are commercial hydrocarbon solvents, whose composition and commercial applications provide the primary justification for evaluating these substances as a category. The majority of chemicals in this category are multi-constituent chemicals, some containing 30 to 50% cycloparaffins.

Based on structure and composition, the category has been divided into three subcategories. A general description of compositions of subcategory members with CAS RNs are as follows (see also table 1 and 2 in the appendix):

n-Paraffins Subcategory - 3 CAS RNs, each composed of a single, normal paraffin

- 142-82-5 Linear C₇ paraffin, n-heptane
- 111-65-9 Linear C₈ paraffin, n-octane
- 111-84-2 Linear C₉ paraffin, n-nonane

Iso-Paraffins Subcategory - 3 CAS RNs, one composed of a single isoparaffin and two composed of a range of isoparaffins predominantly in the C₇ to C₈ or C₇ to C₉ range, which includes 2,2,4-trimethylpentane that may also contain some normal paraffin content

- 540-84-1 Alkyl-branched C₈ isoparaffin, 2,2,4-trimethylpentane
- 70024-92-9 Alkanes, C₇₋₈, iso- [a multi-constituent substance that can be composed predominantly of alkyl-branched C₇ and C₈ isoparaffin isomers that can include 2,2,4-trimethylpentane as a constituent; other constituents can include methyl- hexanes and heptanes, dimethyl- pentanes and hexanes, and trimethylpentanes]
- 90622-56-3 Alkanes, C₇₋₁₀, iso- [a multi-constituent substance that can be composed predominantly of branched C₇, C₈, and/or C₉ isoparaffin isomers, which can include methyl- hexanes, heptanes, and/or octanes; dimethyl- pentanes, hexanes, and/or heptanes; and trimethyl-pentanes and/or -hexanes]

Multi-constituent Subcategory - 7 CAS RNs composed of predominantly C₇ to C₉ paraffins with varying compositions of normal paraffins, isoparaffins, and/or cycloparaffins.

- 8032-32-4 Ligroine; petroleum ether (<1% aromatics, may contain up to 3% aromatics)
- 64741-63-5 Naphtha, (petroleum), light catalytic reformed
- 64741-84-0 Naphtha, (petroleum), solvent-refined light
- 64742-48-9 Naphtha, (petroleum), hydrotreated heavy
- 64742-49-0 Naphtha, (petroleum), hydrotreated light
- 64742-89-8 Solvent naphtha, (petroleum), light aliphatic
- 92045-53-9 Naphtha (petroleum), hydrodesulfurized light, dearomatized

For the environment, ECOSAR and read-across approaches have been used to address and support the data gaps for the category members. The available toxicology data show that the C₇-C₉ Aliphatic Hydrocarbon Solvents have similar levels of toxic potency under a variety of experimental conditions.

The category has been defined for members with specific purity/impurity profiles or composition as outlined in the full SIDS Initial Assessment Report and the SIDS Dossiers.

The conclusions of this assessment do not necessarily apply to substances with the same CAS number but different purity/impurity profiles or compositions.

Analog Identification

Analog chemicals (used to support the category members) contain hydrocarbon constituents that fall within the carbon number range of category members and consequently their data can be considered when assessing the potential toxicity of category members. The analog multi-constituent substances that contain up to 12% aromatics compared to multi-constituent category members that have a typical aromatic content of <1% with a few members containing up to approximately 3%; represent a worst-case example. Where data for streams with higher aromatic content are used to characterize mammalian toxicity endpoints, those substances are considered as conservative analogs (read-across candidates), which would be expected to exhibit greater toxicity than category members. n-Hexane was not used as a worst-case material because of its low content in multi-constituent C₇-C₉ hydrocarbon solvents (= < 5 percent; typical less than 0.1%). The use of multi-constituent analogs with much broader hydrocarbon number ranges and higher aromatic content is limited to the human health endpoints only [acute toxicity, repeated dose toxicity, reproductive/developmental toxicity]. Although the carbon number range for some of the analogs exceeds the category definition of C₇-C₉ hydrocarbon solvents, the use of those data to support the characterization of category members is a valid application of read-across techniques because the constituents outside the category carbon number are similar in that they are homologous with category member constituents, some of which may act by the same mode of toxic action, and exhibit toxicities that are comparable to category members. For example, for the developmental/reproductive endpoint, the light alkylate naphtha analog (CAS RN 64741-66-8) vapor contains ~40% C₇-C₉ isoparaffins with the balance of paraffins in the C5 range. The analog composition overlaps that of category member CAS RN 64742-89-8. The absence of adverse reproductive/developmental effects at a vapor concentration of 8000 ppm (24.7 mg/L) in which the C₇-C₉ isoparaffin content is fairly high, suggests that C₇-C₉ aliphatic hydrocarbons are unlikely to produce reproductive/developmental toxicity.

As identified by the US EPA TSCA Inventory, multi-constituent analog chemicals CAS RN 8032-32-4 (ligroine) and CAS RN 64741-63-5 (light catalytic reformed naphtha) have the same CAS RN designations as multi-constituent subcategory members but a broader hydrocarbon range and approximately 12% aromatics. This is because assignment of CAS RNs for hydrocarbon substances in the TSCA Inventory is generally based on a hierarchy of considerations including hydrocarbon type(s), carbon number and/or range, distillation temperature and/or range, and last processing step. These criteria may allow the same CAS RNs to be applied to different hydrocarbons and petroleum-derived substances (hydrocarbon streams). This may include somewhat different compositions and applications (e.g., solvents, fuels, lubricants, etc.). Similarly, different CAS RNs can be applied to substances of similar composition and application.

Data from CAS RN 108-87-2, methyl cyclohexane, is included to demonstrate the similarity in mammalian toxicity of those cycloparaffins, contained in multi-constituent paraffins. Other multi-constituent analogs with known composition information are used to support the aquatic toxicity endpoints because of their similar mode of toxic action, non-polar narcosis.

Data for the following analogs are also presented to support the characterization of selected endpoints.

Analog (CAS RN)	Composition	Endpoint(s) Characterized	Data Location (Dossier CAS RN)
108-08-7	2,4-Dimethylpentane (99+%)	Water solubility	90622-56-3
108-87-2	Methyl cyclohexane (toluene ~3%)	Acute toxicity (inhalation) Repeat dose toxicity (inhalation)	8032-32-4
108-87-2	C7-C8, cycloalkanes (methyl cyclohexane ~99%; C8 cycloparaffins ~1%)	Acute fish toxicity	64741-49-0
565-75-3	2,3,4-Trimethylpentane (99+%)	Acute invertebrate toxicity	90622-56-3
589-81-1	3-Methylheptane (99+%)	Water solubility	90622-56-3
591-76-4	2-Methyl hexane (99+%)	Water solubility	90622-56-3
2216-34-4	4-Methyloctane (99+%)	Water solubility	90622-56-3
3522-94-9	2,2,5-Trimethylhexane (99+%)	Water solubility	90622-56-3
8032-32-4	Ligroine, C ₇ -C ₉ (n-/isoalkanes ~55%, cycloalkanes ~32%, and aromatics ~12%, which included 0.1% benzene)	Acute toxicity (inhalation) Repeat dose toxicity (inhalation)	8032-32-4
64741-63-5	Light catalytic reformed naphtha (paraffins ~86% and aromatics ~12%, which included 6%	Reproductive and developmental toxicity (inhalation)	64741-63-5

	benzene and 6% toluene)		
64741-66-8	Light alkylate naphtha (primarily C5-C9 iso-paraffins ~97%)	Repeat dose toxicity (inhalation) and reproductive and developmental toxicity (inhalation)	64742-89-8
64742-48-9	C9-C10, n-, iso-, cycloalkanes, <2% aromatics (paraffins ~99%)	Biodegradation	64742-48-9
64742-49-0	C9-C10, n-, iso-, cycloalkanes, <2% aromatics (paraffins ~98%)	Acute fish and invertebrate toxicity Alga toxicity Biodegradation	64742-49-0

Physicochemical Properties

The members of the C₇-C₉ Aliphatic Hydrocarbon Solvents Category are liquids at room temperature. The melting point values range from -127 to -51°C. The boiling points range from approximately 90 to 151°C. The vapour pressure values range from 5.9 to 61.3 hPa at 25°C. Water solubility values range from 0.12 to 28.4 mg/L with a relative density range of 0.68 to 0.76 g/cm³. The log K_{ow} values for the category members range from 3.6 to 5.7.

Human Health

Toxicokinetics, Metabolism, and Distribution

C₇-C₉ Alkanes are readily absorbed and distributed through the body. Normal alkanes are readily metabolized and excreted in urine and expired as CO₂. Iso-alkanes are less readily metabolized to a range of metabolites that are excreted in the urine. Tissue/blood ratios are greater than unity (for C₉ a brain/blood ratio of 11 and fat/blood ratios above 100 have been detected in rats), but biological concentrations decreased slightly with prolonged administration. For n-alkanes, there appears to be a very low rate of metabolism to potentially neurotoxic gamma diketones, and no such metabolism for the isoalkanes.

Metabolic profiles for C₇-C₉ alkanes correlate with toxicity results from animal studies. Low concentrations of n-nonane in the blood and high accumulation potential in the brain were seen within 1 day following inhalation exposure. In a study with n-heptane, the presence of low concentrations of the neurotoxic metabolite 2,5-heptanedione from inhalation treatment with n-heptane did not appear sufficient to produce clinical evidence of neurotoxicity. Metabolic studies with n-octane or n-nonane administered orally did not show any evidence of neurotoxic gamma diketones; results that correlate with the absence of clinical signs of neurotoxicity in repeated dose animal studies.

Comparison of excretion profiles following inhalation of the nephrotoxic isoalkane, 2,2,4-trimethylpentane (isooctane) with the non-nephrotoxic n-alkane, n-octane demonstrated that isooctane was absorbed and excreted more slowly than n-octane. These results suggested that greater exposure in the kidney to potentially toxic higher molecular weight metabolites of isooctane than to those of n-octane could be a factor in differences in nephrotoxicity between these materials.

These examples of similarities in metabolic profiles and animal toxicity for C₇-C₉ alkanes support the grouping of these substances as a category.

Acute Toxicity

The available acute toxicity data demonstrate that hydrocarbon solvent substances tested in the C₇-C₉ Aliphatic Hydrocarbon Solvents Category show a low order of toxicity by the oral, dermal, and inhalation routes of exposure. Clinical signs indicative of transient CNS depression were observed primarily with inhalation exposure at relatively high concentrations. Effects resolved within 2 days post-exposure. There was no apparent difference in inhalation toxicity (LC₅₀ values) based on chemical structure as normal, branched, cyclic or multi-constituent product.

Acute Inhalation Toxicity

Multi-constituent Paraffins Subcategory

LC₅₀ for category member C₇-C₉ (CAS RN 64742-49-0; < 0.1% aromatics) ranged from greater than 23 mg/L or greater than 33 mg/L to less than 42 mg/L in 2 separate studies. The LC₅₀ of the analog chemical ligroine (CAS RN 8032-32-4; approx. 12% aromatics) was 16 mg/L. Since the analog chemical ligroine is considered a worst-case material in this sub-category due to 12% aromatic content, the LC₅₀ value of 16 mg/L can be used for read-across purposes, a value which falls in the conservative end of the inhalation acute toxicity range.

The LC₅₀ for a cycloparaffin analog, methylcyclohexane (CAS RN 108-87-2) was greater than 40-50 mg/L demonstrating that cycloparaffins are unlikely to contribute significantly to acute toxicity in these complex substances.

Isoparaffins Subcategory

LC₅₀ values were greater than 14 mg/L for 2,2,4 trimethyl pentane (CAS RN 540-84-1) and greater than 21 mg/L for a C₇-C₉ isoalkane (CAS RN 90622-56-3).

n-Paraffins Subcategory

LC₅₀ ranged from 17 and 23.4 mg/L for n-nonane (CAS RN 111-84-2) to greater than 29.3 mg/L for n-heptane (CAS RN 142-82-5).

Acute Dermal Toxicity

The dermal LD₅₀ in rabbits was greater than 2920 mg/kg bw (multi-constituent subcategory, CAS RN 64742-49-0) and greater than 3160 mg/kg bw for iso-paraffins category (C₇-C₉ isoalkanes, CAS RN 90622-56-3 and 2,2,4-trimethylpentane, CAS RN 540-84-1). No data were available for n-paraffins.

Acute Oral Toxicity (gavage administration)

The oral LD₅₀ values in rats was greater than 15 g/kg bw for the n-paraffin, n-heptane (CAS RN 142-82-5). Two isoparaffin samples (2,2,4-trimethylpentane, CAS RN 540-84-1 and C₇-C₉ isoalkanes, CAS RN 90622-56-3) had LD₅₀ values of greater than 5 g/kg bw and 10 ml/kg bw, respectively. In the multi-constituent subcategory, category member C₇-C₉ (CAS RN 64742-49-0; < 0.1% aromatics) had an oral LD₅₀ in rats of greater than 5.8 g/kg bw and the analog methylcyclohexane (CAS RN 108-87-2) had an LD₅₀ between 4-4.5 g/kg bw in rabbits. For each subcategory, the oral LD₅₀ in rats exceeded 5 g/Kg. Since aliphatic hydrocarbons are low viscosity materials, the possibility of an aspiration hazard if orally ingested by humans should be considered.

Irritation

Members of the C₇-C₉ Aliphatic Hydrocarbon Solvents Category (tested for multi-constituent CAS RN 64742-49-0) are moderate skin irritants and cause irritation of the respiratory tract at high concentrations. No eye irritation was observed in rabbits. The category members do not have a potential to cause skin sensitization.

Repeated Dose Toxicity (Inhalation)

Five repeated dose inhalation studies conducted on C₇-C₉ aliphatic hydrocarbon substances and three analogs in the multi-constituent subcategory used to support the category consistently showed a low order of systemic toxicity. The no observed adverse effect level was often the highest concentration tested. The only generally significant effect observed in the animal inhalation studies was transient CNS depression. Male rat kidney effects consistent with alpha 2μ globulin nephropathy were observed in the isoparaffins, CAS RN 90622-56-3, 2,2,4 - trimethyl pentane (CAS RN 540-84-1), and the multi-constituent analog, light alkylate naphtha (CAS RN 64741-66-8) based on differential staining of kidney tissue. This nephropathy can be induced by exposure to long chain isoalkanes interacting with alpha 2μ globulin in the kidney, with a positive-structure activity response related to the degree of alkane branching. The content and distribution of iso-paraffins in multi-constituent substances would likely determine the expression of alpha 2μ globulin-related nephropathy. This nephropathy in male rats has been determined not to be relevant to human risk assessment. On the issue of neurotoxicity, several metabolism studies have demonstrated that the potentially neurotoxic 2,5-heptanedione is the n-heptane metabolite present in lowest concentrations in urine of rats and humans. However, none of the repeated dose studies, including a 28 week and a 16 week inhalation study with n-heptane, produced any overt signs of neurotoxicity.

Multi-constituent Paraffins Subcategory

A 13-week study employing a distillate vapour of an analog light alkylate naphtha (CAS RN 64741-66-8) compositionally similar to category member CAS RN 64742-89-8 resulted in an NOAEC of 6646 ppm, the highest dose tested (similar to OECD TG 413 with neurotoxicity endpoints). The NOAEC for the analog chemical ligroine (CAS RN 8032-32-4; approx 12% aromatics) was 1200 ppm, the highest dose tested in a 13-week study with rats or dogs (similar to OECD TG 413). Since ligroine is considered a worst-case material in this sub-category due to 12% aromatic content, the NOAEC value of 1200 ppm can be used for read-across purposes. Similar results were seen for the cycloparaffin analog, methylcyclohexane (CAS RN 108-87-2) in rabbits with an NOAEC of 1162 ppm administered for 10 weeks. Higher doses administered for differing durations to the rabbits produced body weight loss, respiratory effects, light narcosis, and convulsions prior to death. At non-lethal but high concentrations varying degrees of inflammatory responses and vascular lesions in various organs were seen with histopathology.

Iso-paraffins Subcategory

NOAEC for a C₇-C₉ isoalkane (CAS RN 90622-56-3) in a 13-week study in rats was 1180 ppm, the highest dose tested. There was no treatment related mortality and clinical/systemic findings were unremarkable with the exception of male rat nephropathy, which is not considered relevant to human.

Supplemental information: Numerous studies have been performed by the oral route and one subchronic study by inhalation (Short et al, 1989a) to explore the nephrotoxic activity of 2,2,4-trimethyl pentane (CAS RN 540-84-1) and alpha 2μ globulin (IRIS, 2007). Since these studies are often single dose levels and are not conducted according to guidelines and do not provide NOAEC values they are cited here to confirm the alpha 2μ globulin mediated nephrotoxicity induced by 2,2,4-trimethyl pentane.

n-Paraffins Subcategory

NOAEC values of one 28-week and one 16 week study in rats via inhalation with n-heptane (CAS RN 142-82-5) demonstrated no adverse effects at a dose of 1500 [only dose level tested – 16 weeks] or a maximum dose of 2970 ppm [highest dose tested, similar to OECD TG 413] respectively. In the 28-week study (NOAEC = 2970 ppm) labored or rapid breathing, slight prostration were observed during the first week. Other in-chamber clinical signs abated by the end of the second week of study. The NOAEC in a 13-week study for n-nonane (CAS RN 111-84-2) [protocol similar to OECD TG413] was 590 ppm [mid-dose] with a LOAEC of 1600 ppm [highest dose] based on decreased body weight gain and clinical signs, which included salivation and lacrimation, and mild loss of coordination and fine tremors during the first 4 days. Although a decrease in NOAEC was seen as the carbon number increased from 7 (n-heptane) to 9 (n-nonane), these data do not appear to reflect a major difference based on chemical structure.

Mutagenicity

All genetic toxicity studies were performed with category members, no analogs were employed. In vitro genotoxicity testing of C₇-C₉ aliphatic hydrocarbon solvent substances conducted in both bacterial and mammalian cells, including human cells, showed no indication of genotoxic activity. The dominant lethal study on the isoparaffinic hydrocarbon, CAS RN 90622-56-3 in this category showed no evidence of in vivo germ cell genotoxicity. A multi-constituent sub-category member, CAS RN 64742-49-0 did not induce cytogenetic damage in a mouse micronucleus assay (OECD TG 474), and genetic damage and repair (UDS) was not observed in laboratory animals treated with the isoparaffin 2,2,4-trimethylpentane (CAS RN 540-84-1). Results of these studies indicate that members of the C₇-C₉ Aliphatic Hydrocarbon Solvents Category do not cause genotoxicity in laboratory animals.

Reproductive and Developmental Toxicity

A weight-of-evidence approach using available data from the inhalation developmental toxicity study on a C₈ isoparaffinic substance (CAS RN 90622-56-3) and inhalation reproductive/developmental toxicity screening tests on two multi-constituent analog test substances (CAS RN 64741-63-5 and CAS RN 64741-66-8) combined with absence of adverse effects on reproductive organs from repeated exposure studies show no evidence that exposure to substances in the C₇-C₉ Aliphatic Hydrocarbon Solvents Category results in reproductive or developmental toxicity.

Reproductive Toxicity***Multi-constituent Paraffins Subcategory***

Reproductive toxicity studies are available on two analogs.

Light catalytic reform naphtha vapour (CAS RN 64741-63-5), an analog containing approximately 4% n-hexane, 1% n-heptane, 11-12 % C₇-C₉ aliphatics and 12% aromatics (6% benzene and 6% toluene) was tested in a combined reproductive/developmental toxicity study according to modified OECD TG 421. The NOAEC for male parental effects was 2500 ppm (11.6 mg/L) based on increased relative liver to body weight ratio at 7500 ppm (34.9 mg/L). Parental male rats also showed increases in absolute and relative kidney weights consistent with alpha 2μ-globulin nephropathy but no differential staining was performed. The NOAEC for parental female (maternal toxicity) and developmental/reproductive effects was 7500 (34.9 mg/L), the highest dose tested.

The NOAEC for light alkylate naphtha vapour (CAS RN 64741-66-8, an analog containing ~40% C₇-C₉ isoparaffins) in the reproductive/developmental screening test was 8000 ppm (24.7 mg/L) the highest dose tested. The absence of reproductive toxicity at the high exposure concentration of 8000 ppm (24.7 mg/L) of light alkylate naphtha vapour comprised of ~40% C₇-C₉ isoparaffins indicates that C₇-C₉ aliphatic hydrocarbons do not adversely affect reproduction. Negative results from the light catalytic reformed naphtha (CAS RN 64741-63-5) vapour study also demonstrated a NOAEC value of 7500 ppm (34.9 mg/L) for reproductive endpoints. Although this chemical vapour contained approximately 12% C₇-C₉ aliphatics, the

absence of adverse reproductive effects supports the light alkylate naphtha results and further demonstrates that the presence of 4% n-hexane or 12% aromatics did not induce reproductive toxicity in this system.

No adverse effects were reported in reproductive organs (testes, epididymides, ovaries) in inhalation repeat dose studies for the multi-constituent subcategory analog chemicals light alkylate naphtha (CAS RN 64741-66-8), ligroine (CAS RN 8032-32-4, 12% aromatics) in rats or methylcyclohexane (CAS RN 108-87-2) in rabbits.

The absence of reproductive or developmental toxicity for these worst-case materials supports the position that chemicals in the C₇-C₉ Aliphatic Hydrocarbon Solvents Category do not cause any developmental or reproductive toxicity.

Isoparaffins Subcategory

No reproductive toxicity studies are available. No adverse effects were reported in reproductive organs (testes, epididymides, ovaries) examined in a 12- week inhalation repeat dose study with CAS RN 90622-56-3.

n-Paraffins Subcategory

No reproductive toxicity studies are available. No adverse effects were reported in reproductive organs (testes, epididymides, ovaries) examined in a 28-week inhalation repeat dose studies with n-heptane (CAS RN 142-82-5) or in a 13-week inhalation repeat dose study with n-nonane (CAS RN 111-84-2).

Developmental Toxicity

Multi-constituent Paraffins Subcategory

See reproductive toxicity endpoint above.

Isoparaffins Subcategory

A standard inhalation teratology study (Segment II) on C₇-C₉ isoalkane, CAS RN 90622-56-3, showed no evidence of embryonic or teratogenic in rats. The NOAEC was 1200 ppm, the highest dose tested.

n-Paraffins Subcategory

No data are available; read-across will be used from the multi-constituents subcategory.

The absence of embryonic or teratogenic toxicity in the standard developmental study (Segment II) with the isoparaffin CAS RN 90622-56-3 considered in conjunction with the absence of developmental toxicity in the reproductive/developmental studies with the multi-constituent analog substances CAS RN 64741-66-8 and CAS RN 64741-63-5 (modified OECD TG 421) indicate that members of the C₇-C₉ aliphatic hydrocarbons solvents category are unlikely to be developmental toxicants.

Carcinogenicity

No standard carcinogenicity studies are available with members of the category. Negative results were found in a non-guideline 2-year dermal carcinogenicity study in mice with light alkylate naphtha (LAN, CAS RN 64741-66-8 - analog). No category members contain benzene levels above 0.01%.

Neurotoxicity

No overt clinical signs of neurotoxicity were induced by C₇-C₉ aliphatic hydrocarbon solvent substances in animal repeated dose toxicity studies although transient CNS depression was observed in acute and repeated dose toxicity studies. Measurement of various parameters of neurobehavioral response in showed minimal to no adverse effects and in all cases values were comparable to controls after a recovery period. Studies in experimental animals do not produce peripheral neuropathies using n-heptane. However data from a tire worker study and a case-report suggested “minimal” peripheral neuropathy may be induced by exposure to high concentrations of solvents including n-heptane although the effects among tyre workers were subclinical and expressed by electrophysiological data and a separate case report involved exposure to mixed solvent glue. Another worker study at lower exposure levels showed no clinical signs of neurotoxicity. Overall the substances in this category do not produce neurotoxic metabolites similar to 2,5-heptanedione from n-heptane and are unlikely to present a hazard as neurotoxicants.

These chemicals may possess properties indicating hazard for human health (moderate skin irritation, irritation of the respiratory tract, and transient CNS effects at high exposure concentrations). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

Members of the C₇-C₉ Aliphatic Hydrocarbon Solvents Category are not expected to undergo hydrolysis in

the environment, due to the lack of hydrolyzable functional groups. All chemicals in this category have the potential to rapidly volatilize from surface waters, based on Henry's Law constants (HLC) representing volatility for category members that range from 29,559 to 302,171 Pa-m³/mole. In the air, category members have the potential to degrade through indirect photolytic processes mediated primarily by hydroxyl radicals ([•]OH) with calculated degradation half-lives ranging from 4.8 to 27.7 hours or 0.4 to 2.3 days, based on a 12-hr day and a [•]OH concentration of 1.5 x 10⁶ [•]OH/cm³.

Guideline and non-guideline studies are available to evaluate the biodegradability of category members. Members of the n-paraffins subcategory have the potential to biodegrade rapidly based on results that support their characterization as readily biodegradable (CAS RN 142-82-5, CAS RN 111-65-9, CAS RN 111-84-2). In comparison, members of the iso- subcategory are considered as not readily biodegradable based on results for one of the multi-constituent isoparaffinic substances, which was shown not to be readily biodegradable, 22.4% by day 28 using OECD TG 301F (CAS RN 90622-56-3). Multi-constituent subcategory members are expected to be readily biodegradable based on results from several studies that resulted in greater than 60% biodegradation after 28 days using OECD TG 301F, but not meeting the 10-day window criterion (CAS RN 92045-53-9, CAS RN 64742-49-0 analog, CAS RN 64742-48-9 analog). The result for each multi-constituent substance (UVCB) characterizes the biodegradability of that substance as a whole, but it does not suggest that each constituent of the UVCB is equally biodegradable. As with all ready biodegradation test guidelines, the test system and study design used with these substances (OECD TG 301F) is not capable of distinguishing the relative contribution of the substances' constituents to the total biodegradation measured (constituents with higher branching/cyclic structures may degrade to a lesser extent than linear and less branched structures).

Mackay Level III modeling indicates that category members partition primarily to the air and water compartments when an equal emission rate (1000 kg/hr) to the air, water, and soil compartment is assumed. When release occurs only to either the air or water compartment, members are indicated by the model to partition largely to the compartment to which they are released. When release occurs only to the soil compartment, members are indicated in the modeling to partition to the air and soil compartments. For three representative chemicals from this category, Level III percent partitioning results using an emission rate of 1000 kg/hr to each of the air, water, and soil compartments are as follows:

n-Octane (n-Paraffins Subcategory)

- Air 10.3
- Water 33.9
- Soil 11.7
- Sediment 44.1

2,2,4-Trimethyl Pentane (Iso-Paraffins Subcategory)

- Air 20.2
- Water 64.3
- Soil 1.9
- Sediment 13.6

1,2,4-Trimethyl Cyclohexane (Multi-constituent Subcategory)

- Air 12.7
- Water 46.1
- Soil 26.1
- Sediment 15.1

When released primarily to the air compartment, the primary mode of removal would be via photodegradation. Although the substances and their chemical constituents demonstrate a range of water solubility with some constituents having relatively low solubility, wet deposition of category chemical constituents is not likely to play a significant role in their atmospheric fate because of their rapid photodegradation. Volatilization to the air can contribute to the loss of category chemical constituents from aqueous and terrestrial habitats.

Category members are expected to sorb to organic matter in soil, sediment, and wastewater solids based on estimated log K_{oc} values ranging from 3.0 to 4.7. Category members have a potential to bioaccumulate, based on a measured BCF value of 199 in a mussel (*Mytilus edulis*) for n-octane that used a limited study design and calculated BCF values (BCFBAF v3.0 model from the EPI Suite Program) that range from 105 (n-nonane) to 1216 (n-octane) (log BCF = 2.02 to 3.08) for the single substances. These predictions capture the range of log K_{ow} within the category and do not consider biotransformation. These data suggest a low to moderate order of bioaccumulative potential for category members.

Aquatic Toxicity

Acute Toxicity

Sufficient data are available to characterize the fish and invertebrate acute toxicity and alga toxicity of the C₇-C₉ Aliphatic Hydrocarbon Solvents Category. Category members are expected to exhibit 48- to 96-hour effect concentrations for the three subcategories within a relatively narrow range based on measured and calculated results that range from 0.04 to 1.6 mg/L for the n-paraffins subcategory, 0.11 to 0.4 mg/L for the iso-subcategory, and 0.13 to 0.7 mg/L for the multi-constituent subcategory.

Multi-constituent Subcategory

There are measured aquatic toxicity data for five members of the multi-constituent subcategory and two analog substances. Measured 96-hr fish LC₅₀ values range from 0.3 to 1.3 mg/L. Measured 48-hr daphnid EC₅₀ values range from 0.7 to 0.9 mg/L. The algae effects data are from three studies, one of which reported measured values for a substance that is largely C₉ to C₁₀. The measured 72-hr EC₅₀ value is 0.4 mg/L.

There are measured chronic aquatic toxicity data for one member of the multi-constituent subcategory that can be used to characterize the chronic toxicity of category members. The 21-day NOELR value was 1.0 mg/L and the NOEC value was 0.17 mg/L, based on reproduction. The 21-day LOELR value was 2.0 mg/L and the LOEC value was 0.32 mg/L, based on reproduction. The 21-day EL₅₀ and EC₅₀ values from this study were 1.6 and 0.23 mg/L, respectively. These data are representative of the category as a whole because the substance contains the range of carbon numbers and hydrocarbon types found in the three subcategories.

Iso-Paraffins Subcategory

There are calculated and measured aquatic toxicity data for the single analog chemical substance, 2,3,4-trimethylpentane (2,3,4-TMP) that are used as read-across data to 2,2,4-trimethylpentane (2,2,4-TMP), and measured acute aquatic toxicity data for hydrocarbons, C₇-C₉, isoalkanes (CAS RN 90622-56-3). Additionally, data from the multi-constituent subcategory can also be used as read-across data because these substances contain significant amounts of isoparaffins and have carbon number ranges that are similar to and overlap with the two multi-constituent members, CAS RN 70024-92-9 and CAS RN 90622-56-3. Calculated and measured 96-hr fish LC₅₀ values for two subcategory members range from 0.11 to 1.28 mg/L. Measured 48-hr daphnid data, 0.2 mg/L, and 96-hr LC₅₀ marine invertebrate data, 0.4 and 0.9 mg/L, are available for 2,3,4-TMP. These data are consistent with the data identified for the multi-constituent subcategory, which is expected given the reasons mentioned above. The alga data used to characterize the iso-paraffin subcategory are from the multi-constituent subcategory with a 72-hr EC₅₀ value of 0.4 mg/L.

n-Paraffins Subcategory

The acute aquatic toxicity of the three members of the n-paraffins subcategory can be characterized using calculated and measured data for these substances, as well as read-across data from the iso- and multi-constituent subcategories. Calculated acute data for fish (96-hr) are 0.49, 0.14, and 0.06 mg/L, for n-heptane, n-octane, and n-nonane, respectively. Although there are no measured data for these three members, the use of the calculated data are supported by the measured values from the iso- and multi-constituent subcategories, which range from 0.11 to 1.3 mg/L, as well as the measured daphnid data. The daphnid 48-hr effect values are 1.5, 0.3, and 0.2 mg/L, for n-heptane, n-octane, and n-nonane, respectively. All other measured invertebrate results (96-hr values) that show effects are for two marine species and range between 0.1 to 0.2 mg/L for the three paraffins. Calculated toxicity data for green alga (72-hr) are 0.56, 0.24, and 0.14 mg/L, for n-heptane, n-octane, and n-nonane, respectively. Although there are no measured data for these three members, the use of the calculated data are supported by the measured values from the multi-constituent subcategory, which exhibited a low 72-hr EC₅₀ value of 0.4 mg/L, as well as the measured acute fish and daphnid data that ranged from 0.06 to 1.5 mg/L.

Chronic Toxicity

There are measured chronic aquatic toxicity data for one member of the multi-constituent subcategory, containing C₇-C₉ n-alkanes, isoalkanes, and cyclics. The 21-day LOEC value was 0.32 mg/L and the NOEC value was 0.17 mg/L, based on reproduction. The 21-day EC₅₀ value from this study was 0.23 mg/L, based on survival. Additional estimated daphnid chronic toxicity data for n-heptane, 2,2,4-trimethylpentane, and nonane range from 0.23 to 0.06 mg/L.

Chemicals in this category possess properties indicating a hazard for the environment (acute toxicity for fish, invertebrates, and algae; chronic toxicity for invertebrates values <1 mg/L). Category members have a low to moderate bioaccumulative potential. Multi-constituent and n-paraffin category members are readily biodegradable, while isoparaffinic members are not. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Production/Use/Exposure

Production

As reported to the U.S. Environmental Protection Agency for the year 2005, companies produced or imported the following volumes of C₇-C₉ hydrocarbon solvents:

- n-Heptane, CAS RN 142-82-5: 4500-22,500 metric tons (10 million to < 50 million pounds)
- n-Octane, CAS RN 111-65-9: 450-4500 metric tons (1 million to < 10 million pounds)
- n-Nonane, CAS RN 111-84-2: 225-<450 metric tons (500,000 to < 1 million pounds)
- Pentane, 2,2,4-trimethyl-, CAS RN 540-84-1: 45,000-225,000 metric tons (100 to <500 million pounds)
- Alkanes, C₇₋₈, iso-, CAS RN 70024-92-9: 450-4500 metric tons (1 million to < 10 million pounds)
- Alkanes, C₇₋₁₀, iso-, CAS RN 90622-56-3: No data
- Lignoine; petroleum ether, CAS RN 8032-32-4: < 225 metric tons (< 500,000 pounds)
- Naphtha, (petroleum), light catalytic reformed, CAS RN 64741-63-5: 450,000 or greater metric tons (1 billion pounds or greater)
- Naphtha, (petroleum), solvent-refined light, CAS RN 64741-84-0: 450,000 or greater metric tons (1 billion pounds or greater)
- Naphtha, (petroleum), hydrotreated heavy, CAS RN 64742-48-9: 450,000 or greater metric tons (1 billion pounds or greater)
- Naphtha, (petroleum), hydrotreated light, CAS RN 64742-49-0: 450,000 or greater metric tons (1 billion pounds or greater)
- Solvent naphtha, (petroleum), light aliphatic, CAS RN 64742-89-8: 225,000 to < 450,000 metric tons (500 million to < 1 billion pounds)
- Naphtha (petroleum), hydrodesulfurized light, dearomatized, CAS RN 92045-53-9: No data

Use

Hydrocarbon solvents in the C₇-C₉ range have several applications including uses in paints, coatings, and adhesives. They are also used as degreasers and gasoline additive diluents, and in chemical reactions. However, because of their evaporative properties the predominant commercial use of many category members is in paints and coatings.

Common names for substances in the C₇-C₉ Aliphatic Hydrocarbon Solvents Category include, heptane, isooctane, Varnish Makers & Painters Naphtha (VM&P naphtha), and special boiling point (SBP) aliphatic solvent. Heptane is used to purify pharmaceuticals and isooctane is used to carry out synthetic organic chemical reactions in the pharmaceutical industry that are difficult or impossible in other solvents. Another use of category members is indicated by the generic name, Lacquer Diluent, which identifies an application where the purpose of the solvent is to dilute and reduce the cost after a resin has been dissolved in the primary active solvent. Lacquers are still commonly used for wood furniture coatings. VM&P naphtha is used primarily in industrial coatings and finishes. Other process applications include printing (press operation and ink mixing), adhesion, and fiberglass and polyurethane molding.

Exposure

The sources for potential environmental exposure to C₇-C₉ aliphatic hydrocarbon solvent substances could include releases from chemical and petroleum manufacturing/processing facilities, releases from facilities that use C₇-C₉ aliphatic hydrocarbon solvent substances, releases from consumer products that include C₇ to C₉ aliphatics, automotive sources (fuel evaporate emissions and exhaust), and possibly biogenic and combustion sources.

C₇-C₉ Aliphatic Hydrocarbon Solvents Category members are used in paints, coatings, and adhesives, and as chemical reaction media, degreasers, and gasoline additive diluents. However, the predominant commercial use of category members is in paints and coatings where their performance is based on their evaporative properties. Therefore, the primary route of exposure is expected to be inhalation from evaporative emissions resulting from these uses.

Occupational exposure includes workers exposed during the manufacture of the product stream and includes office workers. In general, occupational (manufacturing) exposure to category members is well within applicable exposure limits, and office air data are comparable to ambient residential levels.

A database was compiled of occupational air concentration data from approximately 100 journal articles, which were selected from an initial list of 22,000 papers, and the hydrocarbon solvent data published from those articles. The authors selected 35 "indicators", defined as constituents of, or surrogates for category members. They included heptane, VM&P Naphtha (Hydrocarbons, C₇-C₉, n-alkanes, isoalkanes, cyclics), octane, and nonane; expressing concentrations as a fraction of the TLV (threshold limit value), the authors reported values for these 4 indicators as less than 3, 4, 1, and 1%, respectively. In general, hydrocarbon levels have decreased four-fold over the period 1960 to 1998 and the average level has been below 40% of the TLV

since 1980.

One company supplied industrial hygiene data for category members covering the period 1996 to 2003. The tasks associated with these data were either operations or distribution, which involved loading operations. The geometric mean for the category member concentration in air was below 1 (both ppm and mg/m³) with a range of 0.001 to 12 ppm (0.004 to 56 mg/m³).

Hodgson and Levin (2003) reported air concentrations of some of the C₇-C₉ category substances (n-heptane, n-octane, n-nonane, 2,2,5-trimethylhexane, and methylcyclohexane) in office buildings. They reported central tendency (geometric mean or median) and maximum concentration. Of the C₇ to C₉ category chemicals detected in office buildings, all concentrations were low (under 2 ug/m³). Maximum values were reported as 2.9, 60, 29, 2.9, 3.1, and 1.6 ug/m³ for n-heptane, n-octane, n-nonane, 3-methylhexane, methylcyclohexane, and 2,2,5-trimethylhexane, respectively. These levels are only slightly higher than those reported for residences.

Qualitative exposure data by occupational category is provided by the National Household Products Database. These data indicate that workers in a variety of industries are potentially exposed to products containing C₇ to C₉ category substances. These include those manufacturing or otherwise exposed to adhesives and sealants, paints and coatings, vinyl flooring, ceiling tiles, cabinetry, wall coverings, HVAC insulation, construction, maintenance, landscaping, pesticides, and auto products.

Non-occupational exposure includes ambient outdoor air exposure and indoor air exposure in the home. Such exposures could occur from using consumer products containing the solvent and from indirect sources including ambient air, drinking water, food, and natural sources. A potentially significant source of exposure unrelated to hydrocarbon solvents is from petroleum fuels and transportation.

APPENDIX (will be removed when SIAP and SIAR are merged)

Table 1. Predominant carbon number range and paraffin class percent composition of commercial solvents under CAS RNs in the iso-paraffins and multi-constituent subcategories of the C₇-C₉ Aliphatic Hydrocarbon Solvents Category

Subcategory and CAS Number	Carbon Number / Range	n-, Iso-Paraffins (%)	Cyclo-paraffins (%)
Iso-Paraffins			
70024-92-9	7-8	100	0
90622-56-3	7-9	100	0
Multi-constituent*			
8032-32-4	7-9	~40-42	~56-57
64741-63-5	7	~90	~10
64741-84-0	6-8	na	na
64742-48-9	7-10	~40-52	~44-52
64742-49-0	6-9	na	na
64742-89-8	7-10	~1-91	~9-99
92045-53-9	7	na	na

na not available

* data only pertain to category members with boiling-point ranges within 90-151 degrees Celsius.

Table 2. Representative characteristics of C₇-C₉ aliphatic hydrocarbon solvents

Property or Characteristic	Value Range or Constituents
Predominant carbon number range	7 to 9
Distillation range, °C (°F)	~90 to ~151 (194 to 304)
Aromatics (%)	<1, typical (a few members may contain up to approximately 3.0%)
n-Hexane (%)	<0.1, typical (a few members may contain up to approximately 5%)
Benzene (ppmv)	<100
Sulfur (ppmv)	<100
Typical n-paraffins*	n-Heptane n-Octane n-Nonane
Typical iso-paraffins*	2-Methylhexane 2,4-Dimethylpentane 3-Methylheptane 2,2,4-Trimethylpentane 2-Methyloctane 4-Methyloctane
Typical cyclo-paraffins* (naphthenics)	Methylcyclohexane Ethylcyclohexane 1,2,4-Trimethylcyclohexane 2,2,5-Trimethylcyclohexane

- * typical constituents representing multi-constituent category members were selected on the basis of carbon number, chemistry/structure, measured distillation ranges, and hydrocarbon process (distillation) knowledge

Table X (# to be determined once placed in SIAR). A comparison between typical C₇-C₉ Aliphatic Hydrocarbon Solvents Category member parameters, study summary compositions, and production parameters listed for multi-constituent substances in technical specification sheets and MSDSs.

CAS RN	Name	Boiling Range °C (°F)	Aromatics* (% wt)	Benzene (% wt)	n-Hexane** (% wt)	Paraffins, n-, iso- (% wt)	Paraffins, cyclo- (% wt)	Composition Notes (% wt)
	C ₇ -C ₉ Aliphatic Hydrocarbon Solvents Category	~90 to ~151 (~194 to ~304)	<1 (typical)	<0.01 (typical)	<0.1 (typical)	~1 to ~99	~1 to ~99	n-, iso-, and/or cyclo- paraffins that fall primarily within the C7 to C9 range
64742-49-0	Hydrocarbons, C6- C7, n-alkanes, isoalkanes, cyclics, <5% n- hexane (European)	87 to 101 (189 to 214)	<0.0005	0.0003	3	~65	~35	na
	Hydrocarbons, C7, n-alkanes, isoalkanes, cyclics	na	<0.0005	na	na	~67	~33	C6 paraffins ~3 C7 paraffins ~95 C8 paraffins ~1
	Hydrocarbons, C7, n-alkanes, isoalkanes, cyclics (European)	95 to 99 (203 to 210)	<0.0005	<0.0003	<0.1	~70	~30	na
	Hydrocarbons, C7, n-alkanes, isoalkanes, cyclics (Asia Pacific)	94 to 98 (203 to 210)	<0.1	<0.01	<1.0	~70	~30	na
	Hydrocarbons, C7- C9, n-alkanes, isoalkanes, cyclics (European)	100 to 120 (212 to 248)	~0.0002	0	0	na	na	C7 n-, iso- paraffins ~27 C7 cycloparaffin ~28 C8 paraffins ~45
	Hydrocarbons, C7- C9, n-alkanes, isoalkanes, cyclics (European)	98 to 140 (208 to 284)	~0.04	0	~1	na	na	C6 n-, iso- paraffins ~2 C6 cycloparaffin ~2 C7 n-, iso- paraffins ~17 C7 cycloparaffin ~14 C8 paraffins ~38 Unk paraffins ~37
	Hydrocarbons, C7-	na	na	na	na	~52	~43	C7 paraffins <1.0

	C9, n-alkanes, isoalkanes, cyclics (U.S.)							C8-C9 n-paraffins ~14 C8-C9 isoparaffins ~38 C8-C9 cycloparaffins ~43 Unk paraffins ~4
	Hydrocarbons, C7-C9, n-alkanes, isoalkanes, cyclics (U.S.)	129 to 144 (265 to 291)	~0.5	<2x10 ⁻⁷	na	~43	~57	C7-C9 n-, iso, paraffins ~43 C7-C9 cycloparaffins ~57
	Hydrocarbons, C7-C9, n-alkanes, isoalkanes, cyclics	na	~0.1	na	na	~63	~37	C7 paraffins ~32 C8 paraffins ~57 C9 paraffins ~11
	Hydrocarbons, C7-C9, n-alkanes, isoalkanes, cyclics (European)	106 to 136 (223 to 277)	<0.0005	<0.0001	<0.1	~65	~35	na
64742-89-8	Hydrocarbons, C7-C8, cyclics	na	na	na	na	~1-5	~95-99	C7 n-, iso- paraffins ~1-5 C7-C8 cycloparaffins ~95-99
	Hydrocarbons, C7-C9, n-alkanes, isoalkanes, cyclics	na	na	na	na	~47	~51	C6 paraffins ~2 C7 paraffins ~74 C8 paraffins ~22 Unk paraffins ~2
	Hydrocarbons, C7-C9, n-alkanes, isoalkanes, cyclics	na	na	na	na	~46	~48	C7 paraffins ~6 C8 paraffins ~49 C9 paraffins ~39 Unk paraffins ~6
64742-48-9	Hydrocarbons, C8-C10, cyclics (European)	na	na	na	na	~1	~99	C8 cycloparaffins ~2% C9 cycloparaffins ~85% C10 cycloparaffins ~11% C11 cycloparaffins ~1%
92045-53-9	Hydrocarbons, C7, n-alkanes, isoalkanes, cyclics	na	na	na	na	~55	~45	C7 n-paraffin ~25 C7 isoparaffins ~30 C7 cycloparaffin ~45
	Hydrocarbons, C7, n-alkanes, isoalkanes, cyclics (European)	94 to 99 (201 to 210)	~0.001	na	na	~78	~22	C6 cycloparaffin ~1 C7 n-paraffin ~30 C7 isoparaffins ~48 C7 cycloparaffin ~21

90622-56-3	Hydrocarbons, C7-C9, isoalkanes	na	na	na	na	na	na	na	C7 isoparaffins ~3% C8 isoparaffins ~97%
	Hydrocarbons, C7-C9, isoalkanes	na	na	na	na	na	na	na	C8 isoparaffins ~68% C9 isoparaffins ~22% C10 isoparaffins ~10%
	Hydrocarbons, C7-C9, isoalkanes (European)	95 to 108 (203 to 226)	~0.002	na	na	na	~99	~1	C7 isoparaffins ~3% C8 isoparaffins ~97%
	Hydrocarbons, C7-C9, isoalkanes (European)	113 to 143 (235 to 289)	~0.005	na	na	na	100	0	C8 isoparaffins ~72% C9-C10 isoparaffins ~28%

* a few members may contain up to approximately 3%

** a few members may contain up to approximately 5%

na = not available

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	103-09-3
Chemical Name	2-Ethylhexyl Acetate
Structural Formula	CH ₃ -C(=O)-CH-CH(CH ₂ -CH ₃)-CH ₂ -CH ₂ -CH ₂ -CH ₃

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Rationale**

Several of the health endpoints for 2-ethylhexyl acetate that are dependent upon systemic exposure make use of data from 2-ethylhexanol experiments. Acetate esters of primary alcohols undergo rapid hydrolysis, catalyzed by esterases and proteases found in mammalian tissues and gastric fluids. The rapid and complete hydrolysis of 2-ethylhexyl acetate to 2-ethylhexanol has been demonstrated to occur *in vitro* within blood (half life of 2.3 minutes) and *in vivo*. The use of 2-ethylhexanol studies to identify hazards associated with 2-ethylhexyl acetate exposure are limited to toxicity endpoints dependent upon systemic exposure (e.g. repeated exposure, reproductive and developmental toxicity carcinogenicity) and not for direct exposure to the parent compound (e.g. eye and skin irritation). Therefore, toxicity data from studies conducted with 2-ethylhexanol have been used to identify the these hazards associated with 2-ethylhexyl acetate exposures.

Physical-Chemical Properties

2-Ethylhexyl acetate is a liquid at standard temperature and pressure, with a boiling point of 199 °C and a melting (freezing) point of -93 °C. It is less dense than water with a specific gravity of 0.8718 g/cm³ at 20°C. The solubility limit in water has been measured as 3.9 mg/L at 20°C. 2-Ethylhexyl acetate is combustible with a flash point of 76 °C and a flammability range of 0.76 to 8.14% by volume. It has a vapour pressure of 0.31 hPa at 25 °C. Given its solubility limits of 3.9 mg/L at 20 °C and its molecular weight of 172.27 g/mole, the Henry's law constant at 25 °C has been calculated to be 1.51 x 10⁻³ atm-m³/mole (153.0 Pa-m³/mol). An octanol/water partitioning coefficient (Log K_{ow}) value of 3.74 has been estimated for 2-ethylhexyl acetate.

Human Health

The hydrolysis of 2-ethylhexyl acetate to 2-ethylhexanol is rapid as demonstrated with *in vitro* and *in vivo* experiments. The subsequent metabolism of 2-ethylhexanol to 2-ethylhexaldehyde is presumed to occur with subsequent oxidation of the aldehyde intermediate to 2-ethylhexanoic acid. Metabolism and toxicokinetics studies with 2-ethylhexanol have demonstrated the presence of 2-ethylhexanoic acid in the plasma as well as glucuronide conjugates and oxidation products of 2-ethylhexanoic acid metabolism in the urine following intravenous, dermal and oral exposures. Elimination of 2-ethylhexanol metabolites following oral exposure was complete within 24 hours. Comparison of 2-ethylhexanol and 2-ethylhexanoic acid metabolic/toxicokinetics information and toxicity databases suggests that the metabolic processes necessary to convert 2-ethylhexanol to 2-ethylhexanoic acid explain the difference in toxicity of these chemicals. 2-Ethylhexanol toxicity information is most relevant for 2-ethylhexyl acetate hazard identification since 1) 2-ethylhexanol is the product of the initial hydrolysis reaction of 2-ethylhexyl acetate and 2) the limited toxicity information for 2-ethylhexyl acetate suggests a similar toxicity profile with 2-ethylhexanol. Metabolism data in humans for 2-ethylhexyl acetate is not available.

The oral LD₅₀ value for 2-ethylhexyl acetate is >3200 mg/kg bw in rats and mice, with weakness and ataxia reported at this dose level. The dermal LD₅₀ in rabbits is >20 ml/kg (17,436 mg/kg bw); the substance was applied undiluted and under occlusion for 24 hours followed by a 10-day observation

interval. Inhalation exposure of rats (3/group) for 6 hours caused no deaths at 7.8 mg/L (1106 ppm). 2-Ethylhexyl acetate is a mild skin irritant and a mild eye irritant in rabbits. No respiratory irritation has been reported in the acute inhalation study in rats. 2-Ethylhexyl acetate was negative for skin sensitisation when applied as 4% in petrolatum in humans.

There were no repeated dose toxicity studies conducted with 2-ethylhexyl acetate. There are thirteen week oral and inhalation studies available with 2-ethylhexanol. The NOEC from the thirteen week inhalation rat study with 2-ethylhexanol was 0.639 mg/L (120 ppm; the highest vapour concentration achievable). A thirteen week gavage study with 2-ethylhexanol in rats caused stomach irritation, increased reticulocytes and liver effects (increased liver weight, decreased serum cholesterol, albumin and total protein, liver histopathology (reduced number and incidence of fatty infiltration of the peripheral lobules) and peroxisome proliferation) in the 500 mg/kg bw/day male and female rats. Milder liver effects indicative of peroxisome proliferation was noted in male and female rats at 250 mg/kg bw/day. The NOAEL in male and female rats was 125 mg/kg bw/day. A similar study in mice produced a NOAEL of 125 mg/kg bw/day based on increases in relative liver weights in male mice at the 250 mg/kg bw/day dose level. The ability of 2-ethylhexanol to induce hepatic peroxisome proliferation in rats and mice following 14 days of oral exposure has been demonstrated.

In vitro studies demonstrate that 2-ethylhexyl acetate was not mutagenic to *Salmonella typhimurium* or *Escherichia coli* at concentrations up to 5000 µg/plate with and without metabolic activation. In addition, 2-ethylhexanol was not genotoxic in four Ames assays, an *in vitro* cell transformation assay, a mouse lymphoma assay, a CHO mutation assay and was negative for unscheduled DNA synthesis in primary rat hepatocytes. *In vivo*, 2-ethylhexanol did not induce an increase in micronuclei in peripheral erythrocytes and was negative in a dominant lethal assay in mice. 2-Ethylhexanol also did not cause chromosomal aberrations in CHO cells at concentrations up to 500 µg/mL, with and without metabolic activation. 2-Ethylhexyl acetate and the primary metabolite, 2-ethylhexanol, is not genotoxic *in vitro* or *in vivo*.

In oral (gavage) assays with 2-ethylhexanol in rats using dose levels of 0, 50, 150 or 500 mg/kg bw/day (24 months), reduced body weight gain was noted in rats in the 150 (males, 11%; females, 9%) and 500 (males, 23%; females, 21%) mg/kg bw/day dose groups. Laboured breathing and poor condition was noted in the 500 mg/kg bw/day animals. Dose-related increases in relative liver, stomach, and kidney weights were noted at sacrifice in the 150 and 500 mg/kg bw/day groups. Mortality in female rats (52%) was markedly increased at 500 mg/kg bw/day. The sum of the hepatocellular adenomas and carcinomas was less in the male treated groups (7) than in the two male control groups (8). The incidence of hepatocellular carcinomas in the female water control group was 1, in the 500 mg/kg bw/day was 0, and were a total of three in the 50 and 150 mg/kg bw/day groups combined. 2-Ethylhexanol was not oncogenic in rats.

In oral (gavage) assays with 2-ethylhexanol in mice, using dose levels of 0, 50, 200 or 750 mg/kg bw/day (18 months), no dose-related changes were noted in mice receiving 50 or 200 mg/kg/day. At 750 mg/kg/day, reduced body weight gain (12% in males and 14% in females), decreased feed consumption (9% in males and 12% in females) and increased mortality were noted (30% in males and females by weeks 79-81). Increases in relative kidney (females only), liver (females only) and stomach weights (males and females) were noted at sacrifice in the 750 mg/kg bw/day group. The test material was not considered oncogenic in male mice. An increase in hepatocellular carcinomas in the female 750 mg/kg bw/day group was statistically significant when compared to the vehicle control group but not when compared to the concurrent water control group. This led to the conclusion that 2-ethylhexanol was considered a weak or equivocal liver carcinogen in female mice at this dose level. Interpretation of this data is complicated by the severe toxicity (increased mortality) noted in mice at the 750 mg/kg bw/day dose level, the known ability of 2-ethylhexanol to induce peroxisome proliferation in rodent liver (as a potential mechanism of action for tumour formation) and the background incidence of liver tumours in this strain of mice.

No reproductive or developmental toxicity studies were available for 2-ethylhexyl acetate. 2-Ethylhexanol is not considered a reproductive toxicant based on data from repeated exposure studies as well as *in vitro* investigations. 2-Ethylhexanol causes developmental toxicity (reduced foetal body weights (-9.5%), a single type of skeletal vertebral malformation, reduced skeletal ossification) in rats only at oral dose levels of 650 mg/kg bw/day (861 mg/kg bw/day for 2-ethylhexyl acetate), a dose level causing significant maternal toxicity. The highest dose level (1300 mg/kg bw) caused

maternal deaths, reduced feed consumption and body weight gain in the dams, increased resorptions, foetal death and decreased foetal weights and malformations in the surviving foetuses. 2-Ethylhexanol is not a developmental toxicant via the dermal (up to 2,520 mg/kg bw/day) or inhalation routes of exposure (up to 0.85 mg/L) in rats. There were no treatment-related histological changes in either the testes or ovaries (in mice and rats) after 13 weeks of treatment with 2-ethylhexanol at dosages up to 500 mg/kg bw/day.

2-Ethylhexyl acetate possesses properties indicating a hazard for human health (mild skin and eye irritation). Adequate screening-level data are available to characterize the hazard for the human health purposes of the OECD HPV Programme.

Environment

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with an estimated half-life of 11.723 hours. Abiotic hydrolysis is predicted to occur with an estimated half-life of 121 days at pH 8 and 3.3 years at pH 7. A 28-day aerobic test, OECD TG 301B, using 2-ethylhexyl acetate, was conducted using municipal wastewater activated sludge. Biodegradation was 16%, 49%, 66%, and 70% after 3, 7, 12, and 28 days, respectively. These data indicate the material is readily biodegradable.

Fugacity modelling (Level III) was conducted for 2-ethylhexyl acetate. The resulting distributions are 7.65% to air, 25.7% to water, 65.4% to soil and 1.23% to sediment. Using the log K_{ow} of 3.74, a BCF of 151 was calculated for 2-ethylhexyl acetate.

The Henry's law constant is 1.51×10^{-3} atm-cu m/mole at 25°C. This value suggests that volatilization of 2-ethylhexyl acetate from the water phase is not expected to be significant. The K_{oc} of 2-ethylhexyl acetate is estimated at approximately 222, which suggests that 2-ethylhexyl acetate has moderate mobility in soil.

The critical study that evaluated the toxicity of 2-ethylhexyl acetate to fish was conducted in a 96 hour static-renewal assay with *Oncorhynchus mykiss*. The study used a water accommodated fraction (WAF) with measured concentrations of 0, 0.284, 0.57, 1.34 or 2.51 mg/L. The 96-h LC50 was reported as 8.27 mg/L.

The critical study that evaluated the toxicity of 2-ethylhexyl acetate to aquatic invertebrates was conducted with *Daphnia magna* using static-renewal 48 hour exposure according to OECD TG 202. The study used a WAF with measured concentrations of 0, 0.828, 2.06, 4.12, 7.99, or 15.7 mg/L. The 48-hour EC₅₀ for immobilization of *Daphnia magna* is 22.9 mg/L.

Results are available from a 72 hour growth inhibition study in green algae (*Pseudokirchneriella subcapitata*, formerly known as *Selenastrum capricornutum*). The study used a WAF with measured concentrations of 0, 1.42, 2.70, 5.27, 10.3, or 21.0 mg/L. The 72-hour EC₅₀ for growth inhibition for 2-ethylhexyl acetate was >21.9 mg/L, and the NOEC_{growth inhibition} was 10.3 mg/L.

2-Ethylhexyl acetate possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). The chemical is readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

2-Ethylhexyl acetate had a production and/or import volume in the United States between 454 and 4,540 tonnes during 2005. 2-Ethylhexyl acetate is produced by the esterification of 2-ethylhexanol with acetic acid. Virtually all of the 2-ethylhexyl acetate produced is used as a solvent in the manufacture of various types of industrial and consumer paints and coatings. Minor use as a component of fragrances is also reported. No monitoring data within production and processing sites in the United States are available. It has a low odour threshold (0.007 ppm) and a sweet odour. 2-Ethylhexyl acetate is manufactured in an enclosed, continuous process and engineering controls and vapour collection systems are used during production, transfer, and loading operations. These measures are used to minimize workplace exposure and odour complaints. Workplace and consumer exposure may occur via the inhalation of vapours during the application and drying of paints and coatings containing 2-ethylhexyl acetate. Minor dermal exposure may also occur. Some consumer

exposure occurs due to the reported use of 2-ethylhexyl acetate as a component in fragrances. Scrubbers and other emission controls are usually employed to minimize release of 2-ethylhexyl acetate during manufacture and use. However, 2-ethylhexyl acetate may be released to the environment as a fugitive emission during production.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-05-7
Chemical Name	2-Ethylhexaldehyde
Structural Formula	O=CH-CH(CH ₂ -CH ₃)-CH ₂ -CH ₂ -CH ₂ -CH ₃

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Rationale**

Several of the health endpoints for 2-ethylhexaldehyde make use of data from 2-ethylhexanol and 2-ethylhexanoic acid experiments. The logic for this “metabolic series” approach includes the metabolism of alcohols (2-ethylhexanol) proceeding via a readily reversible reaction with alcohol dehydrogenase(s) to rapidly form the respective aldehydes (2-ethylhexaldehyde). The aldehydes are short-lived due to the enzymatic activity of aldehyde dehydrogenase that forms the respective organic acids (2-ethylhexanoic acid). Assuming 2-ethylhexaldehyde behaves as other aldehydes, direct exposure to 2-ethylhexaldehyde will result in the rapid formation of both 2-ethylhexanol and 2-ethylhexanoic acid. The metabolic processes of these two chemicals are well characterized. Toxicity data from studies conducted with 2-ethylhexanol and 2-ethylhexanoic acid have been used to identify the hazards associated with systemic exposure to 2-ethylhexaldehyde and therefore are useful in identifying hazards associated with 2-ethylhexaldehyde systemic exposures. Structural analogues are used to address several Environmental Hazard endpoints: 2-methyl propionaldehyde (CAS No.78-84-2), 2-ethyl butyraldehyde (CAS No.97-96-1), 2-methyl valeraldehyde (CAS No. 123-15-9), valeraldehyde (CAS No. 110-62-3), hexaldehyde (CAS No.66-25-1), and octylaldehyde (CAS No. 124-13-0).

Physical-Chemical Properties

2-Ethylhexaldehyde is a liquid at standard temperature and pressure, with a boiling point of 163 °C and a melting (freezing) point of <-100 °C. It is less dense than water with a specific gravity of 0.854 g/cm³ at 20°C. The solubility limit in water is approximately 400 mg/L at 25 °C. 2-Ethylhexaldehyde is combustible with a flash point of 44 °C. It has a vapour pressure of 2.61 hPa at 25 °C. Given its solubility limits of 400 mg/L at 25 °C and its molecular weight of 128.22 g/mole, the preferred Henry's law constant at 25 °C has been calculated to be 7.59X10⁻⁴ atm-cu m/mole. The estimated log Kow is 2.71.

Human Health

2-Ethylhexaldehyde is formed from the metabolism of 2-ethylhexanol and is presumed to undergo subsequent oxidation to 2-ethylhexanoic acid. Although 2-ethylhexaldehyde formed from 2-ethylhexanol has not been demonstrated in vivo, metabolism and toxicokinetics studies with 2-ethylhexanol have demonstrated the presence of 2-ethylhexanoic acid in the plasma as well as glucuronide conjugates and oxidation products of 2-ethylhexanoic acid metabolism in the urine following intravenous, dermal and oral exposures. Elimination of 2-ethylhexanol metabolites following oral exposure was complete within 24 hours. Comparison of 2-ethylhexanol and 2-ethylhexanoic acid metabolic/toxicokinetics information and toxicity databases suggests that the metabolic processes necessary to convert 2-ethylhexanol to 2-ethylhexanoic acid explain the difference in toxicity of these chemicals. When other aldehydes are administered in vivo, both the parent alcohol and the acid metabolite are formed initially. Assuming that 2-ethylhexaldehyde undergoes similar metabolic processes, 2-ethylhexanol and 2-ethylhexanoic acid are expected to be formed following exposure to the aldehyde. Therefore, toxicity information from these two

chemicals are relevant for 2-ethylhexaldehyde hazard identification. The rapid, irreversible formation of 2-ethylhexanoic acid from 2-ethylhexaldehyde suggests that this chemical is most relevant for identification of toxicity properties for 2-ethylhexaldehyde. The site of contact toxicity noted in the 28-day repeated dose toxicity study of 2-ethylhexaldehyde limits the exposure concentrations that could be used in a repeated dose toxicity study and therefore the data from 2-ethylhexanol and 2-ethylhexanoic acid are considered adequate to assess the systemic toxicity of 2-ethylhexaldehyde.

The oral LD₅₀ values for 2-ethylhexaldehyde are 3,078 mg/kg bw and 3,536 mg/kg bw for male and female rats, respectively. Clinical signs from all acute oral studies include central nervous system signs (weakness, narcosis or prostration) and/or gastrointestinal tract irritation with >2500 mg/kg bw and slight weakness noted in animals treated with 1250 mg/kg bw. Inhalation exposure of rats (5/group) for 4 hours caused no deaths at 6.83 mg/L (1279 ppm) with gradual reduction in respiratory rate, response to external (noise) stimuli and irritation of mucosal surfaces noted at this concentration. The dermal LD₅₀ in male and female rats is >20 ml/kg bw (17,080 mg/kg bw); the substance was applied undiluted under an occlusive wrap for 24 hours and produced erythema at the application site. 2-Ethylhexaldehyde is a moderate to severe skin irritant in rabbits and guinea pigs and a severe eye irritant in rabbits. Respiratory tract irritation has been reported in the acute inhalation toxicity studies at 6.83 mg/L (1,279 ppm and higher). An RD₅₀ sensory irritation value of 1.2 mg/L (225 ppm) was reported in mice. 2-Ethylhexaldehyde was negative for skin sensitization in a Kligman human patch test with 2% in petrolatum.

A 28-day repeated exposure inhalation study with limited histopathology is available for 2-ethylhexaldehyde. Effects observed at the highest concentration (1.34 mg/L; 250 ppm) included porphyrin tears, reduced body weights and feed efficiency, decreased lymphocytes and increased neutrophils, decreased serum glucose and cholesterol, increased serum triglycerides, increased alkaline phosphatase activity, decreased thymus weights, increased testes, heart (males only), liver, adrenal, kidney and lung weights. No histopathological effects were noted in the testes or liver (the only tissues examined). Increased alkaline phosphatase activity was also noted at the 0.134 mg/L (25 ppm) and 0.536 mg/L (100 ppm) concentrations. Biochemical measures of peroxisome proliferation were found at the 0.536 and 1.34 mg/L exposure concentrations. Several metabolism studies with 2-ethylhexanol have demonstrated the primary metabolite to be 2-ethylhexanoic acid; presumably via the 2-ethylhexaldehyde metabolite. Therefore, information on both 2-ethylhexanol and 2-ethylhexanoic acid have been included to supplement the toxicity data for 2-ethylhexaldehyde. The NOEC from the thirteen week inhalation rat study with 2-ethylhexanol was 0.639 mg/L (120 ppm; the highest vapour concentration achievable). A thirteen week gavage study with 2-ethylhexanol in rats caused stomach irritation, increased reticulocytes and liver effects (increased liver weight, decreased serum cholesterol, albumin and total protein, liver histopathology and peroxisome proliferation) in the 500 mg/kg bw/day male and female rats. Milder liver effects indicative of peroxisome proliferation was noted in male and female rats at 250 mg/kg bw/day. The NOAEL in male and female rats was 125 mg/kg bw/day. A similar study in mice produced a NOAEL of 125 mg/kg bw/day based on increases in relative liver weights in male mice at the 250 mg/kg bw/day dose level. The ability of 2-ethylhexanol to induce hepatic peroxisome proliferation in male and female rats and mice following 14 days of oral exposure has been demonstrated. Two-week and 13-week dietary studies in rats and mice with 2-ethylhexanoic acid demonstrated effects on the liver (increased absolute and relative liver weights, hepatocytes hypertrophy, increased cholesterol and decreased triglyceride serum levels, and peroxisome proliferation). The lowest NOEL from these studies was 180 mg/kg bw/day in male mice from the subchronic study.

In vitro studies demonstrate that 2-ethylhexaldehyde was not mutagenic to *Salmonella typhimurium* at concentrations up to 666 µg/plate, with and without metabolic activation. *In vivo*, 2-ethylhexaldehyde did not induce micronuclei in bone marrow of male and female mice following an oral limit dose of 2000 mg/kg bw/day. In addition, 2-ethylhexanol (via intraperitoneal injection) and 2-ethylhexanoic acid (by oral gavage) did not induce an increase in micronuclei in erythrocytes in mice.

In oral (gavage) assays with 2-ethylhexanol in rats using dose levels of 0, 50, 150 or 500 mg/kg bw/day (24 months), reduced body weight gain was noted in rats in the 150 (males, 11%; females, 9%) and 500 (males, 23%; females, 21%) mg/kg bw/day dose groups. Laboured breathing and

poor condition was noted in the 500 mg/kg bw/day animals. Dose-related increases in relative liver, stomach, and kidney weights were noted at sacrifice in the 150 and 500 mg/kg bw/day groups. Mortality in female rats (52%) was markedly increased at 500 mg/kg bw/day. The sum of the hepatocellular adenomas and carcinomas was less in the male treated groups (7) than in the two male control groups (8). The incidence of hepatocellular carcinomas in the female water control group was 1, in the 500 mg/kg bw/day was 0, and were a total of three in the 50 and 150 mg/kg bw/day groups combined. The test material was not oncogenic in rats.

In oral (gavage) assays with 2-ethylhexanol in mice using dose levels of 0, 50, 200 or 750 mg/kg bw/day (18 months), no dose-related changes were noted in mice receiving 50 or 200 mg/kg/day. At 750 mg/kg/day, reduced body weight gain (12% in males and 14% in females), decreased feed consumption (9% in males and 12% in females) and increased mortality were noted (30% in males and females by weeks 79-81). Increases in relative kidney (females only), liver (females only) and stomach weights (males and females) were noted at sacrifice in the 750 mg/kg bw/day group. The test material was not considered oncogenic in male mice. An increase in hepatocellular carcinomas in the female 750 mg/kg bw/day group was statistically significant when compared to the vehicle control group but not when compared to the concurrent water control group. This lead to the conclusion that 2-ethylhexanol was considered a weak or equivocal liver carcinogen in female mice at this dose level. Interpretation of this data is complicated by the severe toxicity (increased mortality) noted in mice at the 750 mg/kg bw/day dose level, the known ability of 2-ethylhexanol to induce peroxisome proliferation in rodent liver (as a potential mechanism of action for tumour formation) and the background incidence of liver tumours in this strain of mice.

2-Ethylhexaldehyde is a developmental toxicant. A rat oral gavage study conducted with 2-ethylhexaldehyde reported maternal toxicity (piloerection, reduced activity, 23% reduction in body weight gain, 8% reduction in body weight, reduced feed consumption) and developmental toxicity (overt malformations and a 34% reduction in foetal body weights) at the 798 mg/kg bw/day dose level. At the 300 mg/kg bw/day dose level, no maternal toxicity was reported while evidence of foetal developmental delay (increased incidence of fetuses with incomplete ossification of the 5th/6th sternbrae and of the sacrocaudal vertebral arches) was present. No foetal abnormalities were noted at 100 mg/kg bw/day. 2-Ethylhexanol causes developmental toxicity (reduced foetal body weights (-9.5%), a single type of skeletal vertebral malformation, reduced skeletal ossification) in rats only at oral dose levels of 650 mg/kg bw/day, a dose level causing significant maternal toxicity. The highest dose level (1300 mg/kg bw) caused maternal deaths, reduced feed consumption and body weight gain in the dams, increased resorptions, foetal death and decreased foetal weights and malformations in the surviving foetuses. 2-Ethylhexanol is not a developmental toxicant via the dermal (up to 2,520 mg/kg/day) or inhalation routes of exposure (up to 0.85 mg/L) in rats. 2-Ethylhexanoic acid is a developmental toxicant in rats with a NOAEL of 100 mg/kg bw/day and maternal and foetal findings similar to those for 2-ethylhexaldehyde.

No reproductive toxicity studies were available for 2-ethylhexaldehyde. The 28-day inhalation study in rats with 2-ethylhexaldehyde did not find any histopathological effects on the testes. 2-Ethylhexanol is not considered a reproductive toxicant based on data from repeated exposure studies as well as *in vitro* investigations. There were no treatment-related histological changes in either the testes or ovaries (in mice and rats) after 13 weeks of treatment with 2-ethylhexanol at dosages up to 500 mg/kg bw/day. 2-Ethylhexanoic acid is not a reproductive toxicant. 2-Ethylhexaldehyde is not considered a reproductive toxicant.

2-Ethylhexaldehyde possesses properties indicating a hazard for human health (severe skin and eye irritation, respiratory tract irritation and developmental toxicity). Adequate screening-level data are available to characterize the hazard for the human health purposes of the OECD HPV Programme.

Environment

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is a likely route of degradation, and is predicted to occur with an estimated half-life of 3.7 hours. A 28-day aerobic test, OECD TG 301F, using 2-ethylhexaldehyde, was conducted using activated sludge. Biodegradation was 70-80% after 28 days, indicating the material is readily biodegradable.

2-Ethylhexaldehyde is stable in water, as it has no hydrolysable groups. Fugacity modelling (Level III) was conducted for 2-ethylhexaldehyde. The resulting distributions are 2.02% to air, 24.9% to

water, 72.8% to soil and 0.246% to sediment. An octanol/water partitioning coefficient ($\log K_{ow}$) value of 2.71 has been estimated for 2-ethylhexaldehyde. This value suggests that 2-ethylhexaldehyde will not significantly bioconcentrate in aquatic organisms. Using the $\log K_{ow}$ of 2.71, a BCF of 24 was calculated, which further indicates a low bioaccumulation potential.

The vapour pressure of 2-ethylhexaldehyde is 2.61 hPa at 25°C, and the Henry's law constant is 7.59×10^{-4} atm-cu m/mole at 25°C. These values suggest that volatilization of 2-ethylhexaldehyde from the water phase is expected to be moderate, with estimated half-lives for a model river and model lake at 4.6 hours and 5 days, respectively. The K_{oc} of 2-ethylhexaldehyde is estimated at approximately 54, which suggests that 2-ethylhexaldehyde has medium mobility in soil.

There were no fish toxicity data available for 2-ethylhexaldehyde. The ECOSAR estimated 96-hr LC_{50} for 2-ethylhexaldehyde in fish is 6.43 mg/L. Several studies examining the toxicity of 2-methyl propionaldehyde, 2-ethyl butyraldehyde, valeraldehyde, 2-methyl valeraldehyde, n-hexaldehyde, and n-octylaldehyde in fish are available. A study with branched- and straight-chain aldehydes in fish used guppy (*Poecilia reticulata*) in a 14-day static renewal test system. The 14-day LC_{50} was 26.8, 7.8, 13.0, 9.8, and 7.9 mg/L for 2-methyl propionaldehyde, 2-ethyl butyraldehyde, valeraldehyde, n-hexaldehyde, and n-octylaldehyde, respectively. Acute flow-through tests were conducted with fathead minnows (*Pimephales promelas*) with hexaldehyde, valeraldehyde, and 2-methyl valeraldehyde. The 96-hr LC_{50} values were reported as 14.0, 12.4, and 18.8 mg/L, respectively. The test solutions in all studies were not buffered.

The critical study that evaluated the toxicity of 2-ethylhexaldehyde to aquatic invertebrates is a study conducted with *Daphnia magna*. The 48-hour EC_{50} for immobilization is 11.5 mg/L. The test solutions were not buffered.

An acute toxicity study in algae (*Scenedesmus subspicatus*) with 2-ethylhexaldehyde reported a 96-hour EC_{50} for growth inhibition of 52.1 mg/l.

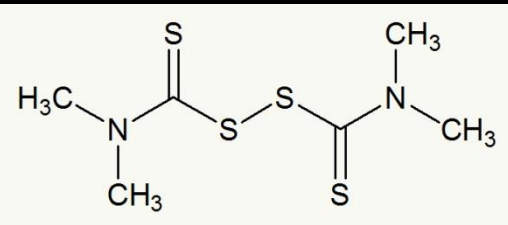
The results of these studies indicate that aquatic vertebrates, invertebrates and algae are all similar in response to exposures of 2-ethylhexaldehyde and surrogate aldehydes.

2-Ethylhexaldehyde possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L in unbuffered systems). However, the chemical is readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

2-Ethylhexaldehyde had a production and/or import volume (aggregated across companies) in the United States between 22,680 and 45360 tonnes (50 million and 100 million pounds) during 2005. Virtually all of the reported production of 2-ethylhexaldehyde in the United States is for use as an industrial intermediate in the manufacture of 2-ethylhexanoic acid. There are some reports of minor uses of 2-ethylhexaldehyde as a component in fragrances. 2-Ethylhexaldehyde is a naturally-occurring volatile found in baked potatoes. It has also been detected in the emissions from particle board. No monitoring data within production and processing sites in the United States were available. 2-Ethylhexaldehyde is a combustible liquid with a pungent odour. This material may undergo hazardous polymerization on exposure to heat, accelerators/initiators, and other contaminants. 2-Ethylhexaldehyde can form organic peroxides of unknown stability. 2-Ethylhexaldehyde is manufactured in an enclosed, continuous process and engineering controls and vapour collection systems are used during production, transfer, and loading operations. These measures are used to minimize workplace exposure and odour complaints. Emission controls are usually employed to minimize release of 2-ethylhexaldehyde during manufacture and use. However, 2-ethylhexaldehyde may be released to the environment as a fugitive emission during production and use.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	137-26-8
Chemical Name	Bis(dimethylthiocarbamoyl)disulfide; Thiram
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical and chemical properties**

Bis(dimethylthiocarbamoyl)disulfide is a white or colourless to yellow crystalline powder with a melting point of 155.6 °C. Under normal atmospheric pressure, the substance decomposes before the boiling point is reached. It has a density of 1.29 g/cm³ at 20 °C and a measured vapour pressure of 2.3 x 10⁻³ Pa at 25 °C. The measured octanol-water partition coefficient log K_{ow} is 1.73 and measured water solubility is ≤ 18 mg/L at room temperature.

Human Health

Bis(dimethylthiocarbamoyl)disulfide can be metabolised to toxic products such as carbon disulfide, hydrogen sulfide and dimethylamine. Experiments were carried out to investigate whether bis(dimethylthiocarbamoyl)disulfide is transformed by microsomal monooxygenase to carbon disulfide (CS₂) in rats. Adult male rats were given 15, 30 or 60 mg/kg of bis(dimethylthiocarbamoyl)disulfide in corn oil by intraperitoneal injection. The formation of CS₂ was dose dependant and was increased by pretreatment of rats with phenobarbital and decreased by SKF 525-A. Furthermore, measurement of the hepatic microsomal and serum enzymes activities at 5 hours and 24 hours following bis(dimethylthiocarbamoyl)disulfide treatment indicated significant loss of cytochrome P-450 and benzphetamine N-demethylase activity only at the 24 hour interval. Significant elevation of sorbitol dehydrogenase (SDH) and serum glutamic oxalacetic transaminase (SGOT) activity was observed at 5 and 24 hours after treatment.

A single oral dose of ¹⁴C-bis(dimethylthiocarbamoyl)disulfide was administered to male and female rats to determine its absorption, excretion and final distribution. Only 32% of the administered dose was recovered, mainly from the urine (25%). About 3% was recovered from the various organs (blood, bone and liver). Only 3% of the administered dose was recovered in the faeces. Dose level or sex did not affect total recovery. Approximately 70% of the administered bis(dimethylthiocarbamoyl)disulfide, not recovered, may have been metabolized to CO₂ or other volatiles in the expired air or by bacterial action in the faeces or urine during the intervals between collections.

After 14 days of pretreatment with bis(dimethylthiocarbamoyl)disulfide at a dose level of 2 mg/kg bw/day, five rats/sex received a single dose of ¹⁴C-bis(dimethylthiocarbamoyl)disulfide. The radioactivity was determined in urine, faeces and expired air at intervals up to 96 hours, and the radioactivity content in tissues was determined at 96 hours after dosing. ¹⁴C-bis(dimethylthiocarbamoyl)disulfide was well absorbed by both sexes. Radioactivity was excreted in the urine (35-40% of dose within 96 hours), faeces (2-5%), and expired air (41-48%). Excretion was more extensive and rapid in urine and expired air within the first 12 hours post-dosing, while the majority of the faecal radioactivity was excreted after 24 hours. Trace levels of radioactivity were detected in all tissues: the highest in liver, blood cells and kidneys, and the lowest in brain, plasma, and skeletal muscle.

In an acute oral toxicity, bis(dimethylthiocarbamoyl)disulfide was administered via gavage to rats and mice. Ataxia and hyperactivity followed by inactivity, loss of muscular tone, and alopecia were observed. Deaths were occurred 2 to 7 days after exposure. Acute oral LD₅₀ values for females and males were 1,900 and 4,000 mg/kg

bw, respectively, in rats and 3,800 and 4,000 mg/kg bw, respectively in mice.

No reliable studies of acute inhalation and dermal toxicity were available in experimental animals. A lower quality rat study indicated a 4-h inhalation LC₅₀ value of 4.42 mg/L.

Bis(dimethylthiocarbamoyl)disulfide is reported as irritating to skin, eye and sensitising to skin in experimental animals.

In a 13-week dietary study, bis(dimethylthiocarbamoyl)disulfide was administered at dose of 0, 0.05, 0.1 or 0.25% (equivalent to 0, 30, 58 or 132 mg/kg bw/day) to male rats (20 animals/dose). Treatment related reductions in body weight and food consumption were observed at all doses. Mortality was observed at 58 and 132 mg/kg bw/day. At 58 mg/kg bw/day a mild increase in blood urea nitrogen (BUN) was observed, and at 132 mg/kg bw/day mild elevations of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were noted. Moderate tubular degeneration of the testes with atypical spermatids in the epididymis occurred in some rats fed 132 mg/kg bw/day. Based on the testicular changes at 132 mg/kg bw/day and mild elevations of blood biochemical parameters at 58 and 132 mg/kg/day indicating renal or hepatic dysfunction, the NOAEL was 30 mg/kg bw/day.

In a 80-week study, groups of 24 male and 24 female rats were fed bis(dimethylthiocarbamoyl)disulfide at dosage levels of 0, 0.01, 0.04 or 0.1% (equivalent to 0, 5, 20 or 52 mg/kg bw/day for males and 0, 6, 26 or 67 mg/kg bw/day for females). Dose-dependent decreases in body weight and food consumption were observed in males at 5 mg/kg bw/day and in females at 26 mg/kg bw/day. In males, fatty infiltration in the pancreas was noted. The high-dose males and females also had slight increases in squamous metaplasia of the thyroid. Based on the slight growth depression and fatty infiltration of the pancreas, the chronic LOAEL was 5 mg/kg bw/day.

Bis(dimethylthiocarbamoyl)disulfide was administered via the diet to 64 rats/sex/dose at 0, 3, 30 and 300 ppm (equivalent to 0, 0.1, 1.2 or 11.6 mg/kg bw/day for males and 0, 0.1, 1.4 or 13.8 mg/kg bw/day for females, respectively) for 104 weeks. Increased mortality rate was observed at mid and top dose in females only. Decreased body-weight gain and reduced food intake were observed in both sexes at the high dose. Anemia and regressive changes in the sciatic nerve accompanied by atrophy of the calf muscle were seen in females at 13.8 mg/kg bw/day. In high-dose groups, progression of myocardial lesions of the heart and chronic nephrosis of the kidney were depressed in males and females, respectively. Mid and top dose female rats had decreased development of skin mass. Based on the effect on mortality, anemia, nerve degeneration, muscle atrophy and skin mass, the NOAEL of 0.1 mg/kg bw/day was determined in rats.

In an oral repeated dose study, dogs (4/sex per group) were treated orally via capsule with the compound at 0, 0.4, 4, or 40 mg/kg bw/day for 104 weeks. Top dose animals showed severe toxic signs, including nausea or vomiting, salivation, and occasional clonic convulsion, and all were subjected to unscheduled necropsy before Day 203 of treatment. The dogs also had ophthalmological changes such as fundal hemorrhage, miosis, and desquamation of the retina which were consistent with the retinal lesions shown by histopathology. Anemia was evident in the 4 and 40 mg/kg bw/day groups. All mid and top dose animals developed liver failure, and mid and top dose females also showed kidney damage. Based on the anemia and the effects on the liver, the NOAEL was 0.4 mg/kg bw/day.

In a bacterial reverse mutation assay [OECD TG 471] with multiple strains of *Salmonella typhimurium* and *E. coli* WPuvrA, bis(dimethylthiocarbamoyl)disulfide showed equivocal results both with and without metabolic activation (S9 mix). An *in vitro* chromosomal aberration test with mammalian cell was negative both in the absence and presence of metabolic activation (S9 mix). An *in vivo* micronucleus assay with male and female hamsters was negative up to the maximum tolerated dose (500 µg/kg bw). An *in vivo* germ cell cytogenetics assay and spot test, both in mice, were also negative. Overall, the substance is not genotoxic. Further *in vitro* and *in vivo* studies were reported with equivocal results, probably due to evidence of impurities in the test substance.

In an oral carcinogenicity study in rats, the test substance was administered via the diet to 50 animals/sex/dose at 0, 0.05 or 0.1 % for 104 weeks. Calculated total intake of bis(dimethylthiocarbamoyl)disulfide in the diet were 18.3 mg/kg/day and 39.2 mg/kg/day for males and 20.2 mg/kg/day and 42.3 mg/kg/day for females in the low and high dose groups, respectively. There was no significant difference in survival between treated and control animals. Except for dose-dependent reduction of spontaneous leukaemia in both sexes and slightly reduced incidences of pituitary and thyroid adenomas in females, no significant lesions or tumor induction attributable to the treatment were observed.

In a 104-week study, bis(dimethylthiocarbamoyl)disulfide was administered via the diet to 64 rats/sex/dose at 0, 3, 30 or 300 ppm (equivalent to 0, 0.1, 1.2 or 11.6 mg/kg bw/day for males and 0, 0.1, 1.4 or 13.8 mg/kg bw/day for females). Death was observed in the 1.4 and 13.8 mg/kg bw/day females. No evidence of carcinogenic potential

was observed.

Simultaneous feeding to rats of bis(dimethylthiocarbamoyl)disulfide with sodium nitrite was carried out to assess the possibility of formation of carcinogenic N-nitroso derivatives *in vivo*. Groups of 24 male and female rats/dose were fed 0 or 500 mg/kg bw/day (750 mg/kg bw/day for the first three weeks) of bis(dimethylthiocarbamoyl)disulfide alone in diet or in combination with 2,000 mg/kg of diet sodium nitrite in diet for 104 weeks. Fifteen percent of the rats receiving bis(dimethylthiocarbamoyl)disulfide alone had died. No evidence of carcinogenic potential was observed in rats treated with bis(dimethylthiocarbamoyl)disulfide. Based on these results, bis(dimethylthiocarbamoyl)disulfide alone was not carcinogenic in rats. However, high incidence of papillomas of the forestomach was also seen in the rats of both sexes given the combined treatment.

In a two generation dietary reproduction and fertility study, rats (26/sex/dose/generation) received bis(dimethylthiocarbamoyl)disulfide at 0, 20, 60, or 180 ppm through 2 generations (2 litters/generation). Average dose-treated daily intake calculated for the F0 and F1 premating periods was 1.4-1.8, 4.2-5.4 and 12.2-16.4 mg/kg bw/day at 20, 60 and 180 ppm, respectively. Body weights decreased in both sexes of F0 parents at 180 ppm and F1 parents at > 60 ppm. Mean body weight decreased in F0 females (F1a generation) during gestation and lactation at 180 ppm. Decreases, though statistically significant, were minimal (< 10%, except day 0 lactation). These effects were not seen with the F0 females (F1b generation) during gestation or lactation. F1 females (F2a generation) had statistically significantly, but minimally decreased body weights during gestation and lactation at 180 ppm. Food consumption decreased in both sexes of F0 and F1 parents at 180 ppm. Because of lack of toxicologically relevant effects, the reproductive NOEL was 180 ppm (equivalent to 12.2-14.9 mg/kg bw/day in males and 14.0-16.4 mg/kg bw/day in females). Based on decreased body weight in pups at 180 ppm (F0) and > 60 ppm (F1) throughout lactation, the pup NOAEL was 20 ppm (equivalent to 1.4-1.7 mg/kg in males and 1.6-1.8 mg/kg in females).

In a dietary reproduction toxicity study, bis(dimethylthiocarbamoyl)disulfide was administered at doses of 0, 30, 58 or 132 mg/kg bw/day for male rats and 0, 30 or 96 mg/kg bw/day for female rats (20 animals/sex/dose). Weanling males were treated for at least 13 weeks before mating with untreated females. Virgin females were treated for at least 14 days, and then mated with untreated males. After mating, all females were fed the control diet. Death occurred in 70% of the male rats in the 132 mg/kg bw/day group, and the absence of fat was noted at necropsy. Average body weight and food consumption was depressed in both sexes.

At the high dose, decreased fertility in male rats was observed after 13 weeks of treatment; high dose females for 14 days treatment had prolonged the diestrous phase of the oestrus cycle. At 30 mg/kg bw/day, decreased litter size was observed. Based on the decreased the litter size, bis(dimethylthiocarbamoyl)disulfide was considered to adversely affect fertility at doses of 30 mg/kg bw/day and above.

In a developmental toxicity gavage study, the test substance was administered to pregnant female rats at doses of 0, 40, 90, 136, 164 or 200 mg/kg bw/day during gestation days 6-15 (10-32 animals/sex/dose). Average body weight gain and food consumption decreased in treated dams. A significant decrease in the number of implants per dam at doses of 164-200 mg/kg bw/day was observed. The number of fetuses per dam decreased, accompanied by a corresponding increase in resorptions at doses of 136-200 mg/kg bw/day. Fetal body weight was decreased in all treated groups. The following teratogenic effects were seen in the group given 136 mg/kg bw/day, domed cranium, hydrocephalus, unossified sternbrae, incompletely ossified supraoccipital, and centra split or lobed. Based on the fetal mortality, the fetal body weight reduction and increased incidence of abnormalities in fetuses, the LOAEL was 40 mg/kg bw/day.

In a teratology study, 4 groups of 25 female rats were administered dose levels of 0, 7.5, 15 or 30 mg/kg bw/day by gavage on day 6-15 of gestation. At 15 and 30 mg/kg bw/day a transient, dose-related, loss of body-weight was observed. There were no adverse effects upon implantation or upon fetal survival, but fetal and placental weights were significantly reduced at 30 mg/kg bw/day. At 30 mg/kg bw/day there was evidence of fetal immaturity e.g., reduced skeletal ossification and increased incidence of space between the body wall and organs, and there was a slightly increased incidence of subcutaneous oedema. Three fetuses with diaphragmatic hernia were observed, two at 7.5 and one at 30 mg/kg bw/day. The toxic effects on fetuses (immaturity and increased incidence of 13th ribs of reduced size) at higher doses were considered a result of maternal toxicity. The NOAEL for fetal toxicity was 7.5 mg/kg bw/day. Based on the reduced maternal body weight and placental weight, the NOAEL for maternal toxicity was 7.5 mg/kg bw/day.

Overall, the developmental adverse effects were observed in the range of maternal toxic doses

In a neurotoxicity study, bis(dimethylthiocarbamoyl)disulfide was administered via diet to 24 male and female rats. In the first experiment (duration of 80 weeks) active bis(dimethylthiocarbamoyl)disulfide intake were around

0, 5.3, 20.4 or 52.0 mg/kg bw/day for male rats and 0, 6.1, 25.5 or 66.9 mg/kg bw/day for female rats. In a second experiment (duration of 36 weeks) active bis(dimethylthiocarbamoyl)disulfide intake was around 0 or 65.8 mg/kg bw/day for female rats. Top dose females from first experiment and females from second experiment developed ataxia and paralysis. Abnormal nerve conduction, neuropathology and behavioural effects were observed in top dose rats from the first experiment and females from second experiment. The walking pattern of the hind legs was altered with decreases in stride width and the angle between contra lateral steps. These rats required significantly more shock-motivations and cleared a lower height in a jump/climb ability test. An open-field study indicated that this substance caused hyperactivity in the non-ataxic rats of both sexes. Based on the results, the NOAEL for neurotoxicity was 20 (and 26) mg/kg bw/day

In a subchronic diet neurotoxicity study, rats (15/sex/dose) were exposed to bis(dimethylthiocarbamoyl)disulfide at doses of 0, 1.74, 7.3, or 28.63 mg/kg/day for male rats and 0, 2.04, 8.07, or 31.82 mg/kg bw/day for female rats. Significant decreases in weight gain in both male and female rats were observed at 28.6 mg/kg bw/day dose level. Functional observational battery observations revealed an increased incidence of hyperactivity along with significantly increased occurrences of rearing events in male rats at 8 and 13 weeks at the high dose and females at mid and high doses. Necropsy and histopathology examinations of the highest dose animals revealed no compound related abnormalities. Based on these results, LOAEL was 8.1 mg/kg bw/day (based on increased numbers of rearing events and elevated incidences of hyperactivity in female rats). The NOAEL was 2.04 mg/kg bw/day for female rats, and 7.3 mg/kg bw/day for male rats.

In an acute neurotoxicity gavage study rats (15/sex/dose) received 0, 5, 150, or 600 mg/kg bw of bis(dimethylthiocarbamoyl)disulfide, and were subsequently evaluated in functional observational battery (FOB) at 2 hours and 7 and 14 days, and motor function observations were conducted at 3 hours, and 7 and 15 days. FOB effects occurred at the two highest dose levels two hours post dosing. FOB findings at 7 and 14 days indicated nothing remarkable. Male and female rats from the mid and top doses showed reduced mean motor activities at 3 hours, and 7 and 14 days. Absolute mean brain weights in 150 and 600 mg/kg male rats were significantly decreased. Mean brain weights for females from mid and top dose were also lower than those of their controls, but there was no statistical significance. There were no indications of any other adverse neuropathological effects in the brains or in any of the central or peripheral nervous system tissue which were examined following sacrifice. The NOAEL for neurotoxicity was 5 mg/kg bw and the LOAEL (FOB effects at 2 hours post-dosing; reduced motor activity at 3 hours, and at 7 and 14 days post treatment) was 150 mg/kg bw.

Bis(dimethylthiocarbamoyl)disulfide possesses properties indicating a hazard for human health (skin and eye irritation and skin sensitization, oral repeated-dose toxicity, reproductive toxicity and neurotoxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The hydrolysis half-life measured for bis(dimethylthiocarbamoyl)disulfide at pH 3.8, 5.7, 7 and 8 were 9.5, 108, 1,123 and 3,316 hours, respectively. The photolysis half-life of bis(dimethylthiocarbamoyl)disulfide in water was 4.3 hours. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.03 days. No biodegradation was measured by biochemical oxygen demand (BOD) testing and the percentage biodegradation of bis(dimethylthiocarbamoyl)disulfide observed by HPLC analysis was 42.9% after 28 days at pH 7.8~8.0 [OECD TG 301C]. Bis(dimethylthiocarbamoyl)disulfide is not readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that bis(dimethylthiocarbamoyl)disulfide will distribute mainly to the soil (80.4%) and water (19.0%) compartments with minor distribution to the sediment compartment (0.6%) and negligible amount in the air compartment. If released only to the soil compartment, bis(dimethylthiocarbamoyl)disulfide stays in the soil compartment (99.0%) with negligible amounts in other compartments. A Henry's law constant of 3.26×10^{-7} atm-m³/mole suggests that bis(dimethylthiocarbamoyl)disulfide is expected to be essentially non-volatile from moist soil and water surfaces. A K_{oc} value of 676 has been measured for bis(dimethylthiocarbamoyl)disulfide. This K_{oc} value suggests that bis(dimethylthiocarbamoyl)disulfide is expected to have low mobility in soil.

Bis(dimethylthiocarbamoyl)disulfide is not expected to bioaccumulate in the aquatic environment based on bioconcentration factors of 1.1-4.4 and <3.4 which were measured in carp at concentrations of 25 and 2.5 µg/L, respectively.

Acute aquatic and terrestrial toxicity of bis(dimethylthiocarbamoyl)disulfide was performed with OECD test guidelines (TGs).

The following acute toxicity test results have been determined for aquatic species:

Fish [OECD TG 203, <i>Oryzias latipes</i>]	96 hours LC ₅₀ = 0.17 mg/L
Invertebrate [OECD TG 202, <i>Daphnia magna</i>]	48 hours EC ₅₀ = 0.036 mg/L
Algae [OECD TG 201, <i>Pseudokirchneriella subcapitata</i>]	72 hours E _r C ₅₀ = 0.19 mg/L
	72 hours E _y C ₅₀ = 0.060 mg/L

The following acute toxicity test results have been determined for terrestrial species:

Plant [OECD TG 208, <i>Lactuca sativa</i>]	7 days EC ₅₀ = >32 to <100 µg/g soil
Plant [OECD TG 208, <i>Lactuca sativa</i>]	14 days EC ₅₀ = 54 µg/g soil

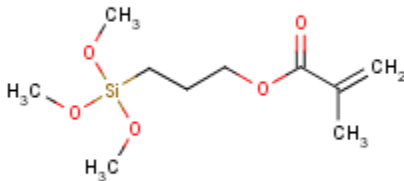
Bis(dimethylthiocarbamoyl)disulfide possesses properties indicating a hazard for environment (acute aquatic toxicity lower than 1.0 mg/L for fish, invertebrates and algae, toxicity to terrestrial plants). The substance is not readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

In the Republic of Korea (sponsor country), the production, use and import volume of bis(dimethylthiocarbamoyl)disulfide was 604, 836 and 694 tonnes, respectively in 2006. Bis(dimethylthiocarbamoyl)disulfide is used for vulcanising agents in the rubber industry, complexing agents, adhesive agents, binding agents, intermediates, catalyser, oxidising agents and as a fungicide on turf, fruit and vegetables in the Republic of Korea. It is also used as a seed disinfectant as well as an animal repellent for rodents and certain large animals that cause damage to field crops and as a bacteriostat in soap and antiseptic. Environmental exposure through its use as a fungicide is anticipated. Maximum residue levels of thiram on fruit and vegetables are regulated by European Commission Directive 2007/57/EC of 17 September 2007 (EU).

In the tire industry, bis(dimethylthiocarbamoyl)disulfide is handled in closed system facilities in the Republic of Korea. Occupational exposure is managed with local ventilation systems and personal protective equipments such as dust masks, gloves and goggles. According to the monitoring data, the 8hr-TWA (Time Weighted Average) concentrations of dust for workplaces were 0.05 - 1.07 mg/m³, which were less than occupational exposure limit of 10 mg/m³. Occupational exposure is considered to be negligible in the sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2530-85-0
Chemical Name	3-Trimethoxysilylpropyl methacrylate (MPTMS)
Structural Formula	
SUMMARY CONCLUSIONS OF THE SIAR Analogue Justification 3-Trimethoxysilylpropyl methacrylate (MPTMS) hydrolyzes to form 3 moles of methanol (CAS No. 67-56-1) for each one mole of (γ-methacryloxypropyl)silanetriol (CAS No. 18834-30-5). Additional silanol hydrolysis products may form through subsequent reactions, such as bis-(γ-methacryloxypropyl)-tetrahydroxysiloxane, which has been identified in an inhalation toxicity study. One of the hydrolysis products, methanol has previously been assessed in the OECD HPV Programme (http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=39B5D34A-2F5D-4D53-B000-E497B3A3EE89). Data are presented on the mammalian and aquatic toxicity of MPTMS. However, based on the compound's rapid hydrolysis rate, most of these tests would also have involved exposure to its hydrolysis products. Physical-Chemical Properties MPTMS is a liquid with a measured melting point of less than -20.2 °C, a measured boiling point of 252.9 °C at 1017.1 hPa and a measured vapour pressure of 0.023 hPa at 25 °C. The measured octanol-water partition coefficient (log K_{ow}) is 2.1 at 25°C, and the measured water solubility is 82.62 mg/L at 25 °C (measured after 1 hour) and 7.54 mg/L at 25 °C (measured after 2 hours). The water solubility and log K_{ow} values may not be applicable because the chemical is hydrolytically unstable. Human Health No toxicokinetics data were available for MPTMS; however, hydrolysis of this substance is expected to produce 3 moles of methanol for each mole of (γ-methacryloxypropyl)silanetriol. The 4 hr inhalation LC₅₀ of MPTMS in rats is greater than 2.28 mg/L, the highest attainable aerosol concentration. Clinical signs of exposure included slow righting reflex and laboured breathing. The dermal LD₅₀ in rats and male rabbits was greater than 2090 mg/kg bw. Clinical signs of exposure included slight erythema and oedema in rats; no findings were noted for rabbits. The oral LD₅₀ of MPTMS in rats has been shown in several studies to be greater than 2000 mg/kg bw. Clinical signs of exposure included wet and/or dried yellow and/or clear material around the mouth, forelimb(s), anogenital area and/or base of tail.	

MPTMS is slightly irritating to the skin and eye of rabbits. In a guinea pig maximization test, MPTMS was a weak skin sensitizer.

In three 14-week repeated exposures in rats to an aerosol of MPTMS and its hydrolysis products at concentrations up to 0.1 mg/L, a no observed adverse effect concentration was not established. MPTMS produces histopathological changes in the upper respiratory tract at concentrations greater than or equal to 0.005 mg/L, the major findings being cytoplasmic hyalinization and the formation of laryngeal granulomas. In three 4-week repeated aerosol exposures in rats, there were similar findings; the LOAEC was 0.0135 mg/L.

MPTMS did not induce gene mutations in bacterial or mammalian cells *in vitro* but did induce chromosomal aberrations in mammalian cells *in vitro*. All *in vitro* studies were conducted with and without metabolic activation. MPTMS was negative for sister chromatid exchange *in vitro* and in a mouse micronucleus assay *in vivo*. MPTMS is not considered to be genotoxic *in vivo*. No data were available for the carcinogenicity of MPTMS.

Repeated inhalation of aerosolized and hydrolyzed MPTMS at concentrations up to 0.1 mg/L for 14 weeks showed no adverse histopathological effects on the reproductive organs of male and female rats; the NOAEC was established at 0.1 mg/L. In an OECD TG 414 developmental toxicity study at concentrations of 0, 522.5, 2090 or 5225 mg/kg bw/day, maternal and developmental effects were noted at 2090 mg/kg bw/day or higher. Maternal toxicity included staining of fur, incoordination, reductions in body weight and food consumption, increases in the absolute and relative liver and kidney weights and mortality at 2090 and/or 5225 mg/kg bw/day. Developmental effects included decreased foetal weights, increases in the incidence of soft tissue malformations and delayed ossification at 2090 and/or 5225 mg/kg bw/day. Based on these results, the NOAEL for maternal and developmental toxicity was 522.5 mg/kg bw/day. Developmental effects, consistent with a general profile of developmental delay, were observed only at the mid- and high-dose levels.

3-Trimethoxysilylpropyl methacrylate possesses properties indicating a hazard for human health (skin and eye irritation, skin sensitisation, repeated-dose toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The EPISuite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although measured data are included in some of the training data sets); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

Based on measured values at 0°C, 10°C and 20°C, the half-life time of the hydrolysis reaction of MPTMS at 25 °C was calculated to be 3 hours at pH 7.0. MPTMS is reactive and hydrolytically unstable; the likely hydrolysis products are methanol and (γ -methacryloxypropyl)silanetriol. In the atmosphere, indirect photo-oxidation by reaction of MPTMS with hydroxyl radicals is predicted to occur with an estimated half-life of 5.1 hours. In two separate 28-day ready biodegradability studies, MPTMS achieved a breakdown rate of 69% in a manometric respirometry test and 74% in a dissolved organic carbon (DOC) die-away test, but did not meet the 10-day window for either study, indicating the test substance is not readily biodegradable. Based on the hydrolysis of this material, some potential for biodegradation of the hydrolysis product, methanol, is likely. Neither (γ -methacryloxypropyl)silanetriol nor condensed silanetriol materials are expected to be readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments estimated that MPTMS will distribute mainly to the soil (76.4%) compartment with minor distribution to the water and sediment compartments (21.6 and 1.19%, respectively) and negligible amount in the air compartment. However, MPTMS is unlikely to be found in the environment, as this material is hydrolytically unstable. The estimated Henry's Law constant of 3.05×10^{-2} Pa-m³/mole (estimated; Bond method) suggests that volatilization from the water phase for

MPTMS is not expected to be high.

The BCF for MPTMS cannot be predicted accurately, but the bioaccumulation potential is expected to be low based on the estimated BCF value of 11.3.

Due to the hydrolysis of MPTMS, aquatic organisms are likely exposed to a mixture of the parent and its hydrolysis products, methanol and (γ -methacryloxypropyl)silanetriol. No toxicity data specifically relating to the silanetriol hydrolysis product were available.

The following acute toxicity test results with MPTMS have been determined for aquatic species:

Fish [*Brachydanio rerio*] 96 h LC₅₀ > 100 mg/L (OECD TG 203; semi-static; nominal)

Invertebrate [*Daphnia magna*] 48 h EC₅₀ > 100 mg/L (OECD TG 202; static; nominal)

Algae [*Scenedesmus subspicatus*] 72-hour E_rC₅₀, E_bC₅₀ > 100 mg/L (OECD TG 201; nominal)

Where: E_bC₅₀ = EC₅₀ based on biomass; E_rC₅₀ = EC₅₀ based on growth rate

Although the reported water solubility of test material was 82.62 mg/L (measured), the functional water solubility of test concentrations were > 100 mg/L.

MPTMS had no inhibitory effect on the respiration rate of activated sludge after the incubation period of three hours; the 3-hour NOEC was at least 1000 mg/L. The bacterial growth inhibition concentration of MPTMS was not reached in a second study, but results can be interpolated using regression analysis; the 7-hour EC₅₀ = 5548 mg/L; the 7-hour EC₁₀ = 2164 mg/L, and the 7-hour EC₉₀ = 14,222 mg/L.

The acute toxicity of MPTMS on the earthworm, *Eisenia foetida*, was determined; no mortality was observed at 1000 mg/kg.

MPTMS does not present hazard for the environment based on its low hazard profile. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

In the United States (sponsor country), production volume in 2005 was approximately 4536 – 22680 tonnes; 2268 - 9072 tonnes were imported into the sponsor country in 2005. MPTMS is also produced in Europe (2268 - 11340 tonnes in 2005) and Japan (2268 - 11340 tonnes in 2005). MPTMS is used as an industrial intermediate and chemical reactant; in sealants and adhesives; as a coupling agent in thermoplastics and thermosetting resins, fibreglass, polymeric filler treatment, and in specialty coatings. The percent used in formulation is <0.1 to 100%. MPTMS is not expected to be found in the final product.

There is no intentional release of MPTMS to the environment.

At the manufacturing site, MPTMS is produced in open and closed systems. Engineering controls include general and local ventilation, vacuum systems, and closed sampling loops. Potential exposure via dermal and inhalation routes is mitigated through the use of personal protective equipment (PPE). Worker exposure due to non-accidental releases at the manufacturing facility is expected to be low. Similarly, at the industrial customer level, the substance is used in open or closed systems. Engineering controls including ventilation devices and related equipment as well as PPE, when used, would help to mitigate worker exposure.

MPTMS is used in consumer products such as sealants and adhesives; the percentage in consumer product formulations is <10%. MPTMS is expected to react with other components and be entrained in polymer matrix in these products, so that the release due to consumer uses is expected to be low (or negligible).

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	27676-62-6
Chemical Name	1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address only the following endpoint(s): [Human Health: acute toxicity, repeated dose toxicity and mutagenicity]. It cannot be considered as a full SIDS Initial Assessment. Nevertheless, the conclusions for the endpoints addressed have been agreed by member countries and may be used for hazard and risk assessment. Results on other endpoints may be relevant for hazard and risk assessment but have not been addressed in the assessment.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law, hazard assessment of existing chemical substances has been conducted. If a chemical substance is evaluated as “not biodegradable (persistent)” and “not highly bioaccumulative”, at least a 28-days repeated dose toxicity and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long-term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid was evaluated as “not biodegradable (persistent)” and “moderately bioaccumulative” by the METI (Ministry of Economy, Trade and Industry), Japan. Biodegradation and bioaccumulation are not parts of the targeted assessment and therefore not presented in ITAP. In order to determine whether the chemical is classified as a Type II monitoring chemical substance, the initial hazard assessment of 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid was conducted for the acute toxicity, repeated dose toxicity and mutagenicity by the MHLW (Ministry of Health, Labour and Welfare), Japan, in November 2004.

Following the hazard assessment under the Japanese Chemical Substances Control Law, the US EPA posted a hazard characterization document for this substance to the High Production Volume (HPV) Challenge Program web site in June 2010 (http://www.epa.gov/chemrtk/hpvis/hazchar/27676626_1,3,5-Tris_3,5-di-tert-butyl-4-hydroxybenzyl_-1,3,5-triazine-2,4,6_1H,3H,5H_-trione_June%202010_%20.pdf). The hazard characterization document was prepared from US EPA’s scientific review of the screening-level hazard data set, and provides further data on the targeted endpoints.

This targeted assessment document was originally based on both the material from the chemical assessment

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council of the MHLW and the hazard characterization document of the US EPA, and the toxicological profile was reassessed for the OECD HPV chemical programme.

Physical-chemical properties

1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid is a white powder with water solubility of less than 10 mg/L at 25 °C. The measured density is 1.145 g/cm³ at 25 °C. The calculated values of melting point and vapour pressure are 349.8 °C and 6.2×10⁻²⁶ Pa at 25 °C respectively. The measured partition coefficient between octanol and water (Log Kow) is more than 5.45. The calculated dissociation constant (pKa) is 11.6.

Human Health

1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid administered orally caused no effects at a dose of 2000 mg/kg bw in rats and the oral LD₅₀ was greater than 2000 mg/kg bw in both sexes (OECD TG 401). In another oral acute dose study (OECD TG 401), no mortality occurred at a dose of 5000 mg/kg bw in rats. In an acute dermal study (OECD TG 402), no mortality occurred at a dose of 2000 mg/kg bw in rats, and the dermal LD₅₀ was greater than 2000 mg/kg bw.

In a repeated dose oral toxicity study in rats following the Guideline for 28-Day Repeated Dose Toxicity Test in Mammalian Species (Chemical Substances Control Law of Japan), 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid was administered via gavage at 0 (vehicle control: 0.5% HPMC), 100, 300, or 1000 mg/kg bw/day for 28 days. Neither death nor clinical signs of toxicity were observed in both sexes at any dose tested. There were no adverse effects in any parameters examined (body weight, food consumption, haematological, blood biochemical and urinalysis parameters, organ weights and histopathological findings). The NOAEL of this study was 1000 mg/kg bw/day in both sexes.

Two 13-week oral repeated-dose toxicity studies in rats exposed via dietary administration showed no mortality or treatment-related effects at the highest concentrations tested; 900 - 750 mg/kg-bw/day (males - females) in one study (OECD TG 407) and 500 - 600 mg/kg-bw/day (males-females) in the second study. A 90-day oral repeated-dose toxicity study revealed no significant treatment effects in dogs exposed via dietary administration at dose of 250 mg/kg-bw/day (highest dose tested).

Based on these results, the NOAEL of repeated dose oral toxicity was 250 mg/kg bw/day.

In a bacterial mutation study using four strains of *Salmonella typhimurium* and an *Escherichia coli* WP2 *uvrA* strain (OECD TG 471), 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid was negative with or without metabolic activation. In another bacterial mutation study using five strains of *Salmonella typhimurium* (OECD TG 471), the substance did not induce gene mutations. In an *in vitro* chromosome aberration test using CHL/IU cells (OECD TG 473), no increase in structural aberrations was observed at any dose with or without metabolic activation, but polyploidy was significantly increased with dose-dependence after short-term and continuous treatment without metabolic activation. Cytotoxicity was not observed in any treatment group in this study. In another *in vitro* chromosome aberration test using Chinese hamster ovary cells (OECD TG 473), the substance did not induce any aberrations. In an *in vivo* micronucleus test, Chinese hamsters received a single oral administration at 5000 mg/kg bw. The test substance did not induce micronuclei.

Based on these results, 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid is not considered to be genotoxic *in vivo*.

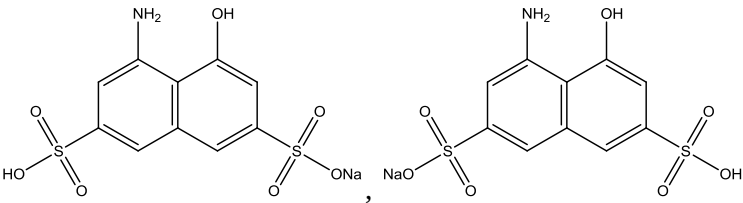
Agreed hazard conclusions

The chemical does not possess properties indicating a hazard for human health endpoints targeted in this assessment.

Available Exposure information

Total volume of production and import of 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid in Japan (sponsor country) was estimated to be 150 tonnes in the fiscal year of 2008. Total volume of production and import in the United States was 1 to 10 million pounds (450 – 4,500 tonnes) in 2006 according to Inventory Update Reporting information by the U.S. Environmental Protection Agency. Worldwide production volume was not available. 1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)isocyanuric acid is used as anti-oxidant for plastics in Japan.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	5460-09-3
Chemical Name	Monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address only the following endpoint(s): [Human Health: acute toxicity, repeated dose toxicity and *in vitro* mutagenicity]. It cannot be considered as a full SIDS Initial Assessment. Nevertheless, the conclusions for the endpoints addressed have been agreed by member countries and may be used for hazard and risk assessment. Results on other endpoints may be relevant for hazard and risk assessment but have not been addressed in the assessment.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law, hazard assessment of existing chemical substances has been conducted. If a chemical substance is evaluated as “not biodegradable (persistent)” and “not highly bioaccumulative”, at least, a 28-days repeated dose toxicity and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long-term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

Monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate was evaluated as “not biodegradable (persistent)” and “moderately bioaccumulative” by the METI (Ministry of Economy, Trade and Industry), Japan. Biodegradation and bioaccumulation are not parts of the targeted assessment and therefore not presented in the ITAP. In order to determine whether this chemical is classified as a Type II monitoring chemical substance, the initial hazard assessment of monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate was conducted for the acute toxicity, repeated dose toxicity and mutagenicity by the MHLW (Ministry of Health, Labour and Welfare), Japan, in December 2006.

This targeted assessment document was originally based on the material from the chemical assessment council of MHLW, and the toxicological profile was reassessed for the OECD HPV chemical programme.

Physical-chemical properties

Monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate is a light brown powder with water solubility of 11,400 mg/L at 20 °C. It is thought that sodium ion of this chemical is dissociated from the sulfonate group in water. The melting point is more than 380 °C. A calculated partition coefficient between octanol and water (Log K_{ow}) is -2.3 for the free acid. A calculated vapour pressure is 9.8×10^{-22} Pa at 25 °C.

Human Health

Monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate administered orally caused no effects at a dose of 2000 mg/kg bw in rats and the oral LD₅₀ was greater than 2000 mg/kg bw in both sexes (OECD TG 401).

In a repeated dose oral toxicity study in rats following the Guideline for 28-Day Repeated Dose Toxicity Test in

Mammalian Species (Chemical Substances Control Law of Japan), monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate was administered via gavage at 0 (vehicle control: 1 w/v% methylcellulose), 30, 100, 300, or 1000 mg/kg bw/day for 28 days. There were no adverse effects on any observations including body and organ weights, blood and urine analyses, and microscopic examination of the liver and kidney. Based on the results, the NOAEL for repeated dose oral toxicity was 1000 mg/kg bw/day in both sexes.

In a bacterial mutation study using four strains of *Salmonella typhimurium* and an *Escherichia coli* WP2 *uvrA* strain (OECD TG 471), monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate was negative with or without metabolic activation. In an *in vitro* chromosome aberration test using Chinese hamster lung (CHL/IU) cells (OECD TG 473), monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate was also negative with or without metabolic activation.

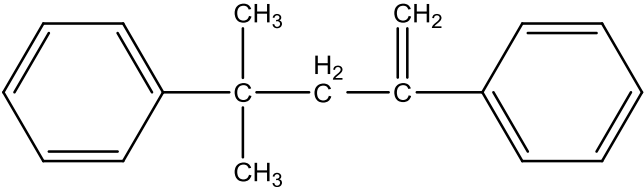
Agreed hazard conclusions

This chemical does not possess properties indicating a hazard for the human health endpoints targeted in this assessment.

Available Exposure information (not part of the targeted assessment)

Total volume of production and import of monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate in Japan (sponsor country) was estimated to be in the range of 100 – 1,000 tonnes in the fiscal year of 2007. Total volume of production and import in USA was 0.5 to 1 million pounds (227 – 454 tonnes) in 2006 according to IUR information by the US-EPA. Worldwide production volume was not obtained. Monosodium 4-amino-5-hydroxynaphthalene-2,7-disulphonate is used as an intermediate for azo dyes and dye mordants. No other use information was obtained in Japan.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6362-80-7
Chemical Name	1,1'-(1,1-dimethyl-3-methylene-1,3-propanediyl)bisbenzene Hereafter this chemical is mentioned as “ α -methylstyrene dimer”
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

α -Methylstyrene dimer is a colourless liquid with water solubility of 0.230 mg/L at 20 °C. Melting point and boiling point are less than -100 °C and 312.1 °C, respectively. Vapour pressure is 6.64×10^{-2} Pa at 25 °C, and partition coefficient between octanol and water (Log K_{ow}) is 6.2.

Human Health

No data were available on ADME (absorption, distribution, metabolism, excretion) concerning α -methylstyrene dimer; however, this chemical was considered to be absorbed through the gastrointestinal tract and well distributed in the body based on observations in the combined repeated dose and reproductive/developmental toxicity test by oral administration of α -methylstyrene dimer.

In an acute oral toxicity study, α -methylstyrene dimer was administered to female rats by gavage at 300 or 2000 mg/kg bw [OECD TG 423 (acute toxic class method)]. The substance caused deaths at 2000 mg/kg bw, and diarrhoea, tremor, clonic convulsions and soiled perineal region were observed at this dose. No effects were observed in the 300 mg/kg bw group. The oral LD₅₀ cut-off value was estimated to be 2,000 mg/kg bw for female rats. No reliable acute inhalation or dermal studies were available for α -methylstyrene dimer.

α -Methylstyrene dimer showed severe irritation on the skin in rabbits. The effects included moderate erythema and slight or moderate oedema after 4-hr application, and the erythema and pigmentation was found after 14-day recovery period. No experimental data were available for irritation on eyes and respiratory tract in animals.

No experimental data were available for skin sensitization in animals.

The repeated dose toxicity of α -methylstyrene dimer has been investigated in a combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422]. α -Methylstyrene dimer was administered via gavage daily to male and female rats at 0, 45, 180 or 720 mg/kg bw/day, for 42 days (from 14-days before mating) for males and 44-56 days (from 14-days before mating to day 6 of lactation) for females. Two females given 720 mg/kg bw/day were found dead, and soiled hair, hypothermia and/or decrease in locomotor activity were observed before death. All surviving male and female rats in the 180 and 720 mg/kg bw/day groups showed transient salivation just after the administration and/or soiled hair. In the 720 mg/kg/day group, body weights were lower than those of controls from day 4 through the last day of treatment in males, and on day-4 of treatment, and days 0, 14, and 21 of gestation in females. No α -methylstyrene dimer related effects on FOB (Functional Observational Battery) parameters, sensory response, grip strength, and spontaneous motor activity were observed for both male and female rats. At the end of the administration period, urinary volumes were increased and specific gravity was decreased in males at 720 mg/kg bw/day. In the hematological examination, decreases of red blood cell and hematocrit were observed in female rats at 720 mg/kg bw/day. There were increases in activated partial thromboplastin time in males given 180 and 720 mg/kg bw/day and in females given 720 mg/kg bw/day, and in the prothrombin time at 180 and 720 mg/kg bw/day and in the fibrinogen level

at 720 mg/kg bw/day in males. In the blood chemical examination, increases of calcium at 180 and 720 mg/kg bw/day and of γ -GTP, total protein, A/G ratio, albumin, total bilirubin and total cholesterol, and a decrease of chlorine were observed at 720 mg/kg bw/day in male rats. In female rats, total protein was increased at 180 and 720 mg/kg bw/day, and a decrease of glucose, and increases in γ -GTP and total bilirubin at 720 mg/kg bw/day were shown. There were increases in absolute/relative weights of the liver in males given 45 mg/kg bw/day and higher and in females given 180 and 720 mg/kg bw/day, and of the kidney in males given 180 and 720 mg/kg bw/day. Increases of the absolute and/or relative thyroid weights were observed at 720 mg/kg bw/day in both sexes. In the histopathological examination, centrilobular swelling and basophilic change of hepatocytes were observed at 45 mg/kg bw/day and above in males and at 180 and 720 mg/kg bw/day in females. There were hyaline droplets in the renal tubular epithelium in male rats at 720 mg/kg bw/day. In the thyroids, the incidence of diffused follicular cell hyperplasia was increased in male rats at 720 mg/kg bw/day group. These effects on the liver, kidneys and thyroids were not completely recovered at the end of 14-day recovery period. Based on these results, the NOAEL for repeated dose toxicity was considered to be below 45 mg/kg bw/day in male rats and 45 mg/kg bw/day in females.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium* and *Escherichia coli* [OECD TG 471], α -methylstyrene dimer was negative both with and without metabolic activation. An *in vitro* chromosomal aberration test [OECD TG 473] using CHL/IU cell line with 24-h continuous exposures without metabolic activation, and 6-h short term exposure with and without metabolic activation was also negative. Based on these results, α -methylstyrene dimer is considered to be non genotoxic *in vitro*.

No data were available for the carcinogenicity of α -methylstyrene dimer.

The reproductive toxicity of α -methylstyrene dimer has been well investigated in a combined repeated dose and reproductive/developmental toxicity screening test in rats [OECD TG 422] described above. In this study, death was observed in females given 720 mg/kg bw/day in the preweaning period. The body weight of dams on day-4 of treatment, and days 0, 14 and 21 of gestation in the 720 mg/kg bw/day group were low. The corpora lutea and implantation scars were decreased in dams treated with 720 mg/kg bw/day. The other reproductive parameters (conceiving days, copulation and fertility index, gestation days, gestation index, delivery conditions and nursing conditions) were not affected by α -methylstyrene dimer treatment. Decreases of the pups born, live pups born and live pups on day 4 of lactation were observed in the 720 mg/kg bw/day group. There was an increase in the mean pups weight and decrease in the total litter weight on days 0 and 4 of lactation in the 720 mg/kg bw/day group. No treatment-related abnormalities on general signs, external observations and necropsy findings of pups were recognized. The NOAEL for reproductive toxicity was considered to be 180 mg/kg bw/day based on the decrease in the corpora lutea and implantation scars in the 720 mg/kg bw/day group. The NOAEL for developmental toxicity was considered to be 180 mg/kg bw/day because of the decreases in the numbers of pups born, live pups born, and live pups on day 4 of lactation at 720 mg/kg bw/day. However, these effects were observed at the high dose, at which significant systemic/maternal toxicity was observed.

α -Methylstyrene dimer may present a hazard for human health (skin irritation and repeated dose toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

In the atmosphere, α -methylstyrene dimer is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.181 days and a rate constant of $59.0 \times 10^{-12} \text{ cm}^3/\text{molecule-sec}$ were obtained by AOPWIN for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

α -Methylstyrene dimer is not hydrolysed due to the lack of hydrolysable functional groups. A hydrolysis test according to OECD Test-guideline 111 showed that α -methylstyrene dimer was stable in water at pH 4, pH 7 and pH 9 at 50 °C for five days.

A test result of α -methylstyrene dimer with activated sludge showed 0 % degradation by BOD after four weeks cultivation period according to the equivalent protocol with OECD test guideline 301C. BIOWIN estimation predicts that α -methylstyrene dimer is not ready biodegradable. According to these results, α -methylstyrene dimer is considered to be not-readily biodegradable.

In a study performed according to the equivalent protocol with OECD test-guideline 305 with carp exposed for a sixty day exposure period at concentrations of 0.01 mg/L or 0.001 mg/L, bio-concentration factors of 5,210 for the 0.01 mg/L treatment and 4,690 for the 0.001 mg/L treatment were obtained. These BCF values were normalized to 5 % lipid content. Taking into account the octanol-water partition coefficient, a bio-concentration factor can be calculated as 5,725 according to a log K_{ow} of 6.2 by BCFBAFWIN. These

results show a relatively high potential for bioaccumulation of α -methylstyrene dimer for aquatic organisms.

Fugacity level III calculations show that α -methylstyrene dimer is mainly distributed to the soil compartment (60 %) and sediment compartment (34 %) if equally and continuously released to the air, soil and water. A Henry's law constant of 82.9 Pa.m³/mole at 25 °C suggests that the volatilisation potential of α -methylstyrene dimer from the water surface is not rapid but possibly significant. Soil adsorption coefficient (log K_{oc}) is estimated to be 5.1.

The following acute toxicity test results have been determined for aquatic species;

Fish [<i>Oryzias latipes</i>]:	96 h LC50 > 0.092 mg/L (measured)
Daphnid [<i>Daphnia magna</i>]:	48 h EC50 = 0.057 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h ErC50 > 0.059 mg/L (measured, growth rate)
	72 h EbC50 > 0.059 mg/L (measured, biomass)

The following chronic toxicity test results have been determined for aquatic species:

Algae [<i>Pseudokirchneriella subcapitata</i>]:	72 h NOEC = >0.059 mg/L (measured; growth rate)
	72 h NOEC = >0.059 mg/L (measured; biomass)

α -Methylstyrene dimer possesses properties indicating a hazard for the environment (acute aquatic toxicity values less than 1 mg/L for invertebrates). The substance is not readily bio-degradable and has high potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

Total volume of production and import of α -methylstyrene dimer in Japan (sponsor country) was 2,000 tonnes – 3,000 tonnes in the fiscal years of 2007 and 2008. Production volume of α -methylstyrene dimer in the USA was less than 500,000 pounds (226.8 tonnes) in 2006 according to IUR information by the US-EPA. Worldwide production volume of α -methylstyrene dimer was not available. α -Methylstyrene dimer is produced by the dimerization of 2-phenylpropene followed by distillation.

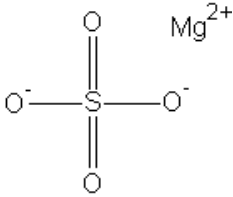
α -Methylstyrene dimer is used as a chain transfer agent for polymer synthesis. Function of α -methylstyrene dimer is to adjust the molecular weight of SB latex polymers and ABS resins. No other use information was obtained in Japan.

α -Methylstyrene dimer is manufactured with continuous process in the closed system in Japan. Waste water from the treatment plant is treated with activated sludge before it is released. No detailed information was obtained during the processing process in Japan.

Occupational exposure to α -methylstyrene dimer through inhalation of mist rather than vapour may be of concern, because its vapour pressure is very low. Dermal intake is also of concern, because α -methylstyrene dimer has a high Log K_{ow} and low water solubility.

As α -methylstyrene dimer is not used in the consumer products, no consumer exposure is expected for α -methylstyrene dimer.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7487-88-9
Chemical Name	Magnesium sulfate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical and chemical properties**

Magnesium sulfate is a colourless crystalline powder that decompose at 1124 °C. It has a density of 2.66 g/cm³ and water solubility of 357 g/L at 25 °C. The boiling point, vapour pressure, dissociation constants and partition coefficients are not applicable to an inorganic salt like magnesium sulfate.

Human Health

Magnesium is a cofactor of many enzymes involved in intermediary metabolism. Magnesium is absorbed in the intestinal tract and excreted into the digestive tract by bile and pancreatic and intestinal juices. There is an apparent obligatory urinary loss of magnesium, which amounts to about 12 mg/day and the urine is the major route of excretion under normal conditions. Unabsorbed magnesium is excreted in the feces.. Magnesium is filtered by the glomeruli and reabsorbed by renal tubules. In the blood plasma, about 65 percent is the ionic form while the remainder is bound to protein. Excretion also occurs via the sweat and milk. Approximately 70 percent of serum magnesium is ultrafilterable, and about 95 percent of the filtered magnesium is reabsorbed, which is an important factor in maintaining magnesium homeostasis. Tissue distribution studies indicate that of 20 g body burden in humans, the majority is intracellular in the bone and muscle including the myocardium, but some magnesium is present in every cell of the body.

In an acute oral toxicity study [OECD TG 423], 2 groups of 3 female rats were administered magnesium sulfate of 300 (1st and 2nd step) and 2,000 mg/kg (3rd and 4th step) bw via gavage. Mortality, body weights and clinical signs were recorded during a 14 days observation period and the animals were subjected to gross necropsy examination. The oral LD₅₀ values were ≥ 2,000 mg/kg bw for female rats. No deaths were observed. Body weights increased normally. Clinical signs such as diarrhea and watery diarrhea were observed in animals dosed with 2,000 mg/kg bw. All rats survived until the experiment was terminated. No treatment related findings were observed during treatment. No experimental data were available for acute dermal and inhalation toxicity in animals.

No reliable data were available for skin and eye irritation.

No reliable data were available for sensitisation.

In a combined oral repeated dose and reproductive/developmental toxicity screening study in rats following OECD TG 422, magnesium sulfate was administered via gavage to 13 animals/sex/dose at 0, 50, 150 or 450 mg/kg bw/day. Males of the main group and both sexes of the recovery group were dosed once daily for a total of six weeks (two weeks each prior to, during and post mating), and females of the main group were dosed once daily for two weeks prior to mating, throughout gestation and for five or six days after delivery. No deaths were observed in either sex. Treatment related effects of clinical signs, increased body weight gain, food

consumption, haematology, clinical biochemistry, organ weight changes, macroscopical/histopathological findings were not observed in males/females at dose levels of 50 and 150 mg/kg bw/day. Based on the effects of soft stool in 450 mg/kg group, the NOAEL for repeated dose oral toxicity was considered to be 150 mg/kg bw/day and the LOAEL for repeated dose oral toxicity was considered to be 450 mg/kg bw/day.

In a bacterial reverse mutation assay [OECD TG 471] with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA, magnesium sulfate was negative both with and without metabolic activation. In an *in vitro* chromosomal aberration test [OECD TG 473] using Chinese Hamster Lung (CHL) cells, both in the absence and the presence of a metabolic activation system, magnesium sulfate was negative with and without metabolic activation. In an *in vivo* micronucleus assay [no guideline followed] using femoral marrow cells of male mice, results were negative up to 500 mg/kg bw (the highest dose tested). Based on these results, magnesium sulfate is considered to be non genotoxic *in vitro* and *in vivo*.

No data were available for the carcinogenicity of magnesium sulfate.

The reproductive/developmental toxicity of the magnesium sulfate has been investigated in a combined oral repeated dose/reproductive and developmental toxicity screening test in rats [OECD TG 422]. Rats were treated by gavage at doses of 0, 50, 150, or 450 mg/kg bw/day. Males in the main group (13 rats per group) were administered for a total of six weeks (two weeks each prior to, during and post mating), and females in main group (13 rats per group) were administered for two weeks prior to mating, throughout gestation and five days (six days in twelve females) after delivery. No deaths were observed in either sex. The gestation indices were 100 %, and the pre-implantation loss rates were 10.5% and 4.8% in the control and 450 mg/kg bw/day groups, respectively. The post-implantation loss rates were 7.9% and 5.5% in the control and 450 mg/kg bw/day groups, respectively, and the live birth indices were 92.1% and 94.5% in the control and 450 mg/kg bw/day groups, respectively. In addition, the viability indices on postnatal day 0 were 97.6% and 99.0% in the control and 450 mg/kg, respectively, and the viability indices on postnatal day 4 were 99.6% and 96.8% in the control and 450 mg/kg bw/day groups, respectively. Furthermore, there were no effects in live birth index, sex ratio, mean litter size, and external findings including eye, ear, mouth, palate, absence of limbs and tail, position, size and shape on day 0 and 4. No dose-related effects on reproductive and developmental parameters were observed up to the highest dose tested. There were no treatment related effects on parental animals observed at any dose. Based on these results, the NOAEL for reproductive and developmental toxicity was considered to be 450 mg/kg bw/day. Also, magnesium sulfate is not considered to be a reproductive and developmental toxicant.

Magnesium sulfate does not present a hazard for human health due to its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

Environmental fate analysis based on log K_{ow} and log K_{oc} and typical fugacity modelling are not applicable to magnesium sulphate due to its inorganic properties. Photodegradation and biodegradation are also not applicable to an inorganic metal salt like magnesium sulfate. Given its high solubility in water, magnesium sulfate will dissociate and release Mg^{2+} and SO_4^{2-} ions. The dissociated Mg^{2+} cation can then transform and form complexes with dissolved ligands present in natural waters. Under anaerobic conditions, the dissociated sulfate ion is reduced to sulfide ion, which establishes an equilibrium with hydrogen ion to hydrogen sulphide. As a macronutrient, magnesium is widespread in living cells and so it is not expected to bioconcentrate in aquatic organisms.

The following acute toxicity test results for magnesium sulfate have been determined for aquatic species:

Fish [<i>Oryzias latipes</i>]	96 h $LC_{50} > 96.4$ mg/L (measured)
[<i>Pimephales promelas</i>]	96 h $LC_{50} = 2,820$ mg/L (nominal)
Invertebrate [<i>Daphnia magna</i>]	48 h $EC_{50} > 88.7$ mg/L (measured)
[<i>Daphnia magna</i>]	48 h $LC_{50} = 1,820$ mg/L (nominal)
Algae [<i>Pseudokirchneriella subcapitata</i>]	72 h $E_rC_{50} > 99.2$ mg/L (growth rate) (measured)
	72 h $E_yC_{50} > 99.2$ mg/L (yield) (measured)

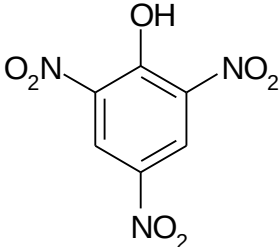
Magnesium sulfate does not present a hazard for the environment based on its low hazard profile. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

In the Republic of Korea (sponsor country), production, import, and export volume were 2,075, 2,408, and 17 tonnes, respectively, in 2006.

Magnesium sulfate is used as a raw material in high polymer, process regulators, fixing agents, cleaning/washing agents and disinfectants, pesticides, fertilisers, stabilisers, synthetic resin, flame retardants and fire preventing agents in the sponsor country. It is also used for weighting cotton and silk, increasing the bleaching action of chlorinated lime, fire-proofing fabrics, dyeing and printing calicos and explosives. In the Republic of Korea, the manufacturing process of magnesium sulfate is handled in a closed system.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-89-1
Chemical Name	Picric acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

Picric acid is a pale yellow, odourless, intensely bitter crystal with relatively high water solubility of 11.8 g/L at 20 °C (measured). Picric acid has an explosive property when shocked or heated, especially reactive with metals or metallic salts. Melting point is 122.5 °C and explodes above 300 °C. Vapour pressure is 5.1×10^{-5} Pa at 25 °C (estimated), and partition coefficient between octanol and water ($\log K_{ow}$) is 0.89 at pH 1.0 (measured). Dissociation constant of $pK_a = 0.16$ at 20 °C (measured) indicates that picric acid exists primarily as an anion in aquatic compartment or moist soil surfaces.

Human Health

Picric acid was administered to male rats by intravenous injection (50 mg/kg bw) or by oral gavage [100 mg/kg bw]. At 24 h after intravenous injection, 81.5% of administered radioactivity was cleared from the blood with 58.9% excreted in the urine and 12.2% in the faeces. The plasma half-life was 13.4 h. After oral administration, approximately 60% of the dose was absorbed within 24 h. The highest concentration of radioactivity was detected, in a decreasing order, in the spleen, kidney, liver, lung, and testes. In the urine collected over a 24-period, approximately 60% of total radioactivity was unchanged parent compound. Major urinary metabolites were N-acetylisopicramic acid (14.8%), picramic acid (18.5%) and N-acetylpicramic acid (4.7%).

The oral LD_{50} values were 492 mg/kg bw for male rats and 283 mg/kg bw for female rats (OECD TG 401). Observed clinical signs included decrease in locomotor activity, abnormal gait, clonic convulsions and loose stool, which were also found in surviving animals at 400 mg/kg bw. In dead animals, pathological changes such as haemorrhage, hard wall and thickening of the wall were observed in the glandular stomach. In another study (not according to OECD guideline), the oral LD_{50} values were 290 mg/kg bw for male and 200 mg/kg bw for female rats. Tremors, violent tonic/clonic convulsions, circumorbital discharge (chromodacryorrhea) of the eye, and a fall in blood pH were observed. No reliable information was available regarding acute toxicity via dermal and inhalation routes.

Although no reliable information on skin irritation was available, it has been reported that picric acid in the form of a crystalline solid as well as aqueous solution can produce skin irritation. As for eye irritation, there is one reliable study, in which rabbits showed minimal irritation to the solid form of picric acid and the recovery within 24 h. Other available information on eye irritation was not reliable, but provided the following: a solution of picric acid was reported to be injurious to rabbit eyes although the details were not available.

Picric acid was positive for skin sensitization in a split adjuvant test in guinea pigs. In humans, only secondary literature reported sensitization dermatitis in munitions workers. This suggests the possibility that picric acid can cause skin sensitization in human.

A 28-day guideline study of the repeated dose toxicity of picric acid was performed. The compound was

administered via gavage to 6 or 12 rats/sex/dose at 0, 4, 20, or 100 mg/kg bw/day 7 days/week for 4 weeks. No deaths were observed in either sex. At the highest dose tested, the absolute and relative spleen weight and the relative liver weight were increased in both sexes. In males of the 100 mg/kg bw group, decrease in the absolute and relative weight of the epididymis was also found. Histopathological and haematological examinations revealed haemolytic anemia, as evidenced by reductions in red blood cells and haemoglobin, and haemosiderin deposition and extramedullary haematopoiesis in the spleen in both sexes in 100 mg/kg bw dose group. Furthermore, altered development of germinal centres in the spleen, ulcers of the cecum and centrilobular hypertrophy of hepatocytes were found in both sexes in the 100 mg/kg bw dose group. Based on these effects, the NOAEL for 28-day repeated dose oral toxicity in male and female rats was considered to be 20 mg/kg bw/day.

In a reproduction/developmental toxicity screening test, rats (12 animals/sex/dose) were administered picric acid by oral gavage at a dose of 0, 4, 20, or 45 mg/kg bw/day (OECD TG 421). The compound was administered to males for 46 days from day 14 before mating to the day before sacrifice and to females from day 14 before mating and throughout mating and pregnancy to day 3 of lactation. No deaths occurred. Reduced body weight gain was noticed among males in the 45 mg/kg bw dose group. Increases in the relative weights of the liver and kidneys and a decrease in the absolute weight of the epididymis in males as well as increases in the absolute and relative weights of the liver and spleen in females were observed at this dosage. Based on these results, the NOAEL for repeated dose oral toxicity was considered to be 20 mg/kg bw/day.

In a bacterial reverse mutation assay (Ames test) conducted according to the OECD TG 471, picric acid was shown to be positive in *Salmonella typhimurium* TA 98 and TA1537 without metabolic activation and in *Salmonella typhimurium* TA100, TA1535, TA98 and TA1537 with metabolic activation. Positive results were also observed in some strains in other bacterial reverse mutation assays. An *in vitro* chromosomal aberration test (OECD TG 473) using cultured Chinese hamster lung cells was positive only at cytotoxic doses (1600 and 1800 µg/mL) without metabolic activation. In a chromosomal aberration test using Chinese hamster ovary cells, negative results were obtained up to 1000 µg/mL without metabolic activation. Both of these chromosomal aberration tests showed negative results under the presence of metabolic activation. Picric acid dose-dependently induced sister chromatid exchange in Chinese hamster ovary cells under the absence of metabolic activation. In a mouse micronucleus test, male and female mice (2 animals/sex/dose) were administered picric acid twice (0 and 24 h) at doses of 0, 22.9, 68.7, or 91.6 mg/kg bw (intraperitoneal injection) or 0, 229, 343, or 458 mg/kg bw (per oral). Micronucleated polychromatic erythrocytes did not increase at any dose. In *Drosophila* SLRL mutation tests, positive results were obtained after injection of picric acid, but feeding studies provided conflicting results. In the reciprocal translocation test with *Drosophila* sp. by injection, the substance showed negative results. Based on these results, picric acid is considered to be genotoxic *in vitro*. Although no induction of micronucleus was observed in mammals, it is not possible to exclude genotoxicity, as the potential for picric acid to cause gene mutations has not been investigated *in vivo*.

No data were available on the carcinogenicity of picric acid.

In the above-mentioned reproduction/developmental toxicity screening test (OECD TG 421), picric acid was administered via gavage to 12 animals/sex/dose at 0, 4, 20 or 45 mg/kg bw/day, for 7 days/week for 46 days in males and from day 14 before mating, throughout the mating and pregnancy periods, to day 3 of lactation in females. Reproductive performances were not affected in parental animals. At necropsy, the absolute weight of the epididymis was decreased among males in the 45 mg/kg bw dose group. In the testes, retention of step-19 spermatid in stage IX-XI was found in two males at 45 mg/kg bw/day. Quantitative analysis of spermatogenesis revealed a decrease in the number of pachytene spermatocytes in stage I-VI at 45 mg/kg bw/day. There was also a slight atrophy of seminiferous tubules in one male each at 20 and 45 mg/kg bw/day. However, such small incidences of atrophic changes with weak severity are occasionally observed in control rats, and also these pathological changes may be justified as an independent phenomenon from the stage (I-VI) specific spermatogenesis effect at the dose of 45 mg/kg bw/day; therefore, these slight atrophy of seminiferous tubules were considered not to be an adverse effect. The NOAEL for this study was considered to be 20 mg/kg bw/day in rats.

The above-mentioned 28-day repeated oral dose toxicity study using rats clearly demonstrated the male reproductive toxicity of picric acid at the higher doses. Organ weight measurements revealed decreases in the absolute and relative weights of the epididymides in the 100 mg/kg bw dose group. Histopathological examination revealed diffuse atrophy of the seminiferous tubules of the testes (6/6 males), cell debris in the lumen (4/6 males) and decrease in the number of sperms in the epididymis (6/6 males) in the 100 mg/kg bw group. These changes were also observed after a 14-day withdrawal period. There were no changes in the weight and histopathology of male reproductive systems in the 4 and 20 mg/kg bw groups. These results suggested that reproductive performances would be affected at the dose of 100 mg/kg bw/day. Based on the

above studies, the NOAEL for reproductive toxicity was considered to be 20 mg/kg bw/day.

As for the developmental toxicity, there have not been any formal investigations (e.g. prenatal developmental toxicity study); however, in the above-mentioned reproductive and developmental toxicity screening test (OECD TG 421), no adverse effects on development were observed up to the highest dose tested. In another study, picric acid was administered by gavage to newborn rats at doses of 0, 4.1, 16.3, or 65.1 mg/kg bw/day from postnatal days 4 to 21 (for a total of 18 days). Lower body weight and higher relative liver weight were observed at a dose of 65.1 mg/kg bw, but the animals exhibited no abnormal changes in developmental landmarks, reflex ontogeny, urinalysis, or sexual maturation at all doses. Based on these results, the NOAEL for developmental toxicity in rats was considered to be 45 mg/kg bw/day.

Picric acid may present a hazard to human health (skin and eye irritation, skin sensitization, acute oral toxicity, repeated dose toxicity, reproductive toxicity and genotoxicity). Adequate screening level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

In the atmosphere, picric acid is expected to be degraded by hydroxyl radicals. A calculated half-life time of 75.914 days and a rate constant of $0.14 \times 10^{-12} \text{ cm}^3/\text{molecule-sec}$ were obtained by AOPWIN for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

Picric acid is not hydrolysed due to the lack of hydrolysable functional groups. A hydrolysis test according to OECD Test-guideline 111 showed that picric acid was stable in water at pH 4, pH 7 and pH 9 at 50 °C for five days.

A test result of picric acid with activated sludge showed 23% degradation by BOD after a 28 day cultivation period according to OECD test guideline 301C. BIOWIN estimation predicts that picric acid is not ready biodegradable. According to these results, picric acid is considered to be not-readily biodegradable.

In a study performed according to the equivalent protocol with OECD test-guideline 305C with carp over a 6 week exposure period at concentrations of 0.5 mg/L or 0.05 mg/L, bio-concentration factors were less than 0.24 for the 0.5 mg/L treatment and less than 2.2 for the 0.05 mg/L treatment. Taking into account the octanol-water partition coefficient, a bio-concentration factor can be calculated as 3.16 according to a $\log K_{ow}$ of 0.89 by BCFBAFWIN. These results show a low potential for bioaccumulation of picric acid for aquatic organisms. As picric acid has $\log K_{oc}$ of 2.0 (estimated with $\log K_{ow}$ of 0.89) and exists as an anion in moist soil, mobility in the soil is expected to be high.

As picric acid is present in dissociated form in the environment mainly in the water phase; the distribution using the fugacity model is difficult to be estimated accurately. Based on its low pK_a value, the substance is expected to be present in the environment in the anionic form. As anions are neither subject to volatilisation nor to adsorption, the hydrosphere is the target compartment for this chemical.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Onchorynchus mykiss</i>]:	96 h LC ₅₀ = 110 mg/L (nominal)
Daphnid [<i>Daphnia magna</i>]:	24 h L(E)C ₅₀ = 85 and 145 mg/L (nominal)
	48 h L(E)C ₅₀ = 85, 86 and 90 mg/L (nominal)
	48 h EC ₅₀ = 55 mg/L (nominal, under two hours UV-A irradiation)
Copepod [<i>Nitocra spinipes</i>]	96 h LC ₅₀ = 92 mg/L (nominal)
Molluscs [<i>Crassostrea virginica</i>]:	144 h LC ₅₀ = 255 mg/L
	144 h EC ₅₀ = 28 mg/L (shell deposition, nominal)
Molluscs [<i>Littorina littorea</i>]:	96 h LC ₅₀ = 57 mg/L (nominal)
Algae [<i>Desmodesmus subspicatus</i>]:	72 h ErC ₅₀ > 500 mg/L (nominal, growth rate)
	72 h EbC ₅₀ = 575 mg/L (nominal, biomass)

The following chronic toxicity test results have been determined for aquatic species:

Fish [<i>Onchorynchus mykiss</i>]:	42 d LOEC = 0.05 mg/L (haemorrhage, measured)
Daphnid [<i>Daphnia magna</i>]:	21 d NOEC = 5 mg/L (reproduction and parent mortality, measured)
Molluscs [<i>Crassostrea virginica</i>]:	Significant growth inhibition at 0.05 mg/L (42 d, measured)
Algae [<i>Desmodesmus subspicatus</i>]:	72 h ErC ₁₀ = 240 mg/L (nominal; growth rate) 72 h EbC ₁₀ = 28 mg/L (nominal; biomass)

Picric acid possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L for invertebrates, and chronic aquatic toxicity value below 0.05 mg/L for fish and invertebrates). However this chemical is considered to be not readily biodegradable and has a low bio-concentration potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

Total volume of production and import of picric acid was reported in the range of 100-1,000 tonnes in the fiscal years of 2006, 2007 and 2008 in Japan (sponsor country). However, picric acid is mainly imported in the sponsor country. Worldwide production volume of picric acid was not available.

Picric acid is used as synthetic raw material for a plant protective (chloropicrin) and dye or used as explosives in the sponsor country. Picric acid is also used as a desulfurization catalyser and a laboratory reagent in Japan. It is mentioned that picric acid is used as explosives, matches, in leather industry, electric batteries, etching copper, manufacture of coloured glass, textile mordant, also as reagent.

Picric acid may be released to waste water during the industrial use. A nation-wide environmental survey of chemicals conducted by the Japanese Ministry of Environment in fiscal year 1980 showed that picric acid was detected neither in environmental surface water nor in sediment in three different places in Japan. According to the Japanese PRTR (Pollution Release and Transfer Register) system, the emission volume of picric acid was reported to be less than 1 tonne in the fiscal years of 2006, 2007 and 2008 in the sponsor country. According to these results, the environmental exposure of picric acid seems to be insignificant in Japan.

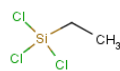
Picric acid is known to be absorbed by all routes of exposure. It is also known that a solution of picric acid is irritating to eyes and to skin. A worker who handles picric acid or products containing picric acid should wear goggles, dust respirator, and protective gloves to minimize contact and intake. A Permissible Exposure Limit of 0.1 mg/m³ (8 to 10 hour Time-Weighted Average) with skin designation and a short term exposure limit of 0.2-0.3 mg/m³ are adopted in the USA, Australia, United Kingdom, and the Federal Republic of Germany.

Consumer exposure to picric acid may occur during the use of explosives, matches and electric batteries. However, the detailed information was not available.

SIDS INITIAL ASSESSMENT PROFILE

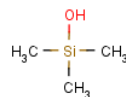
Category Name	Alkyl chlorosilanes (Chlorotrimethylsilane, Dichlorodimethylsilane, Trichloromethylsilane, and Trichloroethylsilane) Category		
CAS Nos.	Sponsored Substances 75-77-4 75-78-5 75-79-6 115-21-9 Hydrolysis Products 1066-40-6 1066-42-8 2445-53-6 5651-16-1 7647-01-0 Analogue Substance 1185-55-3		
Chemical Names	Sponsored Substances Chlorotrimethylsilane (CTMS) Dichlorodimethylsilane (C2DMS) Trichloromethylsilane (C3MS) Trichloroethylsilane (C3ES) Hydrolysis Products Trimethylsilanol (TMS) Dimethylsilanediol (DMSD) Methylsilanetriol (MST) Ethylsilanetriol (EST) Hydrogen Chloride (HCl) Analogue Substance Methyltrimethoxysilane (MTMS)		
Structural Formulae		75-77-4  75-78-5  75-79-6 	

1.1 115-21-9

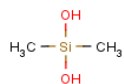


Hydrolysis Products

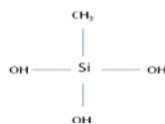
1066-40-6



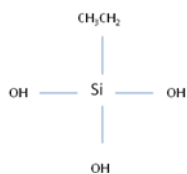
1066-42-8



2445-53-6



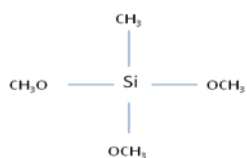
5651-16-1



7647-01-0

Analogue substance

1185-55-3



SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Justification

The category consists of four sponsored chlorosilanes: chlorotrimethylsilane (CTMS, CAS No. 75-77-4), dichlorodimethylsilane (C2DMS, CAS No. 75-78-5), trichloromethylsilane (C3MS, CAS No. 75-79-6), and trichloroethylsilane (C3ES, CAS No. 115-21-9). These chemicals are grouped into a category based on similar molecular structure, high reactivity, physicochemical and toxicological properties.

Similar High Reactivity

The chlorine group is the most active functional group on these molecules and determines many aspects of the behaviour of the category members. These chlorosilanes undergo rapid hydrolysis in the presence of water to form one to three moles of hydrochloric acid and one mole of silanol, depending on the parent substance. Hydrolysis is the primary reaction in aqueous systems and has been shown to occur very quickly (half-life <17 seconds) for CTMS, C2DMS, and C3MS. No data is available for C3ES.

Similar Chemical/Physical Properties

All category members are liquids with melting points, boiling points and vapour pressures that are largely dependent on molecular weight. Due to their high reactivity with water, water solubility and partition coefficient are not relevant endpoints.

Similar Toxicological Properties

These category members are severely irritating and corrosive at the site of contact (i.e., respiratory tract, skin, and eyes).

The approach to address the SIDS endpoints for these chlorosilanes is to utilize available data from the four category members and three hydrolysis products, including hydrogen chloride. Chlorosilanes react rapidly when exposed to water or polar reagents, producing hydrogen chloride (HCl; CAS No. 7647-01-0) and the corresponding silanols. The primary hydrolysis products for these sponsored chlorosilanes are hydrogen chloride (HCl; CAS No. 7647-01-0), common to the hydrolysis of all chlorosilanes and the corresponding silanol. Data are available for two of the silanol hydrolysis products: trimethylsilanol (TMS; CAS No. 1066-40-6) and dimethylsilanediol (DMSD; CAS No. 1066-42-8).

Repeated-dose and reproductive toxicity endpoints for the category members are characterized through the use of data from HCl, and two of the silanol hydrolysis products; TMS and DMSD. Aquatic toxicity endpoints are also characterized with data from the hydrolysis products (HCl, TMS and DMSD) and the structural analogue methyltrimethoxysilane (MTMS; CAS No. 1185-55-3) (which produces methylsilanetriol on hydrolysis, the hydrolysis product of C3MS). MTMS has previously been assessed in the OECD HPV programme: <http://webnet.oecd.org/hpv/ui/Search.aspx>. Hydrogen chloride has also previously been assessed in the OECD HPV programme: <http://www.chem.unep.ch/irptc/sids/oecd/sids/sidspub.html>.

Physical-chemical properties

The EPISuite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training set); therefore, there is greater uncertainty associated with the calculated values and they should be used with caution whenever they are reported below.

These chlorosilanes are very reactive and hydrolytically unstable; they are liquids at normal temperature and pressure. Hydrolysis studies (OECD TG 111) were conducted on three category members. The melting points range from -57.7°C (CTMS) to -105.6 °C (C3ES); boiling points range from 57.6 °C at 1013 hPa (CTMS) to 97.9°C at 1013 hPa (C3ES). Vapor pressures of these chlorosilanes range from 47.83 hPa at 20°C (C3ES) to 250.3 hPa at 25°C (CTMS).

The water solubility and partition coefficient estimates are not reliable because these chlorosilanes are hydrolytically unstable. The water solubility values of the silanol hydrolysis products TMS and DMSD are 920 mg/L and 2790 mg/L, respectively. The water solubility of HCl is 673 g/L at 30°C. The log of the 1-octanol/water partition coefficient (K_{ow}) of the silanol hydrolysis product, TMS is 1.19.

Human Health

There are no data for toxicokinetics of these chlorosilanes. However, chlorosilanes rapidly hydrolyze on contact with water. The hydrolysis products, TMS and DMSD, penetrated through human skin when applied neat in an *in vitro* test system. Also, the systemic effects found in an acute dermal toxicity study in rabbits with CTMS (discoloration of liver and lungs) provide evidence that chlorosilanes or their hydrolysis products can penetrate through the skin. These chlorosilanes may be absorbed via inhalation at high doses based on discoloration in the liver (and spleen for C2DMS) observed in acute inhalation studies. HCl -, a hydrolysis product of all chlorosilanes, will rapidly dissociate in the presence of water; its effects on skin are thought to be a result of pH change.

The range of 1 hour acute inhalation (OECD 403) LC50's for the category members is 8.35 mg/L (C3MS) to 18.92 mg/L (CTMS). The 4-hr nose-only LC50 for C3MS was 5.43 mg/L in rats. The acute inhalation hazard posed by an individual chlorosilane, as defined by an LC₅₀ value, is directly proportional to its chlorine content and subsequently to the HCl that is liberated during hydrolysis. The principal clinical signs were indicative of respiratory and ocular effects. The dermal LD50 for CTMS applied without vehicle using methods similar to OECD TG 402 in rabbits was 1513 (females) and 2030 (males) mg/kg bw; for C3MS (no vehicle; similar to OECD TG 402) the dermal LD50 in rabbits was 1068 (females) and 1719 (males) mg/kg bw. Necrosis, irritation and loss of body weight were common clinical signs for both substances. The primary necropsy findings for CTMS included various discolorations of the liver or lungs; no remarkable findings were noted for C3MS.

The oral (similar to OECD TG 401) LD50 for CTMS in rats was 5636 (females) and 4811 (males) mg/kg bw; for C3MS the oral LD50 in rats was 3594 (females) and 2057 (males) mg/kg bw. Necrosis, irritation and loss of body weight were common clinical signs for both substances; chlorosilanes are widely recognized as corrosive and considered irritants. The primary necropsy findings for CTMS included various discolorations of the liver or lungs; no remarkable findings were noted for C3MS. Reported signs of toxicity for both substances in surviving animals included sluggishness, salivation, dyspnea, rales, prostration, and/or staining/greasy texture of the fur. Body weight gains were reported for all groups of surviving animals exposed to either CTMS or C3MS. There were no remarkable findings at necropsy for surviving animals for either CTMS or C3MS with the exception of the finding of lungs with dark red patches in females dosed with CMS at 2540 mg/kg bw.

Acute toxicity of the hydrolysis products TMS and DMSD resulted in a 4-hour LC₅₀ of 3151 ppm (11.6 mg/L) and an LD₅₀ of >2000 mg/kg respectively. For TMS, common clinical signs included effects on respiration, activity, urogenital and facial staining, increased lacrimation, partial closer of eyes, and decreased urination and defecation. Necropsy findings included discoloration of the lungs, kidney, adrenal gland, liver, spleen and urinary bladder, distension of the urinary bladder, and clear fluid in uterus. For DMSD, clinical signs included impaired equilibrium, hypoactivity, and decreased respiration. There were no remarkable findings at necropsy. These sponsored chlorosilanes are corrosive and highly irritating to the skin, eyes and respiratory tract; these effects are likely due to the rapid production of HCl following hydrolysis. Similar effects are seen following exposure to HCl. The hydrolysis product, TMS, is non-irritating to the skin and slightly irritating to the eyes. No data are available on the sensitisation potential of the alkyl chlorosilanes or their hydrolysis products.

Repeated dose toxicity data for these chlorosilanes are not available. Based on their rapid hydrolysis, data from the primary hydrolysis products are used to fill the repeated dose toxicity endpoint. In 90-day inhalation studies in rats and mice exposed to 0, 0.015, 0.030 or 0.075 mg/L HCl, local effects of irritation were observed at 0.015 mg/L and above. The NOAEL for systemic toxicity for HCl, excluding the local effects of irritation, has been determined to be 0.030 mg/L for rats and mice based on decreased body weight gain (mice; male rats) and decreased liver weights (male mice). In a combined inhalation repeated-dose/ reproductive/developmental toxicity screening test in rats exposed to 0.22, 1.10 or 2.20 mg/L/day hydrolysis product, TMS, there were no treatment-related effects observed up to 2.2 mg/L/day. The NOAEL for inhalation systemic toxicity of TMS was 2.20 mg/L (highest concentration tested). In a combined oral gavage repeated-dose/reproductive/developmental toxicity screening test in rats treated with 0, 80, 250 or 750 mg/kg-bw/day hydrolysis product, TMS, liver effects (increased relative liver weights of 21% in females and histopathological changes) and clinical signs of toxicity (staggering gait) were observed at 750 mg/kg-bw/day. Liver weights were increased by 17% in females at 250 mg/kg-bw/day. The NOAEL for oral systemic toxicity of TMS was 250 mg/kg-bw/day. In a combined oral gavage repeated-dose/reproductive/developmental toxicity screening test in rats treated with 0, 50, 250 or 500 mg/kg-bw/day hydrolysis product, DMSD, clinical signs of toxicity included abdominal, urogenital and muzzle soiling in males at 250 and 500 mg/kg-bw/day and muzzle soiling in females at 500 mg/kg-bw/day. Based on liver porphyria in male rats and liver vacuolation in toxicity group female rats at 500 mg/kg-bw/day, the NOAEL for oral systemic toxicity of DMSD was 250 mg/kg-bw/day.

Data for mutagenicity *in vitro* are available for all category members. *In vitro* and *in vivo* chromosome aberration data are available for CTMS, C2DMS and C3MS. In reverse-mutation assays, CTMS, C2DMS, C3MS and C3ES were negative for mutagenicity in all *Salmonella typhimurium* and *E. coli* strains tested. CTMS, C2DMS and C3MS were negative for mutagenicity in DNA damage and repair assays and/or mammalian cell gene mutation tests with L5178Y mouse lymphoma cells. CTMS and C2DMS were also negative in a sister chromatid exchange (SCE) assay with L5178Y mouse lymphoma cells; C3MS was positive for SCEs with and without metabolic activation. CTMS, C2DMS and C3MS were negative in *in vivo* chromosome aberration studies. CTMS and C2DMS were negative in a chromosome aberration test with L5178Y mouse lymphoma cells; C3MS was considered to have weak clastogenic activity at cytotoxic concentrations. Based on these data, these chlorosilanes are not expected to be genotoxic. No data are available for carcinogenicity on these chlorosilanes.

No data are available on the reproductive toxicity of these chlorosilanes. However; data are available for hydrolysis products, TMS (inhalation route), DMSD (oral route) and HCl. In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), no treatment-related effects on reproduction or development were observed in rats exposed whole-body to TMS at concentrations up to 2.20 mg/L. The NOAEC for reproductive toxicity was 2.20 mg/L (highest concentration tested). The NOAEC for maternal and developmental toxicity was 2.20 mg/L (highest concentration tested). In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), no treatment-related effects on reproduction or development were observed in rats exposed via oral gavage to DMSD at doses up to 500 mg/kg bw/day. The NOAEL for reproductive toxicity was 500 mg/kg bw/day (highest dose tested). The NOAEL for maternal and developmental toxicity was 500 mg/kg bw/day (highest dose tested). No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. However, no effects on the gonads were observed in a 90-day repeated-dose inhalation study. Based on data for the hydrolysis products, these chlorosilanes are not expected to be reproductive toxicants and are unlikely to result in developmental toxicity.

These sponsored chlorosilanes possess properties indicating a hazard for human health (lethality from acute inhalation, severe skin, eye and respiratory tract irritation, corrosivity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The chlorine group is the most active functional group on these molecules and determines many aspects of the behaviour of the category members. These chlorosilanes undergo rapid hydrolysis in the presence of water to form one to three moles of hydrochloric acid and one mole of silanol, depending on the parent substance. Hydrolysis is the primary reaction in aqueous systems and has been shown to occur very quickly (half-life <17 seconds) for CTMS, C2DMS, and C3MS. No data are available for C3ES but the reaction is expected to be as quick as for the other category members.

The overall rate constants for reaction with OH radicals in the atmosphere for these chlorosilanes and resulting half-lives (12 hr day) due to indirect photolysis are estimated to range from 0.15×10^{-12} cm³/molecule-sec and 71 d (C3MS) to 1.2×10^{-12} cm³/molecule-sec and 8.9 d (C3ES). Photodegradation as a mode of removal is unlikely as the alkyl chlorosilanes are hydrolytically unstable. It is assumed that reaction with water vapor is the predominant degradation process in air. CTMS, C2DMS and C3MS hydrolyzed to HCl and the corresponding silanol in less than 17 seconds at pH 4, 7, and 9 and 1.5°C. These chlorosilanes hydrolyze to form one mole of their respective silanol hydrolysis products (TMS, DMSD, methylsilanetriol, and ethylsilanetriol) and one to three moles of HCl. The products resulting from hydrolysis (silanol hydrolysis products) in the atmosphere are expected to further react with hydroxyl radicals. The half-lives (12 hr day) due to the atmospheric oxidation from indirect photolysis of the silanol hydrolysis products were 0.9 d (Ethylsilanetriol) to 2.5 d (TMS); the overall OH rate constants were 3.95×10^{-12} cm³/molecule-sec (TMS) and 7.19×10^{-12} cm³/molecule-sec (DMSD). HCl can react with hydroxyl radicals to form chloride free radical and water and its half-life time is calculated as 11 d. Level III Fugacity modeling, using loading rates of 1000 kg/h each for air, soil, and water, shows the following percent distribution range for the alkyl chlorosilanes: Air = 40.2 (C3ES) to 53.2 (CTMS); Soil = 1.74 (CTMS) to 17.3 (C3ES cm³/molecule-sec and 71 d (C3MS); Water = 39.7 (C3MS) to 44.9 (CTMS); Sediment = 0.145 (C3MS) to 0.225 (C3MS). However, because these chlorosilanes are very reactive and hydrolytically unstable, the substances are unlikely to be found in the environment. Therefore, Level III Fugacity modeling for the hydrolysis products (TMS, DMSD, methylsilanetriol, and ethylsilanetriol) was conducted using loading rates of 1000 kg/h each for air, soil, and water. The model estimated the following percent distribution ranges, when the silanol hydrolysis products are released simultaneously to all three compartments: Air <1.0 (all, except TMS) to 5.26 (TMS); Soil = 64.7 (TMS) to 80.1 (Ethylsilanetriol), Water = 19.8 (Ethylsilanetriol) to 29.9 (TMS); and Sediment <1.0 (all silanols). The Fugacity model cannot be applied for ionized substances such as HCl. The biodegradation of these chlorosilanes was not determined due to their rapid hydrolysis; any potential for biodegradation is likely to be of the hydrolysis products. Consequently, the only potentially biodegradable materials in the test system will be silanols.

The biodegradation of MTMS was not determined due to its rapid hydrolysis; methylsilanetriol is not expected to be readily biodegradable. In an OECD Guideline 310, TMS was not readily biodegradable (0% degradation after 29 days). HCl is an inorganic compound and OECD guideline tests for biodegradation are not applicable. Bioaccumulation is not anticipated since these chlorosilanes are hydrolytically unstable. The estimated BCF values for these chlorosilanes range from 9.8 to 20.6 L/kg wet-wt, suggesting low bioaccumulation potential of the substances. The estimated BCF values for these chlorosilane hydrolysis products range from 2.6 to 3.2 L/kg wet-wt.

Aquatic toxicity data are not available for these chlorosilanes; the substances undergo rapid hydrolysis, which occurs during testing; exposures to the parent chlorosilane is most likely irrelevant and observed toxicity is likely due to HCl and the corresponding silanol hydrolysis product.

The following acute toxicity test results for similar materials and hydrolysis products have been determined for aquatic species:

Test substance	Guideline; Test type	Species	Result (mg/L)
<i>Fish</i>			
<i>Analogous substance – similar structure</i>			
MTMS	OECD TG 203; flow-through	Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-hr LC ₅₀ > 110 (measured) 96-h LC ₅₀ > 62 (calculated methylsilanetriol concentration)
MTMS	ECOSAR	Fish	96-hr LC ₅₀ = 45 (alkoxy silane category) 96-hr LC ₅₀ = 9130 (neutral organic category)
<i>Analogous substance – hydrolysis product</i>			
TMS	OECD TG 203; semi-static	Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-hr LC ₅₀ = 271 (measured)
TMS	Environment Federal Bureau Berlin; static	Zebra-fish (<i>Brachydanio rerio</i>)	96-hr LC ₅₀ > 519 (measured)
TMS	ECOSAR	Fish	96-hr LC ₅₀ = 395
DMSD	OECD TG 203; static	Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-hr LC ₅₀ > 126 (measured)
DMSD	ECOSAR	Fish	96-hr LC ₅₀ = 9320
Ethylsilanetriol	ECOSAR	Daphnid	48-hr EC ₅₀ = 13,000
Methylsilanetriol	ECOSAR	Daphnid	48-hr EC ₅₀ = 1000
HCl	OECD TG 203; semi-static	Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-hr LC ₅₀ = pH 4.3 (4.92 mg/L)
<i>Aquatic invertebrates</i>			
<i>Analogous substance – similar structure</i>			
MTMS	OECD TG 202; flow-through	<i>Daphnia magna</i>	48-hr EC ₅₀ > 122 (measured) 48-h EC ₅₀ > 57 (calculated methylsilanetriol concentration)

MTMS	ECOSAR	Daphnid	96-hr LC ₅₀ = 16 (alkoxy silane category) 96-hr LC ₅₀ = 7990 (neutral organic category)
<i>Analogous substance – hydrolysis product</i>			
TMS	OECD TG 202; semi-static	<i>Daphnia magna</i>	48-hr EC ₅₀ = 124 (measured)
TMS	ECOSAR	Daphnid	48-hr EC ₅₀ = 196
DMSD	OECD TG 202; static	<i>Daphnia magna</i>	48-hr EC ₅₀ > 117 (measured)
DMSD	ECOSAR	Daphnid	48-hr EC ₅₀ = 3680
Ethylsilanetriol	ECOSAR	Daphnid	48-hr EC ₅₀ = 7700
Methylsilanetriol	ECOSAR	Daphnid	48-hr EC ₅₀ = 48,000
HCl	OECD TG 202	<i>Daphnia magna</i>	48-hr EC ₅₀ = pH 5.3 (0.492 mg/L)
<i>Algae</i>			
<i>Analogous substance – similar structure</i>			
MTMS	OECD TG 201; static	<i>Pseudokirchneriella subcapitata</i>	72-hr EC ₅₀ > 120 (nominal) 72-hr EC ₅₀ > 3.6 (measured); 72-hr EC ₅₀ > 80 (calculated methylsilanetriol concentration)
<i>Analogous substance – hydrolysis product</i>			
TMS	OECD TG 201; static	<i>Pseudokirchneriella subcapitata</i>	72-hr EC ₅₀ = 555 mg/L, 72-hr E _b C ₅₀ = 566 mg/L, 72-hr E _r C ₅₀ > 1053 mg/L (measured)
TMS	Similar to OECD TG 201; static	<i>Desmodesmus subspicatus</i>	72-hr E _b C ₅₀ = 806 mg/L (nominal)
TMS	ECOSAR	Green Algae	96-hr EC ₅₀ = 64
DMSD	OECD TG 201; static	<i>Pseudokirchneriella subcapitata</i>	72-hr E _y C ₅₀ and E _r C ₅₀ > 118
DMSD	ECOSAR	Green Algae	96-hr EC ₅₀ = 615
Ethylsilanetriol	ECOSAR	Green Algae	96-hr EC ₅₀ = 5981
Methylsilanetriol	ECOSAR	Green Algae	96-hr EC ₅₀ = 577
HCl	OECD TG 201; static	<i>Selenastrum capricornutum</i>	72-hr EC ₅₀ = pH 5.3 (0.492 mg/L)

Hydrogen Chloride (HCl)

The hazard of hydrochloric acid for the environment is caused by the proton (pH effect). For this reason the effect of hydrogen chloride on the organisms depends on the buffer capacity of the aquatic ecosystem. Also the variation

in acute toxicity for aquatic organisms can be explained for a significant extent by the variation in buffer capacity of the test medium. For example, LC50 values of acute fish toxicity tests varied from 4.92 to 282 mg/L. The toxicity values to *Selenastrum capricornutum* 72h-EC50 is pH 5.1 (0.780 mg/L) for biomass, pH 5.3 (0.492 mg/L) for growth rate and the 72h-NOEC is pH 6.0 (0.097 mg/L) for biomass and growth rate. The 48h-EC50 for *Daphnia magna* is pH 5.3 (0.492 mg/L) based on immobilization.

These chlorosilanes exhibit very rapid hydrolysis in the environment, hence any ecotoxicity will result from their hydrolysis products. Structural analogues of the parent chlorosilane compounds, and silanol hydrolysis products show low toxicity. Another byproduct of the hydrolysis of these chlorosilanes, HCl, has properties that can result in toxicity of < 1 mg/L to aquatic organisms in poorly buffered systems, mainly due to acidification of the test medium. These sponsored chlorosilanes and their hydrolysis products have low potential for bioaccumulation. Silanol degradation products are not biodegradable. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

Chlorosilanes react rapidly when exposed to moisture or polar reagents; this reaction is normally heterogeneous, highly exothermic, and potentially difficult to control, requiring close control of the reaction. To prevent the rapid hydrolysis and subsequent loss of material or exposure of the reactants to atmospheric moisture, chlorosilanes are handled in closed pipes or containers. The following summarizes the 2005 production volumes in tonnes of these chlorosilanes for the North America, Europe and Japan; ranges are provided in order to protect confidential business information.

Sponsored substance	North America	Europe	Japan
CTMS (CAS No. 75-77-4)	13608 - 27216	22680 - 34019	4536-13608
C2DMS (CAS No. 75-78-5)	272155 - 680389	226796- 340194	111130-290299
C3MS (CAS No 75-79-6)	22680 - 45359	11398- 294835	9072 -20412
C3ES (CAS No. 115-21-9)	907-2041	227-680	0

These chlorosilanes are produced and processed in closed systems. Due to the dynamic and exothermic nature of the hydrolysis processes for producing siloxane oligomers and polymers from these chlorosilanes, many engineering controls are in place to prevent occupational exposure such as local ventilation; water scrubber devices and related equipment; and closed sampling systems. Employees involved in chlorosilane production and application are required to use personal protective equipment (PPE) such as safety glasses or goggles, steel-tipped shoes, flame-resistant clothing, hard hat, chemical resistant gloves, and respirator mask. For any situation (e.g. equipment maintenance and repair) where potential exposure to chlorosilanes is expected, the use of acid resistant protective equipment, respiratory equipment and face shield is recommended because of their irritating or corrosive properties. Drivers who transport these chemicals must always have this equipment ready for immediate use. Potential routes of occupational exposure include inhalation and dermal exposure. All of these chlorosilanes are used as chemical intermediates in closed system and worker, and general public exposure is expected to be low. There are no consumer uses of these chlorosilanes.

SIDS INITIAL ASSESSMENT PROFILE

Chemical category	CHLOROFORMATES	
Category Members: CAS Registry Numbers, Chemical Names and their Abbreviations	Sponsored substances: 79-22-1 Methyl chloroformate (MeCF) 541-41-3 Ethyl chloroformate (EtCF) 109-61-5 Propyl chloroformate (PrCF) 108-23-6 Isopropyl chloroformate (IpCF) 17462-58-7 Sec-Butyl chloroformate (SbCF) 106-75-2 Oxydiethylene bis(chloroformate) (ObCF) 24468-13-1 2-Ethylhexyl chloroformate (EhCF) Hydrolysis products: 67-56-1 Methanol (Me) 64-17-5 Ethanol (Et) 71-23-8 1-Propanol (Pr) 67-63-0 Isopropanol (Ip) 78-92-2 Sec-Butanol (Sb) 111-46-6 Diethylene glycol (DEG) 104-76-7 2-Ethyl hexanol (Eh) 7647-01-0 Hydrogen chloride (HCl)	
Category Members: Structural Formulae	Sponsored substances	Hydrolysis products
	MeCF: $\text{Cl}-\overset{\text{O}}{\parallel}-\text{O}-\text{CH}_3$	Me: $\text{HO}-\text{CH}_3$
	EtCF: $\text{Cl}-\overset{\text{O}}{\parallel}-\text{O}-\underset{\text{H}_2}{\text{C}}-\text{CH}_3$	Et: $\text{HO}-\underset{\text{H}_2}{\text{C}}-\text{CH}_3$
	PrCF: $\text{Cl}-\overset{\text{O}}{\parallel}-\text{O}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\text{CH}_3$	Pr: $\text{HO}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\text{CH}_3$
	IpCF: $\text{Cl}-\overset{\text{O}}{\parallel}-\text{O}-\underset{\text{H}}{\overset{\text{CH}_3}{\text{C}}}-\text{CH}_3$	Ip: $\text{HO}-\underset{\text{H}}{\overset{\text{CH}_3}{\text{C}}}-\text{CH}_3$
	SbCF: $\text{Cl}-\overset{\text{O}}{\parallel}-\text{O}-\underset{\text{H}}{\overset{\text{CH}_3}{\text{C}}}-\underset{\text{H}_2}{\text{C}}-\text{CH}_3$	Sb: $\text{HO}-\underset{\text{H}}{\overset{\text{CH}_3}{\text{C}}}-\underset{\text{H}_2}{\text{C}}-\text{CH}_3$

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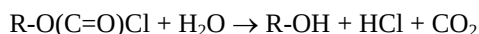
	ObCF:	DEG:
	$\text{Cl}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\text{O}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Cl}$	$\text{HO}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\text{O}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\text{OH}$
	EhCF:	Eh:
	$\text{Cl}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}}{\overset{\text{H}_2\text{C}-\text{CH}_3}{\text{C}}}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\text{CH}_3$	$\text{HO}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}}{\overset{\text{H}_2\text{C}-\text{CH}_3}{\text{C}}}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\underset{\text{H}_2}{\text{C}}-\text{CH}_3$
		HCl: $\text{Cl}-\text{H}$

SUMMARY CONCLUSIONS OF THE SIAR

Category/analogue rationale

The category consists of seven chloroformates: MeCF, EtCF, PrCF, IpCF, SbCF, ObCF and EhCF which are grouped into a category based on similar structure (i.e., the chloroformate group), high reactivity of the chloroformate group and toxicological and environmental effects. The justification for the category is based not only on a similar structure (specifically the $-\text{O}(\text{C}=\text{O})\text{Cl}$ portion of the molecule) but also a similar mechanism of action which results in similar human health effects (i.e., severe irritation at the point of contact) and environmental effects. The chloroformate group on the molecule drives the observed irritation rather than the alkyl side chain.

The chloroformate group (i.e., $-\text{O}(\text{C}=\text{O})\text{Cl}$) is the most active functional group and determines many aspects of the behaviour of the category members. Hydrolysis is the primary reaction in aqueous systems and has been shown to occur very quickly (Half-life ≤ 30 min). All category members hydrolyze in the presence of water or moisture to form hydrochloric acid (HCl), carbon dioxide (CO_2) and the corresponding alcohol (see above) according to the following reaction:



For human health, the chloroformates react and/or hydrolyze at the portal of entry resulting in localized injury. Systemic absorption is expected to be low. However, data for HCl and the corresponding alcohols are available to address potential systemic toxicity. Available toxicological data for the sponsored substances, supplemented by data for the hydrolysis products, support the grouping of these chemicals into a category.

Where appropriate, read-across or data for the corresponding alcohol and HCl are used to address physico-chemical, environmental fate and aquatic toxicity endpoints, and the reproductive toxicity endpoint for human health. Except for propanol, all hydrolysis products have been previously assessed in the OECD HPV Programme (<http://webnet.oecd.org/hpv/ui/Search.aspx>). Diethylene glycol is a member of the Ethylene Glycol category. These documents are available via the OECD Existing Chemicals Database at http://webnet.oecd.org/hpv/UI/SIDS_Details.aspx?Key=ac0359d3-c5c1-402b-9c47-14f61efd98e0&idx=0. 1-Propanol was extensively evaluated under the EU 2nd priority list of existing substances. The Risk Assessment Report is available at <http://ecb.jrc.ec.europa.eu/esis/>.

Physical-chemical properties

Category members

The category members are colourless liquids with measured melting points of <-81 to <-20 °C, except for ObCF which has a measured melting point of -5 to -6 °C. The measured boiling points range from 71 °C (MeCF) to 264.5 °C (ObCF). SbCF, ObCF and EhCF decompose before boiling. A vapour pressure of < 1 hPa was determined for ObCF, whereas the measured vapour pressures of the other category members are between 21.7

hPa (EhCF, 25 °C) and 137.5 hPa (MeCF, 20 °C). Adequate data on the log K_{ow} were not available; read-across from the hydrolysis products is provided. Water solubility ranged from 3 mg/L (20 °C, measured) for ObCF to 49 mg/L for EhCF (25 °C, calculated), and to higher values for other members (1.1×10^4 – 9.3×10^5 mg/L, 25 °C).

Hydrolysis products

The measured log K_{ow} s of the hydrolysis products are Me -0.74, Et -0.31, Pr 0.34, Ip 0.05 (25°C), Sb 0.61 (20°C), DEG -1.98/-1.47 and Eh 2.97 (25°C).

These compounds are fully miscible with water, and the water solubility of Eh was experimentally determined to be 400 – 1000 mg/L (20 °C).

Human Health

No toxicokinetics data were available for the chloroformates; however, hydrolysis of these substances is expected to produce hydrochloric acid (HCl), carbon dioxide (CO₂) and the corresponding alcohols.

The acute toxic effects of the chloroformates are primarily local caustic/irritating effects at the site of contact. Acute inhalation studies are available for the chloroformates category. LC_{50} s in the rat range from 0.46 (MeCF) to > 2.5 (ObCF) mg/L after 1-hour exposures and from 0.06 (MeCF) to < 2.33 (SbCF) mg/L after 4-hour exposures. Clinical findings include bloody/nasal discharge, dyspnoea, gasping, and irregular respiration. Hyperaemic, oedematous, red/haemorrhagic lungs were found at necropsy for multiple chloroformates. Lesser clinical symptoms included hydrothorax and emphysema. By the dermal route, the LD_{50} s >2000 mg/kg bw in rabbits; however, the chloroformates are very irritating and corrosive to the skin. With the exception of EhCF, there were no other gross pathologic findings. For EhCF, focal haemorrhages were observed in the lung and red lungs. The acute oral toxicity for category members in the rat ranges from 40 mg/kg bw (MeCF) up to 3038 mg/kg bw (EhCF) when given undiluted or as an aqueous solution. The acute oral toxicity of the sponsored substances is lower when applied in olive oil and ranges from 313 mg/kg bw (MeCF) up to 5420 mg/kg bw (EhCF) in rats. Clinical signs of toxicity included gastrointestinal irritation, necrosis and haemorrhage.

With the exception of EhCF, all of the sponsored chloroformates caused irreversible damage to the eye in animal tests. Experimental data suggest that chloroformates are moderately to extremely irritating/corrosive to the skin. Corrosive effects have been observed for MeCF, EtCF and PrCF. IpCF, SbCF and ObCF are moderately to severely irritating to the skin of rabbits. EhCF was moderately irritating in one study and corrosive in a second study. The upper respiratory tract irritation observed in rats and mice for these materials is also believed to be due to liberation of HCl. Chloroformates in the vapour phase may hydrolyze due to the water vapour present in the ambient air, water vapour present in the humid inhaled air in the respiratory tract, or upon contact with the mucous layer of the airways. Sensitisation data were not available for the chloroformates category.

Repeated-dose inhalation toxicity studies are available for MeCF (28- and 90-days), EtCF (28-day), and IpCF (28-day). In these repeated-dose studies, the inflammatory response in the respiratory tract was severe and mortality occurred at the highest exposure concentrations. Toxicity to tissues other than the respiratory tract was not noted at concentrations up to approximately 35 ppm (0.0120 mg/L/day) of MeCF, EtCF, and IpCF. In a repeated dose inhalation toxicity study following OECD TG 412, MeCF was administered via inhalation by whole body exposure to rats (5/sex/concentration) at 0 (air), 0.00052, 0.0015, 0.0039, 0.0012, or 0.035 mg/L/day, for 6 hours/day, 5 days/weeks for 28 days. Based on no treatment-related effects to the respiratory tract, the local 28-day NOAEC for MeCF was 0.0039 mg/L/day; based on mortality, decreased body weight and food consumption and changes in haematological/clinical chemistry parameters at 0.035 mg/L/day, the systemic 28-day NOAEC for MeCF was 0.012 mg/L/day. In a repeated-dose inhalation toxicity study following OECD TG 413 (but without haematology or clinical chemistry evaluation and focusing on respiratory tract irritation), MeCF was administered via inhalation by whole body exposure to rats (10/sex/concentration) at 0 (air), 0.0016, 0.0078, 0.0157, or 0.0307 mg/L/day, for 6 hours/day, 5 days/weeks for 3, 10, 20 and 65 exposures (90-day study with interim necropsies after 3, 14 and 28 study days). Based on substance-related pathological alterations and changes in DNA replication in the respiratory tract at 0.0078 mg/L/day and above, the local 90-day NOAEC for MeCF was 0.0016 mg/L/day; based on significant weight loss at 0.0157 mg/L/day, the systemic 90-day NOAEC for MeCF was 0.0078 mg/L/day. In a repeated-dose

inhalation toxicity study comparable to OECD TG 412, IpCF was administered via inhalation by whole body exposure to rats (10/sex/concentration) at 0 (air), 0.021, 0.062 or 0.181 mg/L/day (analytical concentrations), for 6 hours/day, 5 days/weeks for 28 days. Based on effects to the respiratory tract at 0.062 mg/L/day and above, the 28-day local NOAEC for IpCF is 0.021 mg/L/day; based on treatment-related effects to the lungs and thyroid and decreased body weight gain and food consumption at 0.181 mg/L/day, the 28-day systemic NOAEC for IpCF is 0.062 mg/L/day.

The chloroformates category members are not mutagenic *in vitro*, with the exception of MeCF, which was positive for chromosomal aberrations in the presence of metabolic activation. The alcohol moiety hydrolysis products did not induce chromosomal aberrations *in vitro*. Positive results have been obtained in the *in vitro* chromosome aberration test with HCl; however, the positive results were considered to be the effect of low pH or cytotoxicity. The hydrolysis products, Et and Pr, did not induce chromosomal aberrations *in vivo*. The hydrolysis products, Me, Ip, and Eh, did not induce mouse micronuclei *in vivo*. The chloroformates are not expected to be genotoxic. Carcinogenicity data were not available for the chloroformates category.

No reproductive toxicity studies were available for the chloroformates category members. Data are available for all of the hydrolysis products. No effects on fertility were observed in inhalation studies with rats exposed to Me or Et. The inhalation NOAEC for reproductive toxicity ranges from 1000 ppm (1.3 mg/L) for Me to 16000 ppm (30 mg/L) for Et. In an inhalation study with Pr in rats, male fertility was impaired. The NOAEC for reproductive toxicity (males) was 3500 ppm (8.9 mg/L) and females 7000 ppm (17.9 mg/L) (highest dose tested). No effects on the gonads were observed after repeated inhalation exposures to HCl in rats up to 50 ppm. Similarly, there were no effects on the reproductive organs in rats after repeated inhalation exposures to Eh at 0.64 mg/L/day. No significant adverse effects on fertility were observed in drinking water studies with rats exposed to DEG, Sb and Ip. The NOAELs range from 625 mg/kg bw/day (male rat; Ip) to 1500 mg/kg bw/day for Sb and 6125 mg/kg bw/day for DEG. For Et, reproductive effects in rats exposed by the oral route, other than an increase in the number of small pups, were observed at very high concentrations; the NOAEL for reproductive toxicity is >2000 mg/kg/day. For Ip, in an oral 2-generation study in rats, there was a decrease in the male mating index at 1000 mg/kg bw/day. The NOAEL for reproductive toxicity is 500 mg/kg bw/day. No developmental effects were observed in the absence of maternal toxicity for Et, Ip, Sb, DEG, and Eh. Malformations and foetal weight changes were observed following the inhalation exposure of rats to Me. The NOAEC is 6.65 mg/L/day (5000 ppm). Inhalation exposure of rats exposed to Pr showed skeletal malformations at 17.9 mg/L/day. At 25.5 mg/L/day, there was a significant increase in the incidence of skeletal, visceral and external malformations and significant implantation loss. The NOAEC for developmental toxicity is 8.9 mg/L. For HCl, no reliable studies were available. As reproductive and developmental effects are seen only at high doses for the alcohol hydrolysis products, the chloroformates category members are not expected to be reproductive toxicants and are unlikely to show developmental toxicity.

The chloroformates possess properties indicating a hazard for human health (acute inhalation and oral toxicity, irritating/corrosive properties). Methanol (hydrolysis product) exhibits potential hazardous properties for human health (neurological effects, CNS depression, ocular effects, reproductive and developmental effects, and other organ toxicity). HCl (hydrolysis product) exhibits potential hazardous properties for human health (corrosiveness to the skin and the eyes). Adequate screening-level data are available to characterize the hazard to human health for the purposes of the OECD HPV Chemicals Programme.

Environment

Hydrolysis is the primary and major fate process of the chloroformates category members. The category members were shown to have very short half-lives in aqueous solutions (pH 4, 7, 9) ranging from a few minutes (ObCF, IpCF) to about 30 minutes for (EhCF). In the OECD TG 111 studies one of the expected hydrolysis products (corresponding alcohol) were confirmed by gas chromatography. Although stoppered flasks were used, hydrolysis rates could be an overestimation as evaporation during the tests could not be excluded. In the case of PrCF, for which no guideline study was available, results from an older hydrolysis study as well as read-across to an analogue category member (IpCF) were used to confirm its hydrolytic reaction profile. Read across to IpCF is also suitable for SbCF, for which no experimental results on hydrolytic activity were available. The alcoholic hydrolysis products do not have hydrolysable groups and are therefore hydrolytically stable.

In the atmosphere, indirect photo-oxidation of the category members by reaction with hydroxyl radicals is predicted to occur with half-lives ranging from less than 1 day (EhCF and ObCF) to ca. 49 days (MeCF). The estimations refer to a 12-h day with an assumed OH radical concentration of 1.5×10^6 OH/cm³.

Ready biodegradability testing was conducted on EtCF, as well as for all hydrolysis products. EtCF was readily biodegradable in a MITI (I) test following OECD TG 301C. All hydrolysis products, with one exception (DEG), are readily biodegradable (biodegradation > 70% at test end, 10-days window met). The weight of evidence suggests that the category members, with the exception of ObCF, are readily biodegradable, based on their rapid hydrolysis and ready biodegradability of their hydrolysis products.

A level III fugacity model calculation with equal distributions to air, water and soil compartments suggests that the main target compartments of the category members and their hydrolysis products are soil and water. The calculated BCF values for the sponsored substances (2.3 to 95) indicate a low bioaccumulation potential. The (predominantly calculated) BCF values for the hydrolysis products (1 to 42) indicate a low potential for bioaccumulation.

The following acute fish toxicity test results using nominal concentrations have been determined for the parent chloroformate category members, with the exception of IpCF for which mean measured concentrations were extrapolated via chemical analysis of the hydrolysis product isopropanol:

Leuciscus idus, MeCF: 96-h LC₅₀ = 4.5 mg/L (static)

Danio rerio, PrCF: 96-h LC₅₀ = 3.16 mg/L (static)

Danio rerio, IpCF: 96-h LC₅₀ = 8.2 mg/L (semi-static)

Danio rerio, SbCF: 96-h LC₅₀ = 46.4 mg/L (static)

Leuciscus idus, ObCF: 96-h LC₅₀ = 1.78 mg/L (static)

Leuciscus idus, EhCF: 96-h LC₅₀ = 3.16 mg/L (static)

Danio rerio, EhCF: 96-h LC₅₀ = 4.18 mg/L (static)

(pH remained within acceptable limits during all testing)

Due to the short hydrolysis half-lives (≤ 30 min) of the chloroformates category members, results from the hydrolysis products are also used to fulfil the endpoint requirements with respect to ecotoxicology.

The following acute aquatic toxicity test results have been determined with the alcohol hydrolysis products:

Fish [*Leuciscus idus*], 2-ethylhexanol (Eh): 96-h LC₅₀ = 17.1 mg/L (nominal, flow-through)

Fish [several spp.], all other alcohols: 96-h LC₅₀ $\geq$ 3200 mg/L (nominal)

Invertebrate [*Daphnia magna*], 2-ethylhexanol (Eh): 48-h EC₅₀ = 35.2 mg/L (nominal, static)

Invertebrate [*Daphnia magna*], all other alcohols: 24/48-h EC₅₀ $\geq$ 1000 mg/L (nominal, static)

Algae [*Scenedesmus subspicatus*], 2-ethylhexanol (Eh): 72 h EC₅₀ = 11.5 mg/L (nominal)

Algae and aquatic plants [div.], all other alcohols: EC₅₀ > 100 mg/L (nominal)

The following chronic toxicity test results have been determined:

Invertebrate [*Ceriodaphnia dubia*], Ethanol (Et): 9-d NOEC = 9.6 mg/L (nominal)

Invertebrate [*Daphnia magna*], Isopropanol (Ip): 21-d NOEC = 30 mg/L (nominal)

Although the members of the chloroformates category hydrolyze quickly, it is possible that the observed toxicity to fish is partly related to high reactivity of unhydrolyzed chloroformates at the very beginning of the test. The toxicity may be explained by reactions with nucleophiles (such as -NH₂, -SH and -OH) on biological macromolecules.

The hydrolysis product, HCl, is acutely toxic to fish due to the acidification of the test medium. The latter effect, however, is unlikely to be responsible for the toxicity of the chloroformates. The following acute toxicity test results have been determined with the HCl hydrolysis product:

Fish [*Cyprinus carpio*] 96-h LC₅₀ = 4.92 mg/L (pH 4.3)

Invertebrate [*Daphnia magna*] 48-h EC₅₀ = 0.492 mg/L (pH5.3)

Algae [*Selenastrum capricornutum*] 72-h EC₅₀ = 0.780 (pH 5.1) and 0.492 (pH5.3) mg/L for biomass and growth rate, respectively.

The available results from acute toxicity studies on fish show that the chloroformate category members produce toxic effects in aquatic systems. Similar toxic effects would also be expected for other environmental organisms such as daphnia and algae.

The chloroformates possess properties indicating a hazard for the environment (acute aquatic toxicity values between < 1 and 100 mg/L). The substances are readily biodegradable with the exception of ObCF, and all have a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

The worldwide quantity of chloroformate production in 2008 was estimated at 10,000 - 12,000 metric tons for Europe and 3,000 – 5,000 metric tons for Asia. In the United States (sponsor country), chloroformate production ranged from 500,000 to 50 million pounds (225 – 22,500 metric tons) in 2006. Most alkyl chloroformates are discontinuously or continuously prepared by the reaction of the corresponding liquid anhydrous alcohol with molar excess of dry, chloride-free phosgene. Evolving HCl is absorbed in a tower after recovering excess phosgene. Unreacted phosgene is removed from the crude chloroformates by vacuum stripping or gas purging.

Chloroformates are highly reactive and can be used as intermediates in the synthesis of numerous compounds. Derivatization of chloroformates with alcohols and amines leads to carbamates and carbonates which are further processed to solvents, polycarbonates (high temperature resistant), polyurethanes [especially from bis(chloroformic) esters] and plastics of high optical quality. Chloroformates are also valued as general purpose derivatizing agents for gas and liquid chromatographic analysis of molecules containing active functionality such as amines and carboxylic acids. Chloroformates are also used as amino acid blocking agents during the synthesis of complex organic compounds.

Chloroformates are manufactured within enclosed reactors and drums are filled using closed systems. Reactors are housed in enclosed buildings. Occupational exposure is expected to be low because engineering controls (such as room air exchange, local exhaust, automatic phosgene monitoring) and personal protective equipment (respirators, protective rubber suits) are used as standard industry practice to limit occupational exposures during maintenance, cleaning, etc. Additionally, employees are trained on safe use and handling, as well as emergency procedures in the event of an accident.

Chloroformates may be used in chromatographic analyses in laboratory settings, with some potential for occupational exposure. However, once they react during the analysis, exposure is expected to be limited.

Chloroformates are manufactured within enclosed reactors and are filled into tanks, drums or other suitable containers through closed systems, which limits environmental exposure. Available data indicate that in 2008 in the sponsor country, more than 9,500 kg of MeCF and approximately 120,000 kg of EtCF were incinerated (as a waste disposal method). Other releases totalled less than 100 kg of each of these chemicals in 2008.

Chloroformates are not used in consumer products and therefore, exposure is not expected. Any residual content is expected to be low.

INITIAL TARGETED ASSESSMENT PROFILE (Human Health and Environment)

CAS RN and Chemical Name	Sponsored Substances Cobalt [Elemental cobalt]: CAS RN 7440-48-4 Cobalt chloride: CAS RN 7646-79-9 Sulphuric acid, cobalt (2+) salt (1:1) [Cobalt sulphate]: CAS RN 10124-43-3, CAS RN 10393-49-4 Supporting Substances Nitric acid, cobalt salt [Cobalt nitrate]: CAS RN 14216-74-1 Acetic acid, cobalt salt [Cobalt acetate]: CAS RN 5931-89-5
Structural Formula	Sponsored Substances Co CAS RN 7440-48-4 Co²⁺ [Cl]₂ CAS RN 7646-79-9 Co²⁺ · $\left[\begin{array}{c} \text{O} \\ \parallel \\ \text{O}-\text{S}-\text{O} \\ \parallel \\ \text{O} \end{array} \right]^{2-}$ CAS RN 10124-43-3 and CAS RN 10393-49-4 Supporting Substances Co²⁺ · 2 $\left[\begin{array}{c} \text{O} \\ \parallel \\ \text{O}-\text{N}-\text{O} \end{array} \right]^{-}$ CAS RN 14216-74-1 Co²⁺ · 2 $\left[\begin{array}{c} \text{CH}_3 \\ \parallel \\ \text{O}-\text{C}-\text{O} \end{array} \right]^{-}$ CAS RN 5931-89-5

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address the following human health endpoints: toxicokinetics, respiratory irritation, repeated dose toxicity, carcinogenicity and genotoxicity; and the following environment endpoints: environmental fate and bioavailability in water, bioaccumulation potential, and acute and chronic toxicity to aquatic organisms. It cannot be considered as a full SIDS Initial Assessment. Summary information on use and exposure is also reported here. Other endpoints for human health and the environment are included in the Canadian screening assessment but have not been agreed upon by OECD member countries, and thus are not included in this profile.

The final screening assessment has been published under the responsibility of the Government of Canada. [<http://www.ec.gc.ca/eesees/default.asp?lang=En&n=8E18277B-1>]

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its *Canadian Environmental Protection Act, 1999* (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: **inherently toxic** to humans or to the environment and that might be **persistent** and/or **bioaccumulative**; and substances to which people might have **greatest potential for exposure**. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release.

These cobalt substances were identified as high priorities for human health risk because elemental cobalt and cobalt sulphate were considered to pose greatest potential for exposure whereas cobalt chloride was considered to pose intermediate potential for exposure and all three substances had been classified by other agencies on the basis of carcinogenicity. They also met the ecological categorization criteria for persistence, and cobalt chloride and cobalt sulphate met the categorization criteria for inherent toxicity to aquatic organisms. Therefore, they were also identified as priorities for environmental risk. The Primary RN for cobalt sulphate is CAS RN 10124-43-3 while CAS RN 10393-49-4 is an Alternate Registry Number for this substance. In this document, cobalt sulphate refers to both CAS RN 10124-43-3 and CAS RN 10393-49-4: therefore three substances rather than four are mentioned.

Analogue/Category rationale

As shown above, these substances were identified as Canadian priorities for assessment by Canada's categorization process. Other cobalt substances were not considered at this time, but it is recognized that they may also contribute to physiological and environmental loadings via the common moiety of concern discussed below.

In solution, cobalt (II) salts including cobalt chloride and cobalt sulphate are considered to be toxicologically equivalent, as they generate a common moiety of concern, Co^{2+} . Elemental cobalt may also be oxidized under physiological and environmental conditions to produce Co^{2+} cations. Therefore, these substances were considered together in this assessment. Exposure of humans to cobalt from environmental sources was based on total cobalt.

All exposure concentrations are expressed in terms of total cobalt; measurement methods of cobalt in environmental media and foods do not distinguish between forms of cobalt. Much of the available data on cobalt toxicity in laboratory animals is for soluble cobalt (II) salts including the chloride and sulphate, with studies on the nitrate and acetate salts included as supporting information only (see below). These salts are expected to dissociate in physiological media to generate Co^{2+} cations and are therefore considered to be toxicologically equivalent. Studies with both the anhydrous and hydrated forms of the soluble Co(II) salts are considered relevant, as they are expected to be indistinguishable in solution. In biological media, elemental cobalt particles can bind to proteins, and may be oxidized to generate Co^{2+} ions. Blood and urine levels of cobalt (in solution) are well correlated with recent occupational exposure to soluble cobalt salts and cobalt metal. The systemic effects of elemental cobalt are likely primarily due to cations which are released from the particles and absorbed, whereas local effects may be due to both the ions released and the particles themselves at

the point of contact (i.e., lungs or skin) (reviewed in ATSDR 2004, IPCS 2006, IARC 2006).

Although there are data on almost all of the targeted endpoints for elemental cobalt, cobalt chloride and cobalt sulphate, measured data from cobalt's nitrate and acetate salts are also included as supporting information solely for additional information on some of the genotoxicity endpoints (mutagenicity, chromosomal aberration, DNA damage).

Physical-chemical properties

Elemental cobalt, cobalt chloride and cobalt sulphate are solid at room temperature. The melting points of cobalt and cobalt chloride are 1495°C and 724-737°C, respectively. Cobalt sulphate decomposes at 735°C. Even though no experimental data were available, their vapour pressure and Henry's Law constant are likely negligible at ambient temperature. Cobalt chloride and cobalt sulphate have high water solubility ranging from 450 to 562 g/L, and from 362 to 383 g/L, respectively. Elemental cobalt, in the form of powders, has a limited capacity for dissolution in water based on results from a 7-day Transformation Dissolution (T/D) Protocol test (OECD Guidance Document No. 29) indicating dissolved concentrations as high as 0.3 and 12.78 mg/L at loading rates of 1 to 100 mg/L, respectively. Ranges for the log K_{sw} (partition coefficient soil-water), log K_{sdw} (partition coefficient sediment-water) and log K_{spw} (partition coefficient suspended particles-water) for dissolved forms of cobalt are 0.41-3.49, 2.92-3.48 and 4.18-5.83 L/kg, respectively. The dissociation constants (pK_a , pK_b) and the partition coefficients between octanol and water (Log K_{ow}) and between organic carbon and water (Log K_{oc}) are not relevant to its environmental fate and so were not considered.

Human Health Targeted Endpoints

Oral absorption of cobalt in humans depends on the form of cobalt, the dose, and the nutritional status of the individual. Estimates of the absorption of cobalt chloride in humans range from 5 to 44% of the administered dose. There is no human data on the distribution of cobalt following oral absorption, but studies in laboratory animals indicate increased cobalt levels primarily in liver, as well as in other organs. In humans, orally administered cobalt for therapeutic purposes is eliminated primarily in faeces (reviewed in IPCS 2006).

Following inhalation exposure, large cobalt particles are deposited in the upper respiratory tract where they are subject to mechanical ciliary clearance, including transfer to the gastrointestinal (GI) tract. Smaller cobalt particles are, however, deposited in the lower respiratory tract where they may be solubilised and absorbed, or phagocytosed and absorbed. Cobalt solubility of these particles affects clearance from the lung, with faster absorption into blood and subsequent elimination for more soluble cobalt compounds. Data from experimental animal studies suggest that urinary excretion rates correlate with the rate of translocation into blood, and faecal excretion rates correlate with the clearance rate to the gastrointestinal tract (reviewed in IPCS 2006).

In humans, cobalt has been shown to stimulate red blood cell (RBC) production and this property has been used therapeutically. A transient increase in red blood cell numbers and haemoglobin levels was observed in a study of 6 adult male volunteers dosed orally with cobalt chloride at approximately 1mg Co/kg/day for 3 weeks. Similar effects were observed in anephric patients (without functioning kidneys) given cobalt chloride as treatment for anaemia at approximately 0.16 to 0.32 mg Co/kg-bw per day for several months. In contrast, women given lower doses of cobalt chloride (0.45 to 0.62 mg Co/kg-bw per day) during the third trimester of gestation did not have increased haemoglobin and red blood cells.

In short term and subchronic studies on cobalt chloride in rats, polycythemia (high RBC count) and increased haemoglobin were induced at doses equal to or greater than 0.5 mg Co/kg bw/day (lowest LOEL in experimental animals).

In the mid-1960s, a series of clinical case reports were published describing cardiomyopathy in subjects in North America and Europe who consumed large quantities of beer from specific producers containing cobalt sulphate, which was added by these breweries as a foam stabilizer. The exposure to cobalt from beer in these subjects was estimated to be 0.04 to 0.14 mg Co /kg-bw per day, based on a cobalt concentration in beer of 1 to 1.5 mg/L and consumption ranging from 8 to 30 pints per day (lowest LOAEL in humans of 0.04 mg Co/kg-bw per day). Potential influences on the susceptibility to the deleterious health effects included a protein-poor diet and the possibility of existing cardiac damage from prior alcohol abuse.

In rats given cobalt sulphate in the diet (24 weeks at 8.4 mg Co/kg-bw per day), heart enzyme activity and heart mitochondrial ATP production were significantly reduced. The hearts of treated animals were found to have left ventricular hypertrophy and impaired ventricular function. Rats treated with higher doses of cobalt sulphate for shorter periods (26 mg Co/kg-bw per day for 8 weeks or cobalt chloride at 12.4 mg Co/kg-bw per day for 3 weeks) had similar cardiac degeneration. Guinea pigs similarly dosed with cobalt sulphate (20 mg Co/kg-bw per day for 5 weeks) had abnormal EKGs, increased heart weight, and cardiac lesions.

In some anaemic patients, cobalt therapy for longer periods (doses of 2.8 to 3.9 mg Co/kg bw per day for 3 to 8 months) resulted in thyroid hyperplasia and enlargement. Thyroid hyperplasia was also seen in some of the “beer drinkers cardiomyopathic” individuals at autopsy. Direct thyroid necrosis was observed in mice orally dosed with cobalt chloride (at 26 mg Co/kg bw/day) for 15 to 45 days.

The US National Toxicology Program (NTP) reported that in 13-week and 2-year cobalt sulphate inhalation studies (rat and mouse), all tested concentrations (0 to 11.38 mg Co/m³) resulted in a ‘spectrum of inflammatory, fibrotic and proliferative lesions’, in the nose, larynx and lung with increasing severity at higher exposures, consistent with observations in humans. The LOAEC in these studies was 0.1 mg Co/m³; no NOAEC was determined.

In a cross-sectional study¹ of humans (166 men and 28 women in the diamond polishing industry) exposed to cobalt dust, a LOAEC of 0.0151 mg Co/m³ was determined based on a significant increase in the reported prevalence of eye, nose, and throat irritation and cough; and reduced lung function compared to 59 unexposed control workers (46 men and 13 women). A NOAEC of 0.0053 mg Co/m³ was also determined. Cobalt exposure groups were defined based on air measurements at the time of the study, and exposure was confirmed by measurement of cobalt in urine. In another cross-sectional study, workers in a cobalt refinery who were exposed to cobalt metal, salts and oxides (average concentration of 0.125 mg Co/m³) for up to 39 years had increased dyspnoea and wheezing, and decreased lung function compared to unexposed controls. Similarly, asthma symptoms were more prevalent in workers in a cobalt plant who were exposed to cobalt compounds. In a study examining the effects of similar cobalt exposures on the heart, no significant differences were reported in the electrocardiograms, blood pressure, heart rate, or clinical chemistry between 203 cobalt-exposed workers and 94 unexposed controls. It has been proposed that a mixture of cobalt and tungsten carbide may behave as a unique toxicological entity; however, studies on exposure to hard metal were not reviewed for this assessment.

Available studies on the carcinogenicity of cobalt in humans are based on exposures to cobalt in occupational settings, often in the presence of carbides such as tungsten carbide. Due to co-exposure with other substances, the human workplace data were considered insufficient by the International Agency for Research in Cancer (IARC) to conclude on the carcinogenic potential of elemental cobalt alone.

Although the available short-term and subchronic data do not provide any indication of carcinogenic potential following oral exposure to cobalt or soluble cobalt (II) salts, no studies of cancer from oral exposure in humans or experimental animals were identified. Data on the carcinogenicity of elemental cobalt in experimental animals consist of studies done by injection or implantation (intra-muscular, subcutaneous, intra-osseous, intra-peritoneal, intra-thoracic, and intra-renal); and the only study on carcinogenicity of cobalt chloride in experimental animals was carried out by subcutaneous injection. Injection or implantation site tumours were observed in some of these studies; however, the relevance of data from these routes of administration to carcinogenicity in humans resulting from oral or inhalation routes of exposure is unclear.

A US NTP 2 year cobalt sulphate inhalation study conducted in mice and rats, showed that aerosols of 0.11, 0.38, or 1.14 mg Co/m³ induced a concentration-related increase in benign and malignant alveolar/bronchiolar tumours in both species and sexes (significant at high-concentration for male mice and rats; significant at mid- and high-concentrations for female mice and rats). There was also a concentration-related increase in incidence of benign and malignant adrenal tumours (pheochromocytomas) in the exposed female rats (significant at the high dose). Pheochromocytomas, a common age-related tumour in males, are less commonly seen in untreated female rats. The investigators considered the increased incidence of this tumour type to be an “uncertain” finding because it was seen only in the top dose group and was not supported by increased incidence or severity of hyperplasia. In contrast, IARC has classified elemental cobalt and soluble cobalt (II) salts as possibly carcinogenic to humans based on inadequate evidence in humans and sufficient evidence in experimental animals.

In vitro mutagenicity assays in bacteria with soluble cobalt (II) salts were primarily negative both with and without activation. Mixed results were obtained in a bacterial indicator assay for DNA damage (Rec assay in *B. subtilis*). In yeast, mainly positive results were obtained in mutagenicity and gene conversion assays in *S. cerevisiae* strains without activation. In mammalian cells *in vitro*, mutagenicity and cell transformation assays gave mixed results. However, cobalt chloride at high concentrations induced DNA damage (strand breaks and DNA-protein cross links), chromosome damage (micronuclei and sister chromatid exchanges) and aneuploidy in rodent and human cells in culture. In contrast, negative results were obtained for cobalt acetate and cobalt nitrate in chromosomal aberration assays in human cells in culture. Elemental cobalt, though insoluble, as particles

¹ Cross-sectional studies involve data collected at a defined time. They are often used to assess the prevalence of acute or chronic conditions.

induced DNA damage (strand breaks) and chromosome damage (micronuclei) *in vitro*.

In vivo, a single intraperitoneal injection of cobalt chloride induced micronuclei in mouse bone marrow. Cobalt chloride also induced aneuploidy, pseudoploidy and hyperploidy in the bone marrow and testes of hamsters when dosed intraperitoneally over 9 days; and chromosome aberrations in the bone marrow of mice given a single oral dose. In *Drosophila melanogaster*, cobalt chloride was positive in the wing spot test, and cobalt nitrate was positive for gene mutations, chromosomal deletion, non disjunction or mitotic recombination. Mice exposed to cobalt dust by inhalation for 13 weeks did not have an increase in micronuclei in the peripheral blood. There was no indication of increased DNA strand breaks or micronuclei in blood lymphocytes of 35 workers in a cobalt refinery exposed to cobalt dust compared to 27 unexposed workers.

The overall weight of the available evidence shows that cobalt metal particles and soluble cobalt (II) salts have the capacity to cause DNA damage and chromosomal damage *in vitro*. Although *in vivo* data for cobalt particles are limited, the *in vivo* data for cobalt chloride are consistent with the *in vitro* data for soluble cobalt (II) salts.

It is generally accepted that cobalt likely induces DNA damage through the generation of reactive oxygen species (ROS) and increased intracellular oxidative stress. Some of the supporting evidence is described below. Both elemental cobalt particles and Co^{2+} ions have been shown to generate ROS under biologically relevant conditions. An aqueous suspension of elemental cobalt particles (0.1 to 1.5 μm) was found to react with dissolved oxygen, forming a strong oxidant, likely $\text{Co-O-O}^{\bullet}$, and in the presence of either superoxide dismutase or Fe^{2+} ions the oxidant was found to release hydroxyl radicals. Hydroxyl radicals are extremely reactive and can damage virtually all types of key cellular macromolecules (carbohydrates, nucleic acids, lipids and amino acids). Free Co^{2+} ions (pH 7.4 phosphate buffer), promoted the conversion of hydrogen peroxide to the superoxide anion; however in the presence of chelating peptides such as glutathione, conversion of hydrogen peroxide to hydroxyl radicals was observed. This Fenton-type mechanism generated ROS in both *in vitro* and *in vivo* studies.

In vitro and *in vivo*, exposure to soluble cobalt resulted in increased evidence (indices) of oxidative stress. Cobalt (II) ions in the presence of hydrogen peroxide stimulated *in vitro* formation of 8-hydroxy-2'-deoxyguanosine (8-OH-dG), and cobalt sulphate induced DNA strand cross-links. *In vivo*, cobalt acetate, administered as a single intraperitoneal dose, induced oxidative DNA damage in liver, kidneys, and lungs of rats. Additional evidence supportive of an oxidative stress mechanism for causing DNA damage resulting in tumour induction comes from examination of tumours in mice treated with cobalt sulphate. In the tumours from this study, the guanine to thymine base pair transversion frequency in codon 12 of the K-ras oncogene was 55% compared to the zero percent base pair transversions detected in untreated control mice.

A second potential mechanism contributing to the indirect genotoxicity of cobalt is the inhibition of intracellular DNA repair processes, possibly through competition with other essential ions and binding to zinc finger domains in DNA repair proteins. *In vitro*, cobalt (II) inhibits the mammalian repair protein Xeroderma pigmentosum group A (XPA), which contains zinc finger domains. Cobalt chloride and cobalt acetate inhibited DNA repair following UV-induced DNA damage in human cells in culture, by inhibiting the incision and polymerization steps, but not the ligation step. In a small epidemiological study in which workers were exposed to cobalt dust, individuals with variations in several DNA repair genes had higher incidences of genotoxicity markers in the lymphocytes.

As the tumours observed in experimental animals are unlikely to have resulted from direct interaction with genetic material, these substances are considered to be non-genotoxic carcinogens.

Elemental cobalt, cobalt chloride, and cobalt sulphate possess properties indicating a hazard for the following human health endpoints: respiratory irritation, repeated dose toxicity, cardiomyopathy, carcinogenicity and genotoxicity.

Environment Targeted Endpoints

Fate

A fate analysis based on $\log K_{ow}$, K_{oc} and typical mass-balance fugacity modelling is not applicable to elemental cobalt, cobalt chloride and cobalt sulphate, nor to the metal ions they release upon dissolution, because, as for other non-volatile chemicals, these substances exert negligible partial pressure and fugacity in air. Cobalt chloride and cobalt sulphate are highly soluble and, upon introduction in water, will dissociate and release cobalt ions (Co^{2+}). Elemental cobalt powders may also release cobalt ions in solution if discharged to surface waters. In addition to the cobalt ions, the substances will yield a variety of dissolved cobalt species of varying proportions depending on the environmental conditions. Under conditions commonly found in oxic freshwaters (i.e., pH between 5 and 9; E_h between 0.5 and 1 V), Co^{2+} , CoCO_3^0 , and CoHCO_3^+ will be the dominant species in solution. Because of the tendency of cobalt to sorb to solid particles in aquatic media ($\log K_{spw}$ of 4.18-5.83), a

proportion of dissolved forms of this metal will end up in sediments ($\log K_{\text{sdw}}$ of 2.92-3.48), through adsorption to settling suspended particles. When released to dry soils, elemental cobalt will mainly remain there with some of the substance dissolving and leaching locally into ground and/or surface water ecosystems (via runoff) when the soil gets soaked by rain or melting snow/ice. Elemental cobalt is not expected to be found in significant amounts in the water column, considering that its density is greater than that of water. Considering the high solubility of cobalt chloride and sulphate, they are not likely to be found in solid forms in the environment unless they are released in a very dry environment. Being a non-gaseous element with a negligible vapour pressure, cobalt is emitted to air principally in the form of fine particulate matter (PM).

Elemental cobalt, cobalt chloride and cobalt sulphate all release cobalt ions in solution, that cannot be degraded. Therefore, biodegradation, photodegradation and hydrolysis as a function of pH are not applicable to these inorganic metal-containing substances.

Bioavailability

For most metal-containing compounds, it is the potentially bioavailable metal ion that is liberated upon contact with water that is the moiety of toxicological concern. The bioavailability of metals controls their potential to cause adverse effects. Factors such as pH and ligands (e.g., major cations, dissolved organic matter) can in turn influence the bioavailability of dissolved metal ions. Experimental evidence shows that high water hardness and high dissolved organic carbon levels (DOC) decrease uptake of dissolved cobalt ions by aquatic organisms. Other evidence suggests that cobalt complexes with humic and fulvic acids may also be available for uptake.

Bioaccumulation and Biomagnification

Cobalt is an essential micro-nutrient element for bacteria, plants and animals. As such, its uptake is expected to be regulated to some extent by many organisms through mechanisms of homeostasis and detoxification. Thirty-one bioaccumulation and bioconcentration factors (BAF and BCF) values were found to be acceptable from the literature for various species of algae, invertebrates and fish (laboratory and field studies), and range from 7.4 to 3110 L/kg (average is 878 L/kg, with only 2 values > 2000 L/kg). Four biota-to-sediment accumulation factors (BSAF-sediment) values obtained for freshwater invertebrates range from 0.091 to 0.645. Four biomagnification factors (BMF) were found in the literature for cobalt in marine and freshwater environments, with values ranging from 0.004 to 0.087. Overall, considering these values as well as the metal regulation mechanisms that most organisms possess, the bioaccumulation and biomagnification potentials of cobalt in aquatic ecosystems are expected to be low.

Aquatic toxicity

Being soluble in water, elemental cobalt powders, cobalt chloride and cobalt sulphate, like other soluble cobalt compounds, will release cobalt species upon dissolution, in particular the free ion Co^{2+} . Reliable short term (acute) studies for soluble cobalt compounds were identified for 12 invertebrate species and 3 fish species; toxicity values range from 89 to 585 800 $\mu\text{g/L}$ as total dissolved cobalt. Reliable long-term (chronic) studies were identified for 5 plant/algae species, 7 invertebrate species and 3 fish species; toxicity values range from 2.9 to 59 000 $\mu\text{g/L}$ as total dissolved cobalt. A species sensitivity distribution (SSD) was developed using the chronic toxicity data. The Weibull model provided the best fit for the data and the 5th percentile (HC_5), i.e., hazardous concentration to 5% of species, of the SSD plot derived in Canada is 2.5 $\mu\text{g/L}$. Overall, there is experimental evidence that dissolved cobalt has a relatively high potential to cause harm to aquatic organisms following short-term and longer-term exposure at very low concentrations.

Elemental cobalt, cobalt chloride, and cobalt sulphate possess properties indicating a hazard for the environment. They have acute and chronic aquatic toxicity below 1 mg/L (total dissolved cobalt),

Uses / Exposure

Uses

There are a few applications of elemental cobalt; it is predominantly used as a component in alloys and carbides for applications requiring high strength and temperature resistance. Anhydrous cobalt chloride is commonly used as an indicator in desiccants. Cobalt sulphate is the most inexpensive form of ionic cobalt and is used in the electroplating industry and agriculturally as a feed supplement and fertilizer. Cobalt chloride or sulphate may also be used as the cobalt source in storage batteries, porcelain pigments, glazes and ink driers. While the chloride and sulphate salts may be the source of cobalt for applications such as pigments, glazes, and batteries, generally the salt is thermally decomposed or calcined; therefore cobalt sulphate and chloride will not be present in the final product.

Elemental cobalt uses reported under a survey in Canada include pigment manufacturing, chemical and alloy production, cement production, metallurgy, manufactured automotive parts, formulation component,

water/waste treatment chemical, catalyst/accelerator/initiator/activator, and copper refining.

Table 1 shows an estimate of the uses of the three cobalt substances of interest by industrial sector as reported by the Cobalt Development Institute for 2008.

Table 1: World-wide cobalt uses estimated by the Cobalt Development Institute for 2008 for elemental cobalt, cobalt chloride and cobalt sulphate.

Use	Estimated % of the world market	Cobalt substances used for manufacture			
		Elemental	Chloride	Sulphate	Other cobalt compounds
Batteries	27	x	x	-	x
Super alloys	19	x		-	x
Hard Material Tools	14	x		-	x
Colours – Glass, enamels, plastics, ceramics, artists colours, fabrics	10	-		x	x
Catalysts	9	-	x	x	x
Magnets	7	x		-	x
Tire Adhesives, Soaps, Driers for paint and dyes	6	-		-	x
Other Alloys	4	x		-	x
Feedstuffs and others uses	4			x	-

Natural Sources

Cobalt is a naturally occurring element in the terrestrial crust. Cobalt concentrations in the upper continental crust have been determined to average about 25 ppm and to range between 0.1 and 110 ppm. Cobalt is not known to naturally exist in its elemental (metallic) form; naturally occurring cobalt is comprised of various mineral, oxide and salt forms; sources include windblown continental dusts, weathering of rocks, seawater spray, forest fires and volcanoes.

Natural emissions to the atmosphere have been estimated to range between 690 and 11 000 tonnes of cobalt per year globally. Atmospheric fall-out and introduction of cobalt into surface water and soil as a result of natural weathering and erosion processes are reflected in the geochemical background levels in these media.

Anthropogenic Sources

Anthropogenic sources of cobalt include burning of fossil fuels (primarily oxides), sewage sludge, phosphate fertilizers, mining and smelting of cobalt containing ores and industrial processes that use cobalt compounds.

The quantities of elemental cobalt, cobalt chloride and cobalt sulphate that are used, imported or manufactured in Canada, based on a 2006 survey in Canada, range from 100 000 to 10 million kg, 10 000 to 1 million kg, and 64,000 to 10 million kg, respectively. It should be noted that the term “manufacture” as defined in the survey includes the incidental production of a substance at any level of concentration as a result of the manufacturing, processing or use of other substances, mixtures, or products. Also, it should be noted that products containing cobalt, cobalt chloride or cobalt sulphate may enter Canada even if they are not identified as such in the Canadian survey because they may be imported unknowingly in manufactured items, or in quantities below the 100 kg reporting threshold for the survey.

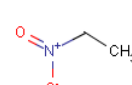
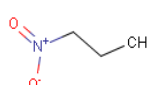
Canada’s National Pollutant Release Inventory (NPRI) data for cobalt are not form-specific and therefore,

represent all forms of cobalt. Between 1995 and 2008, the on-site release over the total release reported decreased from approximately 10% to 2%, while the proportion sent to disposal increased from approximately 15% to 27%. Off-site recycling was the most significant removal pathway corresponding to approximately 70% of the annual total reported between 1995 and 2008. Most of the cobalt produced in Canada is exported, so that in Canada a relatively small proportion of total cobalt releases are associated with the manufacture of consumer products.

Human Exposure Estimates

The principal route of exposure to cobalt by the general population is diet. Cobalt occurs naturally in soil at concentrations ranging between 0.1 ppm and 110 ppm and may enter the food chain via uptake by plants and livestock, consequently cobalt is found in the majority of foods at varying levels. In Canada, the estimated daily dietary intake of cobalt by adults is 17 µg/day, based on the 2002 Canadian Total Diet Study conducted in one major city (Vancouver). Two separate analyses of food samples from the U.S. Food and Drug Administration Total Diet Studies for 1982-1984 reported an average dietary cobalt intake of 11 µg/day and 14 µg/day, respectively, for males in the 25 – 30 years age group. The WHO has estimated daily cobalt intakes via food of 5-45 µg/day. Consumer exposure to cobalt may occur through use of personal care products; however, the actual concentrations and forms of cobalt are generally not known with precision. Occupational exposure was not considered.

SIDS INITIAL ASSESSMENT PROFILE

Category	Short Chain Nitroparaffins
CAS No's.	75-52-5 79-24-3 108-03-2
Chemical Name	Nitromethane Nitroethane 1-Nitropropane
Structural Formulae	 Nitromethane  Nitroethane  1-Nitropropane

SUMMARY CONCLUSIONS OF THE SIAR**Category Justification**

The short chain nitroparaffins category consists of three structurally related nitroalkanes; nitromethane, nitroethane and 1-nitropropane. These chemicals are considered a category because of the similarities in structure, and in chemical and toxicological behaviour. The category members are expected to be absorbed, metabolized, and excreted in a similar fashion, resulting in the release of their respective aldehydes and nitrite.

Physical-Chemical Properties

The category members are liquids at room temperature. The melting points for nitromethane, nitroethane, and 1-nitropropane are -28.4, -89.5 and -104 °C, respectively; the corresponding boiling points are 101.2, 114 and 131.1 °C. The vapour pressures are 37.1, 27.7, and 13 hPa at 25°C for nitromethane, nitroethane, and 1-nitropropane, respectively. The water solubility for nitromethane is 111,000 mg/L at 20 °C. The water solubility for nitroethane is 45,000 mg/L at 20 °C. The water solubility for 1-nitropropane is 15,000 mg/L at 25 °C. Water solubility values are based on a density of 0.9934-1.1322 g/cm³. The measured log K_{ow}s are -0.33, 0.18, and 0.79 for nitromethane, nitroethane, and 1-nitropropane, respectively.

Human Health

The skin absorption of ¹⁴C-labelled category members has been studied in female rhesus monkeys and indicates that none of the chemicals are readily absorbed by the skin but are more likely to evaporate before significant amounts of absorption take place. In rats administered a single oral dose of ¹⁴C-nitromethane, -nitroethane or -nitropropane approximately 9% was retained in the body five days after dosing with excretion occurring via urine and faeces. The absorption following a single oral dose was high at approximately 92-96%. For nitromethane, nitroethane and 1-nitropropane, 19%, 5%, and 14% was excreted in the urine, respectively and 8.5%, 4% and 7% was excreted in the faeces, respectively. The majority (approximately 64%, 82% and 73%, respectively) of the radioactivity was not accounted for, and was presumed to have been exhaled. The short chain nitroparaffins are metabolized into nitrites and the respective aldehydes. In rats inhaling 100 ppm 1-nitropropane for 7 hours, a steady state concentration of approximately 9 µg/ml of the parent compound was obtained after 4 hours of exposure. The elimination T_{1/2} (half-life) was 98 minutes.

Acute toxicity data are available for the inhalation, dermal and oral routes. The inhalation LC₅₀ for nitromethane vapour in rats was >12.75 mg/L for 1 hour (within a 48-hour post-exposure observation period). Clinical signs from this study included

mild sedation and eye irritation. The oral LD₅₀s for nitromethane, nitroethane and 1-nitropropane in rats were 1478 mg/kg-bw, 1256 mg/kg-bw and 506 mg/kg-bw, respectively. Clinical signs of oral toxicity included ataxia and convulsions. At necropsy, severe intestinal haemorrhaging was seen. The 24-hr dermal LD₅₀s of all three category members were greater than 2000 mg/kg-bw in rabbits under occlusion. No clinical signs of toxicity were observed. The category members are not irritating to slightly irritating (nitroethane) to the skin. Nitromethane, nitroethane and 1-nitropropane are slightly to moderately irritating to the eyes.

In an NTP study, rats were exposed to nitromethane vapour at 94, 188, 375, 750, or 1500 ppm (0.23, 0.46, 0.94, 1.87, or 3.74 mg/L) via inhalation for 6 hours/day, 5 days/week for 13 weeks. Animals exhibited changes in haematology indicative of slight anaemia at all concentrations resulting in a systemic LOAEC of 94 ppm (0.23 mg/L). Other effects in this study included increased methaemoglobin and thyroid effects at ≥ 188 ppm (0.46 mg/L), sciatic nerve and spinal cord degeneration and bone marrow hyperplasia at ≥ 375 ppm (0.94 mg/L), hind limb paralysis and decreased strength at 750 ppm (1.87 mg/L) and higher. Changes in various organ weights were also observed at ≥ 188 ppm (0.46 mg/L). Degeneration of the nasal epithelium resulted in a local NOAEC of 188 ppm (0.46 mg/L). All lesions in this study were characterized as minimal to mild. In another study, rats exposed to nitromethane vapour at 98 and 745 ppm (0.26 and 1.86 mg/L) for 7 hours/day, 5 days/week up to 24 weeks exhibited reduced body weight gains, decreased haemoglobin and haematocrit and increased thyroid weights at 745 ppm (1.86 mg/L), resulting in a systemic NOAEC of 98 ppm (0.26 mg/L). Rabbits exposed in this study had thyroid effects at both doses resulting in a LOAEC of 98 ppm (0.26 mg/L). In another NTP study, mice exposed to nitromethane vapour for 6 hours/day, 5 days/week for 13 weeks at the same doses used in the rat 13-week study exhibited minimal increases in kidney weights at all concentrations. Sperm motility was decreased and oestrous cycle length and spleen toxicity were increased at 375 ppm (0.94 mg/L) and higher. Lesions were characterized as mild/minimal. Based on differences in multiple organ weights and effects on sperm motility and oestrous cycle length, the systemic NOAEC is 188 ppm (0.47 mg/L). Based on nasal degeneration, which increased in severity with test concentrations, the local NOAEC is 94 ppm (0.23 mg/L).

Rats were exposed to nitroethane vapour at 100, 350 or 1000 ppm (0.31, 1.0 or 3.0 mg/L) for 6 hrs/day, 5 days/week for 13 weeks. Animals exhibited changes in haematology at all concentrations. Minimal changes in the histopathology of the spleen and salivary glands and time-dependent increase in methaemoglobinemia occurred at all concentrations. Fatty livers were also noted at higher concentrations. The systemic LOAEC was 100 ppm (0.31 mg/L); the NOAEC was not established. Increased nasal degeneration versus controls occurred at ≥ 350 ppm (1.0 mg/L) resulting in a local NOAEC of 100 ppm (0.31 mg/L). In mice exposed to nitroethane vapour for 6 hrs/day, 5 days/week for 13 weeks, organ weight changes and effects on kidney (changes in relative weight and blood urea nitrogen) were seen at all concentration (≥ 100 ppm). At ≥ 350 ppm (1.0 mg/L), methaemoglobin was increased and haematology and liver effects were observed. At the highest concentration, multinucleated spermatids were observed in testes. Based on kidney effects, the systemic LOAEC is 100 ppm (0.31 mg/L); no systemic NOAEC was established. Changes in nasal turbinates resulted in a local NOAEC of 100 ppm (0.31 mg/L).

In a combined inhalation repeated-dose/reproductive developmental screening test (OECD TG 422) rats were exposed to 1-nitropropane vapour at 24, 48, or 96 ppm (0.088, 0.18, or 0.35 mg/L), 6 hr/day, 7 days/week for at least 28 days. At 96 ppm (0.35 mg/L), there was decreased food consumption in both sexes, and slightly decreased body weights of males (by 6.9%) prior to mating. The systemic NOAEC is 96 ppm (0.35 mg/L) the highest dose tested. Histopathologic changes in the nasal tissues were seen at increased incidences at ≥ 48 ppm. Based on these findings, the local NOAEC was 24 ppm (0.085 mg/L). In a 28-day oral gavage study, rats were exposed to 10, 30, or 100 mg/kg bw/day. At 100 mg/kg bw/day, rats showed clinical signs that included ataxia, salivation, hunched posture. Other effects included significant increases in absolute and relative brain weights without corresponding morphologic changes, multiple changes in clinical chemistry and haematology parameters, and increased methaemoglobin. Although certain effects occurred at lower doses, they were minimal, transient and/or not dose-dependent. Based on effects at 100 mg/kg bw/day, the NOAEL was established as 30 mg/kg bw/day.

In vitro bacterial mutagenicity studies are available for nitromethane, nitroethane, and 1-nitropropane. Nitromethane and 1-nitropropane have been tested for chromosomal aberrations *in vitro*. *In vivo* genotoxicity was evaluated in all three category members. High concentrations of nitromethane and nitroethane in air did not induce gene mutations in bacteria. 1-Nitropropane also did not induce gene mutations in bacteria. 1-Nitropropane did not induce micronuclei in mouse or rat bone marrow *in vivo* but was positive for micronuclei in rat liver cells *in vivo*. The members of the short chain nitroparaffins category did not result in genotoxicity *in vitro*, but may result in genotoxicity *in vivo*.

Nitromethane was carcinogenic in mice (B6C3F1) and female rats (F344) via the inhalation route at concentrations ≥ 188 ppm. However, nitroethane and 1-nitropropane were not carcinogenic in Long-Evans rats via the inhalation route at concentrations of 200 and 100 ppm respectively. Based on differences in doses, animal species and use of only one species in nitroethane and 1-nitropropane carcinogenicity studies, firm conclusions regarding carcinogenicity were not possible.

Reproductive organs and performance were evaluated in repeated-dose toxicity studies, and, data for 1-nitropropane are available from the OECD TG 422 study. No histopathological effects were observed in the reproductive organs of rats or mice exposed via inhalation to nitromethane or nitroethane. However, a significant decrease in sperm motility was noted in male rats exposed to 750 ppm (1.87 mg/L) and 1500 ppm (3.74 mg/L) nitromethane. Male rats also had decreased cauda, epididymis and testes weights. Also, a decrease in sperm motility and an increase in oestrous cycle length were noted in mice exposed to ≥ 375 ppm (≥ 0.94 mg/L) nitromethane. At 1000 ppm (3.0 mg/L) nitroethane, multinucleated spermatids were observed in testes of male mice. In the combined repeated-dose/reproductive/developmental toxicity screening test with 1-nitropropane, rats were exposed via inhalation for 6 hours/day, 7 days/week beginning 14 days prior to mating, during mating and for females, through gestation day 19. In parents, body weights of males were slightly decreased at 96 ppm (0.35 mg/L) and changes in nasal tissues were seen at ≥ 48 ppm (0.18 mg/L), resulting in a local NOAEC of 24 ppm (0.088 mg/L). At 96 ppm (0.35 mg/L), litter sizes and mean numbers of pups born live were decreased, resulting in a NOAEC for reproductive/developmental toxicity of 48 ppm (0.18 mg/L). The category members showed potential for reproductive/developmental toxicity; data on developmental effects were limited to gross observations in the OECD 422 study.

The category members possess properties indicating a hazard for human health (acute oral toxicity, repeated-dose toxicity, reproductive/developmental toxicity, genotoxicity and carcinogenicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

Experimental photolysis data are available for nitromethane, nitroethane, and 1-nitropropane using radiolabeled test material irradiated by a mercury vapour lamp. Results after 17 hours indicate 35.2% degradation of nitromethane, 23.9% degradation of nitroethane, and 54.8% degradation of 1-nitropropane. Indirect photolysis half-lives for the three nitroparaffins range from (approximately) 25-82.3 days. Abiotic hydrolysis of these materials is unlikely. These nitroparaffins have no functional groups that are subject to hydrolysis or degradation in water at room temperature with neutral pHs. The organo-nitro group is stable in water under these conditions.

Distribution (fugacity) modelling using Mackay Level III indicates that the category members released into the air compartment (most likely emission scenario based on use pattern and physical/chemical properties) will partition predominantly to air (69.1%, 91.2%, 88.7% for nitromethane, nitroethane, and 1-nitropropane, respectively), water (19.1%, 12.0%, 7.3%, respectively), soil (11.8%, 6.8%, 4.1%, respectively), and sediment ($<0.1\%$ for all three).

The short-chain nitroparaffins are not readily biodegradable.

Acute toxicity test results are available with two fish species for each of the three category members. Laboratory acute aquatic toxicity data are also available for freshwater invertebrates and algae for the nitroparaffins. The weight of evidence clearly suggests that acute exposure EC/LC₅₀ values for the nitroparaffins with standard laboratory species are greater than 100 mg/l except for algae, where the 72-hr inhibition of growth ranges from 6 to >456 mg/L. Modelling toxicity data using Topkat and AIES were used to support nominal test data for nitromethane. The predicted Daphnia 48-hr EC₅₀ was 399 mg/L and the fish 96-hr LC₅₀ was 127 mg/L using the Topkat and AIES models, respectively.

These chemicals are volatile substances and some tests were conducted in open systems, and therefore, were supported by modelling toxicity data. Caution should be exercised in interpreting these test results and the toxicity observed may be underestimated.

Key studies on the acute toxicity of the category members are:

<i>Category Member</i>	<i>Acute Fish Toxicity</i>	<i>Acute Invertebrate Toxicity</i>	<i>Algal Growth Inhibition</i>	
Nitromethane	96-hr LC ₅₀ = 127 mg/L (calculated) OECD 203 96-hr LC ₅₀ = >659.2 mg/L (open system, nominal) 48-hr LC ₅₀ = 460 mg/l (closed system, nominal)	48-hr EC ₅₀ = 399 mg/L (calculated) OECD 202 24-hr EC ₅₀ = 450 mg/L (open system, measured)	OECD 201 72-hour E _r C ₅₀ = 36 mg/L (closed system, measured)	72-hour E _y C ₅₀ = not reported
Nitroethane	OECD 203 96-h LC ₅₀ = 596 mg/L (nominal) 48-hr LC ₅₀ = 880 mg/l	OECD 202 24-hr EC ₅₀ = 1200 mg/l	OECD 201 72-hour E _r C ₅₀ = 6 mg/L (closed system,	72-hour E _y C ₅₀ = not reported

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	(closed system, nominal)	(open system measured)	measured)	
1-Nitropropane	OECD 203 96-hr LC ₅₀ = 227 mg/L (measured) 48-hr LC ₅₀ = 205 mg/L (closed system, nominal)	OECD 202 48-hr EC ₅₀ = 380 mg/L (closed system, measured) OECD 202 24-hr EC ₅₀ = 258 mg/L (open system, measured)	OECD 201 72-hour ErC ₅₀ > 456 mg/L (closed system, measured)	72-hour EC ₅₀ = 263 mg/L (closed system, measured)

The category members possess properties indicating a hazard for to the environment (toxicity to aquatic plants) at concentrations between 1 and 100 mg/L. Category members are not considered readily biodegradable or bioaccumulative. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

The production volumes in the United States (sponsor country) for 2005 were each over 5×10^6 pounds (2268 tonnes).

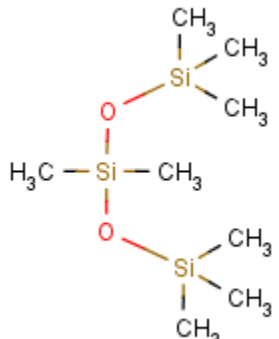
The category members are primarily used as intermediates in the synthesis of other chemicals, as industrial solvents, and in fuels. In production, these materials are handled in closed systems. Engineering controls during production include proper ventilation, containment, safety equipment and actual hardware designed to minimize exposure from splashing, or exposure to the air. Transfer of these materials is in closed pipe systems rather than in open systems.

Environmental exposure is possible through low level losses in process waste waters, which are discharged to a waste water treatment system. Some limited potential exists for release of material to the Publicly Owned Treatment Works (POTWs) after primary biological treatment on site. Industrial customers may have on-site biological treatment facilities but general consumers may only have access to POTW's without pre-treatment. These chemicals are stored in closed tanks and transported in tank cars and tank trucks, and smaller amounts are transported in drums or Intermediate Bulk Containers (IBCs), with the exception of >96% pure nitromethane which is not transported in containers larger than 55-gallon drums.

The most likely route of human exposure to the category members is via inhalation or dermal contact. Occupational inhalation exposure may occur during manufacture or processing; however, these exposures are negligible due to the use of engineering controls such as closed process systems, closed piping systems and local ventilation, as well as the use of personal protective equipment. There are industrial occupational exposure guidelines set for these chemicals in the sponsor country; Occupational Safety and Health Administration (OSHA) permissible exposure limit Time Weighted Average (TWA)-8 hours is 100 ppm for nitromethane, or nitroethane and 25 ppm for 1-nitropropane. Exposure may occur during cleaning or drumming operations, but these exposures are limited by appropriate protective clothing and the existence of appropriate control measures. Bulk storage, handling and transport of product further limit exposure potential by handling in enclosed storage vessels and piping. Automated container filling equipment is used to fill drums and IBC's, thus making exposure during this process highly unlikely.

Products using these short chain nitroparaffin ingredients are not widely available to consumers. However, consumers could be exposed to nitromethane via inhalation during use of hobby or racing fuels, to limited amounts of nitroethane by inhalation through use in certain paints or coatings, and to very small amounts of 1-nitropropane by inhalation where it is present as a minor fuel additive or as a solvent. Dermal exposure may occur at low levels for consumers in these same end-use applications of industrial solvents, paints/coatings, or fuels/fuel additives.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-51-7
Chemical Name	Octamethyltrisiloxane (L3)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-Chemical Properties**

The EPISuite program (v 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain organosilicons in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

Octamethyltrisiloxane (L3) is a liquid with a measured melting point of less than -80 °C, a measured boiling point of 152.6 °C at 1013 hPa and a measured vapour pressure of 5.35 hPa at 25 °C. The measured octanol-water partition coefficient (log K_{ow}) is 6.60 at 24.1 °C, and the measured water solubility is 0.0345 mg/L at 23 °C. The measured Henry's law constant is 2.69×10^6 Pa-m³/mole (1,100, dimensionless) at 20.9 °C. Values of the octanol-air partition coefficient (log K_{oa}) have been measured at temperatures between -4 and 40 °C; the value of log K_{oa} at 23.7 °C is 3.68.

Human Health

Toxicokinetics data were not available for L3.

The four-hour whole-body inhalation (OECD TG 403) LC_{50} value for L3 was > 22.6 mg/L in rats. The LD_{50} after single dermal application (OECD TG 402) to rats was > 2000 mg/kg bw. The acute oral (OECD TG 423) LD_{50} of L3 was determined to be > 2000 mg/kg bw in the rat. By all routes of exposure there were no deaths, no clinical findings, all animals gained weight and there were no significant macroscopic findings noted at necropsy. L3 was not irritating to the skin of rabbits (EPA OPPTS 870.2500); eye irritation data were not available. L3 was not a sensitizer in a human patch test.

In a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422), rats (10/sex/concentration) were exposed via whole-body vapour inhalation to L3 at 0 (filtered air control), 7.74, 15.5 and 31.0 mg/L. There were no test article-related effects on body weight, food consumption, FOB or motor activity

parameters. Male rats exhibited hyaline droplet nephropathy at all concentrations tested, which was consistent with alpha-2 μ nephropathy. Both sexes showed significantly increased liver weights (females ≥ 7.74 mg/L and males at 31.0 mg/L) and significant increases in serum cholesterol (40% increase in males at all doses; 31% and 40% increase in females at 15.5 and 31.0 mg/L, respectively). Centrilobular hypertrophy was observed in females exposed to ≥ 7.74 mg/L, and in males exposed to 31.0 mg/L and was considered an adaptive change. Hepatic porphyria was observed in males at concentrations ≥ 15.5 mg/L. This condition is characterized by an abnormal increase of pigments (porphyrins) in the body. Porphyrins are the main precursor of heme, which is a major constituent of hemoglobin. Based on increased serum cholesterol, the LOAEC for systemic toxicity in males was 7.74 mg/L and the NOAEC was not established. The NOAEC for females was established at 7.74 mg/L based on increased serum cholesterol.

In an oral gavage repeated-dose toxicity study (OECD TG 407), rats were exposed to 0, 5, 25, 250 and 1000 mg/kg bw/day L3 for 28 days. There were no treatment-related effects on food consumption, FOB or motor activity parameters. A treatment-related reduction in the body weight / body weight gain compared to the control animals was recorded in the males at 1000 mg/kg/day at the end of the treatment period. During recovery, a significant compensatory increase in the body weight gain was noted in males and females at 1000 mg/kg bw/day. There were dose-response related increases in liver weights in males at 25, 250 and 1000 mg/kg bw/day, and females at 250 and 1000 mg/kg bw/day. Hepatocellular hypertrophy and protoporphyrin accumulation with associated bile duct proliferation and periportal chronic inflammation was observed in males at 250 and 1000 mg/kg bw/day and in females at the top dose only. Hematological parameters for high dose males showed an increased red blood cell (RBC) count with a reduction in the fraction associated with immature RBCs, and a decrease in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). Increased cholesterol and other changes in clinical chemistry were observed at the two highest doses in males and at the highest dose in females. After the 14-day recovery period, hepatocellular hypertrophy showed complete regression while protoporphyrin accumulation and periportal chronic inflammation was still present in both sexes at 1000 mg/kg bw/day. Bile duct proliferation persisted only in high dose males. There was an increased incidence and severity of hyaline droplets in males at 25, 250, and 1000 mg/kg bw/day and higher levels of alpha-2 μ -globulin in males at all doses, which is not likely to be relevant to humans. Thyroid gland follicular cell hypertrophy of minimal severity was observed in both sexes at 1000 mg/kg bw/day. Hyaline deposits of the male kidneys and follicular cell hypertrophy of the thyroid gland showed complete regression after the 14-day recovery period. Based on multiple effects at 250 mg/kg bw/day, the NOAEL for males was considered to be 25 mg/kg bw/day, while for females it was 250 mg/kg bw/day, based on multiple effects at 1000 mg/kg bw/day.

L3 did not induce gene mutations in bacterial cells *in vitro* nor did it induce chromosomal aberrations in Chinese hamster ovary cells *in vitro*. In an *in vitro* mouse lymphoma assay, L3 induced chromosomal aberrations without metabolic activation, but did not induce aberrations with metabolic activation. Based on these results, L3 is not considered to be genotoxic *in vitro*. No data were available on the carcinogenicity of L3.

In the combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422) described previously, no treatment-related effects were observed in any of the reproductive parameters or developmental endpoints evaluated. Reproductive and developmental parameters evaluated included evidence of mating, pregnancy, duration of gestation, mean litter size, mean live litter size, mean litter weight, and mean ratio of live births/litter size. The inhalation NOAEC for reproductive, maternal and developmental toxicity was 31.0 mg/L (highest concentration tested). Based on results of this screening-level test, L3 is not likely to result in reproductive or developmental toxicity.

Octamethyltrisiloxane possesses properties indicating a hazard for human health (repeated-dose toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

In an OECD TG 111 study, L3 is hydrolytically unstable; at pH 7 and 25 °C the half-life is 329 hours. Hydrolysis is expected to produce the hydrolysis product intermediate, pentamethyldisiloxanol (MDOH), and final hydrolysis products, dimethylsilanediol (DMSD) and trimethylsilanol (TMS). In the atmosphere, indirect photo-oxidation by reaction of L3 with hydroxyl radicals is predicted to occur with a half-life of 8.77 days. In a ready biodegradability

study, the average cumulative percent biodegradation for L3 was -3.7%, indicating the test substance is not readily biodegradable. MDOH and its condensed silanol monomers (TMS and DMSD) are expected to be not readily biodegradable. In an OECD Guideline 310 Test, TMS was not readily biodegradable (0% degradation after 29 days). Based on studies of DMSD (^{14}C -dimethylsilanediol) in four soils at 25 °C, the substance is not readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that L3 will distribute mainly to the air (27%), water (31%), and sediment (41%) compartments, with minor distribution to the soil compartment (1%). Additional simulations based on exclusive emission to a single compartment showed that the resulting distribution was strongly dependent on the compartment of emission. For emission to air or soil, L3 is predicted to remain in, or partition to, the air compartment overwhelmingly. When emission to water is involved, L3 is predicted to distribute between air, water, and sediment, with the exact distribution depending on the actual fraction of the total emission to water.

Modeling of the long range transport potential (LRTP) of L3 using the OECD Tool and GloboPOP models with empirical physical-chemical properties data as inputs indicates that L3 has long range transport potential. Environmental monitoring studies in Nordic countries and the arctic that have demonstrated that L3 is only rarely detected; and when detected is at extremely low concentrations.

In an OECD TG 305 study, *Pimephales promelas* were exposed to ^{14}C -L3 under flow through conditions at concentrations of 1.7 and 21 µg/L, for a 42-day uptake phase at 22 °C, and a 10-day depuration phase. Radiolabeled test material was utilized for the study and parent confirmation was not done routinely. Analysis for metabolites at steady state indicated that 98% of the radiolabeled material was parent. Based on uptake and depuration rates the kinetic BCF values for the 1.7 and 21 µg/L treatment groups were 3610 and 5600, respectively. The estimated BCF values for hydrolysis products MDOH, TMS and DMSD are 32.99, 2.8 and 3.1 L/kg wet-wt suggesting low bioaccumulation potential of the hydrolysis products.

Due to the hydrolysis of L3, aquatic organisms are likely exposed to a mixture of the parent and its hydrolysis products, MDOH (transient intermediate), TMS and DMSD.

The following acute, chronic, and sediment toxicity test results to L3 have been determined for aquatic species:

Acute

Fish [<i>Oncorhynchus mykiss</i>]	
96-hour LC ₅₀	> 19 µg/L (flow-through)*
Invertebrate [<i>Daphnia magna</i>]	
48-hour EC ₅₀	> 20 µg/L (flow-through)*
Algae [<i>Pseudokirchneriella subcapitata</i>]	
72-hour EC ₁₀ , EC ₂₀ , and EC ₅₀	> 9.4 µg/L (closed-bottle)*

Chronic

Invertebrate [<i>Daphnia magna</i>]	
21-day EC ₅₀ (mortality/immobility and reproduction)	> 15 µg/L (flow-through)*
21-day NOEC (for survival, reproduction and growth)	= 15 µg/L*
21-day LOEC (for survival, reproduction and growth)	> 15 µg/L*

Sediment

Invertebrate [<i>Lumbriculus variegatus</i>]	
28-day EC ₅₀ (survival/reproduction/growth)	> 17 mg/Kg*
28-day NOEC (survival/reproduction)	= 1.1 mg/Kg
28-day LOEC (survival/reproduction)	= 1.6 mg/Kg
28-day NOEC (growth)	= 17 mg/Kg*
28-day LOEC (growth)	> 17 mg/Kg*
Invertebrate [<i>Chironomus riparius</i>]	
28-day LC ₅₀ (mortality)	= 166 mg/Kg
28-day NOEC (development time/emergence ratio)	= 84 mg/Kg

28-day LOEC (development time/emergence ratio)	= 210 mg/Kg
28-day NOEC (development rate)	= 84 mg/Kg
28-day LOEC (development rate)	= 39mg/Kg

*These results reflect the highest measured concentration tested and the functional limit of solubility under the conditions of administration (no effects at saturation).

Due to hydrolysis L3 possesses properties indicating a low hazard profile (at the limit of the water solubility), although it has potential to bioaccumulate and is not readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

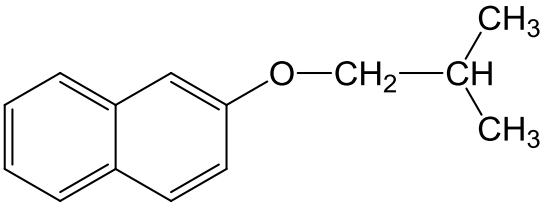
Exposure

In the U.S.A. (sponsor country), production volume in 2005 was ca. 454 – 907 tonnes. L3 is also produced in Europe (45-113 tonnes in 2005) and Japan (45 - 91 tonnes in 2005). L3 is used in personal care and consumer products, as a chemical intermediate and as an intermediate for silicone oligomers and polymers. Percent used in formulation as a chemical intermediate is 0.1-100%; percent used in formulation in personal care products is 25-40%.

At the manufacturing site, L3 is produced in closed systems. Engineering controls such as local ventilation and ventilation devices, closed sampling systems; and fill systems are used. Personal protective safety equipment includes safety glasses or goggles, steel-tipped shoes, flame-resistant clothing, hard hat, chemical resistant gloves. Worker exposure due to non-accidental releases at the facility level is not expected. Potential routes of accidental worker exposure include inhalation and dermal. At the industrial customer level, it is recommended that L3 be used in closed systems. Recommend appropriate engineering controls include general ventilation. Gloves, goggles, and standard protective clothing are recommended when needed; all external customers are supplied with a MSDS for this product. Exposure due to non-accidental releases is not expected. Potential routes of accidental worker exposure include inhalation and dermal.

L3 is used in personal care consumer products; potential routes of consumer exposure include oral, dermal, and inhalation. Environmental exposure through the use of consumer products is likely.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	2173-57-1
Chemical Name	2-(2-Methylpropoxy)naphthalene
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address only the following endpoint(s): Human Health: acute toxicity, repeated dose toxicity and mutagenicity. It cannot be considered as a full SIDS Initial Assessment. Nevertheless, the conclusions for the endpoints addressed have been agreed by member countries and may be used for hazard and risk assessment. Results on other endpoints may be relevant for hazard and risk assessment but have not been presented in this assessment.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law, hazard assessment of existing chemical substances has been conducted. If a chemical substance is evaluated as “not biodegradable (persistent)” and “not highly bioaccumulative”, at least, a 28-day repeated dose toxicity and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long-term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

2-(2-Methylpropoxy)naphthalene was evaluated as “not biodegradable (persistent)” and “moderately bioaccumulative” by METI (Ministry of Economy, Trade and Industry, Japan). Biodegradation and bioaccumulation are not parts of the targeted assessment and therefore not presented in ITAP. In order to determine whether the chemical is classified as a Type II Monitoring Chemical Substance, the initial hazard assessment of 2-(2-methylpropoxy)naphthalene was conducted for the repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in 2007.

This targeted assessment document was originally based on the material from the chemical assessment council of MHLW. We re-assessed the toxicological profile for the OECD HPV chemical programme.

Physical-chemical properties

2-(2-Methylpropoxy)naphthalene is a pale yellow crystal at standard temperature and pressure. Measured melting point and boiling point are 31.75 °C and 305.75 °C respectively. Vapour pressure is calculated to be 0.167 Pa at 25 °C by MPBPWIN. The partition coefficient between octanol and water (log K_{ow}) is calculated to be 4.65 by KOWWIN. Water solubility is calculated to be 1.17 mg/L – 6.91 mg/L at 25 °C by WATERNT and WSKOWWIN.

Human Health

In an acute oral toxicity study, 2-(2-methylpropoxy)naphthalene was administered by gavage to male and female rats. Deaths were observed on 1-6 days and the oral LD₅₀ value was reported to be 5930 mg/kg bw. In this study, wet posterior, coma, rough fur and black, soft stools were observed. No reliable information was identified

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regarding acute inhalation and dermal toxicity of 2-(2-methylpropoxy)naphthalene. Although the quality of data is not sufficiently robust, the secondary literature reported that the dermal LD₅₀ in rabbits exceeded 5000 mg/kg bw.

A repeated dose oral toxicity study in rats was conducted following the OECD Test Guideline 407. In this study, 2-(2-methylpropoxy)naphthalene was administered via gavage at 0, 20, 100 or 500 mg/kg bw/day for 28 days. Loose stools, mucous feces, watery diarrhea and salivation were observed in both sexes, and two females were found dead at 500 mg/kg bw/day. Body weight was lower in both sexes at 500 mg/kg bw/day. In the functional observational battery conducted during the fourth week of administration, the motor activity decreased in males at 500 mg/kg bw/day and decrease in the reactivity to approach contact or touch stimuli and freezing to touch stimuli were found in one male at this dose. Urinalysis showed an increase in urine volume and decrease in osmotic pressure in both sexes and decrease in daily sodium and potassium excretion and neutralization of urine in males at 500 mg/kg bw/day. Browning of urine was found in both sexes at 100 mg/kg bw/day and more, and a positive bilirubin reaction increased in both sexes at 500 mg/kg bw/day. On hematological examination, red blood cell count, hemoglobin and hematocrit decreased in females at 500 mg/kg bw/day. Blood biochemical test revealed a decrease in glucose and an increase in ALT in males and a decrease in total protein and increases in triglyceride and ALP in females at 500 mg/kg bw/day. The relative liver weight increased in males at 500 mg/kg bw/day and in females at 100 mg/kg bw/day and more, the relative kidney weight increased in males at 100 mg/kg bw/day and more, and the relative spleen weight increased in both sexes and the relative adrenal weight increased in males at 500 mg/kg bw/day. On histopathology, dose-related changes were detected in the forestomach (i.e. squamous hyperplasia), cecum and/or colon (i.e. basophilic change and an increase in mitosis in the mucosal epithelial cells), liver (i.e. eosinophilic change and centrilobular hypertrophy of hepatocytes), spleen (i.e. congestion and pigment deposition) and adrenal gland (i.e. angiectasis, vacuolar degeneration, necrosis, accumulation of macrophage and hypertrophy of the cortex) in both sexes, and prostate and seminal vesicle (i.e. acinar atrophy) at 500 mg/kg bw/day. An increase in mitosis in the colon was also found in males at 100 mg/kg bw/day. After the 14-day recovery period, the following findings were found at 500 mg/kg bw/day: histopathological changes in the spleen and adrenal glands in both sexes and in the epididymis and seminal vesicle in males; decreases in red blood cell counts and blood glucose in males and increases in blood triglyceride and total cholesterol in females; increase in the relative spleen weight in males and in the relative liver weight in females. Based on increased mucosal epithelial mitosis in the colon and browning of urine, the NOAEL of this study was 20 mg/kg bw/day.

In a bacterial mutation study using four strains of *Salmonella typhimurium* and an *Escherichia coli* WP2 *uvrA* strain (OECD TG 471), 2-(2-methylpropoxy)naphthalene was negative with or without metabolic activation. In an *in vitro* chromosome aberration test using Chinese hamster lung (CHL/IU) cells (OECD TG 473), 2-(2-methylpropoxy)naphthalene was also negative with or without metabolic activation. Based on these reliable studies, 2-(2-methylpropoxy)naphthalene is considered not to be genotoxic *in vitro*. Regarding the *in vivo* genotoxicity, no reliable study was identified, but an *in vivo* micronucleus test with limited data showed that 2-(2-methylpropoxy)naphthalene did not induce micronuclei in the bone marrow. In this micronucleus study, male and female mice received a single intraperitoneal administration up to 2000 mg/kg bw/day.

Agreed hazard conclusions

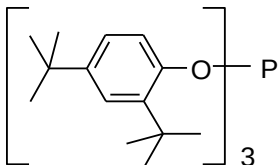
2-(2-Methylpropoxy)naphthalene possesses properties indicating a hazard to human health (repeated dose toxicity) though it is not considered to be genotoxic *in vitro*.

Available Exposure information

According to the notification obligation of the amount of manufacture/import based on the Chemical Substances Control Law in Japan, no production or import of 2-(2-methylpropoxy)naphthalene was reported in fiscal year 2007. Although the reporting is obligatory to manufactures/importers treating the substance with more than 1 kg/year, the production volume and/or import volume of 2-(2-methylpropoxy)naphthalene in Japan seems to be almost zero. Information of the production volume in other areas is not obtained.

This substance is used as a fragrance/flavouring agent in foods. Maximized Survey-derived Daily Intake (MSDI) is 1.2 µg/capita/day in EU. No information of the use pattern of 2-(2-methylpropoxy)naphthalene is obtained in Japan.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	31570-04-4
Chemical Name	Tris(2,4-di-tert-butylphenyl)phosphite
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

Tris(2,4-di-tert-butylphenyl)phosphite is a solid with a typical purity of >99% w/w. It has a melting point of 180 - 186 °C and decomposes above 350 °C. It has a measured vapour pressure of 1.3×10^{-10} hPa at 20 °C. The calculated octanol-water partition coefficient ($\log K_{ow}$) is > 6.0, and the water solubility is <0.005 mg/L at 20 °C.

Human Health

Uptake of tris(2,4-di-tert-butyl-phenyl)phosphite from the gastro-intestinal tract is extremely limited. The main metabolite in rats found in the faeces was tris(2,4-di-tert-butyl-phenyl)phosphate, which might have resulted from direct oxidation in the gastrointestinal tract.

The acute oral and acute dermal LD₅₀-values of tris(2,4-di-tert-butyl-phenyl)phosphite are >6,000 mg/kg bw in the rat, mouse and hamster and >2,000 mg/kg bw in the rat, respectively. Clinical signs observed were limited to sedation, dyspnoea, hunched posture, piloerection and ruffled fur, which are common signs observed in such studies.

The substance is not irritating to the skin and the eyes. In a guinea pig test of limited quality (very low concentrations tested) no sensitization was observed. There are no indications for a sensitising potential of tris(2,4-di-tert-butyl-phenyl)phosphate in humans despite its widespread use.

Repeated oral exposure to tris(2,4-di-tert-butyl-phenyl)phosphite did not induce adverse effects. In a 13-week study in rats, no adverse effects were seen at 1000 mg/kg/day, the highest dose tested.

Negative results were obtained in a limited assay for induction of gene mutation in bacteria. Negative results were also obtained in *in vivo* bone marrow assays for clastogenicity (both micronucleus test and metaphase analysis in hamsters). In addition negative results were obtained in a dominant lethal assay in the mouse. The results indicated that tris(2,4-di-tert-butyl-phenyl)phosphite does not have any significant mutagenic potential.

In a carcinogenicity study in rats treated with doses up to 147 mg/kg bw/day (diet study), tumour incidences were low and could not be related to treatment. No evidence for carcinogenicity was available and the NOAEL is 147 mg/kg bw/day.

In a two-generation study in rats tris(2,4-di-tert-butyl-phenyl)phosphite did not have any adverse effects on reproductive parameters at 292.6 mg/kg bw/day. At 1,030 mg/kg bw/day, a reduced fertility index was detected in the F0 generation. Decreased foetal weight was observed in the F2-generation at the highest dose of 1030 mg/kg bw/day. The NOAEL for reproductive toxicity is 292.6 mg/kg bw/day. The NOAEL for developmental toxicity is 4,000 ppm (412 mg/kg bw/day). The NOAEL for maternal and developmental toxicity in rabbits is ≥ 1200 mg/kg bw/day (the highest dose tested in a teratogenicity study performed according to OECD 414). There was no evidence of teratogenicity.

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Tris(2,4-di-tert-butylphenyl)phosphate does not possess properties indicating a hazard for human health based on its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

Tris(2,4-di-tert-butylphenyl)phosphite has a calculated half-life for photo-oxidation of 5.4 hours (indirect reaction with OH-radicals). Fugacity modelling (Mackay Level III) predicts that tris(2,4-di-tert-butylphenyl)phosphite will partition to soil and sediment (32% and 67% respectively). Based on the log Kow, tris(2,4-di-tert-butylphenyl)phosphite has a high potential for adsorption to soil (predicted Log Koc 4.6). Limited migration from soil to plants and water was shown. Tris(2,4-di-tert-butylphenyl)phosphite is not readily biodegradable under experimental test conditions (OECD 301B; 6% degradation over 28 days).

In a hydrolysis study conducted according to OECD TG 111, tris(2,4-di-tert-butylphenyl)phosphite was shown to be hydrolytically stable under environmentally relevant conditions at pH 4, 7 and 9. A study conducted to assess the biomagnification potential of the substance in fish indicated that it is unlikely to bioaccumulate. Uptake of the substance into test organisms was very low, resulting in a mean lipid normalised whole fish biomagnification factor of 0.0032 ± 0.0020 . Mass balance measurements indicated that the majority of the test substance was present in excreted faeces.

Short-term aquatic toxicity tests at 3 trophic levels are available which show no effects at the water solubility limit in any of the tests. A 96h limit test with the fish *Brachydanio rerio* showed no effects at the nominal concentration of 100 mg/l. In a 24h *Daphnia magna* test, immobilisation was observed at nominal concentrations above 320 mg/l but these effects were due to physical interference with the test substance. No effects were observed at nominal concentrations up to 180 mg/l and it is concluded that the substance is not acutely toxic to *Daphnia magna* at the limit of water solubility. A 72h study with the algae *Scenedesmus subspicatus* showed no effects at the highest nominal test concentration of 75.2 mg/l. (It should be noted that all these tests were conducted at nominal concentrations greatly in excess of the water solubility limit). In a growth inhibition test no effects on activated sludge were found at the water solubility level (3h EC50 > 100 mg/l nominal concentration). There are no sediment or terrestrial effect data.

The substance does not possess properties indicating a hazard for the environment based on its low hazard profile. Adequate screening-level data are available to characterize the environmental hazards for the purposes of the OECD HPV Programme.

Exposure

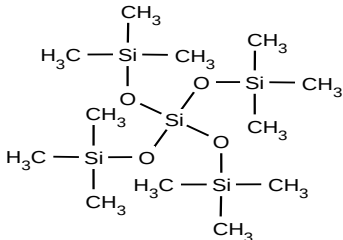
For the year 2002 the global market for tris(2,4-di-tert-butylphenyl)phosphite was about 55,000 tonnes. The substance is used as an antioxidant and/or stabiliser in matrices of polymers (packaging materials).

During production and processing there may be exposure of workers. The inhalatory route will be the most important route of exposure (particle size 10-100 µm diameter (respirable)).

During end-use, consumers may be exposed to the substance due to low migration from the matrix (regulatory migration limit in the United Kingdom for this chemical is 60 mg/kg food).

There is potential environmental exposure during production and processing of tris(2,4-di-tert-butylphenyl)phosphite and by leaching from waste at landfills.

INITIAL TARGETED ASSESSMENT PROFILE

CAS RN	3555-47-3
Chemical Name	Trisiloxane, 1,1,1,5,5,5-hexamethyl-3,3-bis[(trimethylsilyl)oxy]- (M4Q)
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGET ASSESSMENT

NOTE: The present assessment is targeted to address the following environment endpoints: stability in air and biodegradability in water, bioaccumulation potential, and acute and chronic toxicity to aquatic organisms, based on empirical data for the substance and a close structural analogue as well as application of (Q)SAR model predictions. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure potential is also reported here. Other endpoints for human health and the environment are included in the Canadian screening assessment but have not been presented to OECD member countries, and thus are not included in this profile.

The final screening assessment is to be published under the responsibility of the Government of Canada.

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its *Canadian Environmental Protection Act, 1999* (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: **inherently toxic** to humans or to the environment and that might be **persistent** and/or **bioaccumulative**; and substances to which people might have **greatest potential for exposure**. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release.

The substance, M4Q, was identified as a high priority for assessment of ecological risk because it was found to meet the ecological categorization criteria for persistence, bioaccumulation potential and inherent toxicity to aquatic organisms, and was believed to be in commerce in Canada.

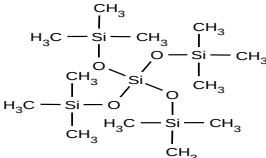
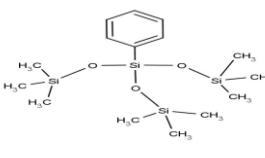
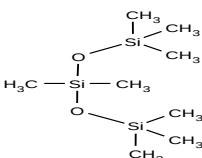
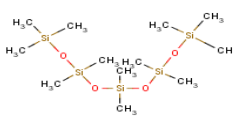
Analogue rationale

No experimental bioaccumulation factor (BAF) or bioconcentration factor (BCF) data were found for M4Q. However, experimental BCF data for two structurally similar substances, Tris(trimethylsiloxy)phenylsilane (PTS; CAS RN 2116-84-9) and Pentasiloxane, dodecamethyl- (L5; CAS RN 141-63-9), were examined and found to be appropriate for use as analogue data for M4Q. In addition, empirical biomagnification data for Trisiloxane, octamethyl- (MDM or L3; CAS RN 107-51-7) were considered in the weight-of-evidence evaluation of bioaccumulation potential. A comparison of relevant physical and chemical properties for these analogue

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substances is presented in Table 1 below.

Table 1. Comparison of physical and chemical properties of M4Q and its analogues relevant to bioaccumulation potential

Property	M4Q (CAS RN 3555-47-3)	PTS (CAS RN 2116-84-9)
Chemical structure		
Chemical formula	$C_{12}H_{36}O_4Si_5$	$C_{15}H_{32}O_3Si_4$
Molecular weight (g/mol)	384.85	372.76
Log K_{ow}	7.8 ^a	8.4 ^a
Water solubility (µg/L)	0.15	6.6
Log K_{oc}	5.2 ^b	5.7 ^b
D_{max} , D_{eff} (nm) ^c	1.3, 1.2	1.2, 1.1
Property	MDM or L3 (CAS RN 107-51-7)	L5 (CAS RN 141-63-9)
Chemical structure		
Chemical formula	$C_8H_{24}O_2Si_3$	$C_{12}H_{36}O_4Si_5$
Molecular weight (g/mol)	236.5	384.9
Log K_{ow}	6.6	7.8 ^a
Water solubility (µg/L)	34	0.07
Log K_{oc}	4.3	5.2 ^b
D_{max} , D_{eff} (nm) ^c	1.2, 0.9	1.7, 1.1

^a estimated using the EVA method in KOWWIN (2008) and empirical log K_{ow} for MDM of 6.6.

^b estimated using MCI method in KOCWIN (2008) given greater consistency of this method with empirical values for VMS in general.

^c conformational analysis performed using the MOPAC calculator and the BCF Baseline Model with Mitigating Factors (Dimitrov et al. 2005) in CPOPs (2008).

Physical-chemical properties

The EPISuite program (v4.00) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain organosilicons in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

M4Q is a branched volatile methylsiloxane (VMS). VMS are organosilicon compounds (polymers containing an alternating silicon-oxygen backbone) having low molecular weight (< 600 g/mol), significant vapour pressure under ambient environmental conditions, low aqueous solubility and high hydrophobicity. M4Q is a liquid with a measured melting point of -60 °C, a measured boiling point of 221.71 °C, a measured vapour pressure of 8.96 Pa at 25 °C and a measured water solubility of 0.00015 mg/L at 23 °C. A calculated octanol-water partition coefficient (log K_{ow}) of 9.84 has been reported. However, a log K_{ow} value of 7.8, derived using the experimental adjustment (EVA) method in KOWWIN (2008) and the empirical log K_{ow} of 6.6 for L3, was considered to more closely reflect the actual log K_{ow} of this substance. This procedure was also applied in the estimation of log K_{ow} values for the two analogue substances, PTS and L5.

Human Health

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Not part of the targeted assessment.

Environment

According to the results of Level III fugacity modelling (EQC 2003, v2.02), M4Q is expected to predominantly distribute into air (99.9%) if released only into that environmental compartment. It will distribute primarily into sediment (92.9%) if released only into water, and into air (64.3%) and soil (35.7%) if released only to soil. When released equally to all three compartments, M4Q will distribute primarily into sediment (87.4%), with lesser proportions in water (6.4%), air (5.0%) and soil (1.2%).

No experimental degradation data were found for M4Q and Q(SAR) models were used to estimate the potential for degradation in the environment. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 5.9 days (AOPWIN 2008, v1.92a). The Transport and Persistence Level III Model (TaPL3 2000, v2.10) and OECD POPs Screening Model (Scheringer et al. 2006, v2.0) indicate that M4Q has some atmospheric transport potential and may be capable of reaching areas a moderate distance from its emission sources. However, the substance lacks the potential to be deposited to water or soil in remote regions and is considered to have low Arctic contamination potential based on the chemical partitioning space plots described by Wania (2003, 2006).

Biodegradation modeling (BIOWIN 2008, v4.10; CATABOL c2004-2008, v5.10.2) predicts that M4Q in water will undergo primary biodegradation in less than 182 days; however, ultimate biodegradation (i.e., complete mineralization) will occur only slowly and the substance and/or its degradation products may therefore be more persistent in the environment. The complex physical structure provides further support for slow biodegradation of this substance. While hydrolysis has been demonstrated for other types of VMS, notably the linear VMS L3, no data were found on the ability of branched VMS such as M4Q to undergo hydrolysis reactions.

No experimental BAF or BCF data were found for M4Q. However, experimental BCF values of 1011 (steady-state) and 2292 (kinetic; Dow Corning Corporation) were reported for an acceptable analogue substance, PTS (CAS RN 2116-84-9), using bluegill sunfish, *Lepomis macrochirus* exposed for 45 days (with 60-day depuration period) to a maximum measured water concentrations of 4.4 µg PTS/L. BCF values of 1240-1430 (steady-state) and 1240-1450 (kinetic; SEHSC) were derived for a second analogue, L5 (CAS RN 141-63-9) using fathead minnow, *Pimephales promelas*, exposed for 35 days (with 35-day depuration period) to a maximum measured water concentrations of 0.04 µg L5/L. An estimated steady-state biomagnification factor (BMF) of 0.045 (lipid-adjusted value 0.16) was reported for rainbow trout, *Oncorhynchus mykiss*, exposed for 42 days (with 28-day depuration period) to 400 µg radiolabelled M4Q per g of food. A kinetic BMF of 0.10 (lipid-adjusted value 0.37; Dow Corning Corporation) was derived from the study, but did not include growth rate dilution of the fish over the study period. A steady-state BMF of 0.11 (lipid-adjusted value 0.38) and kinetic BMF of 0.26 (lipid-adjusted value 0.86; SEHSC) were reported for rainbow trout exposed for 35 days (28-day depuration period) to ~500 µg/g of an acceptable analogue substance, L3 (CAS RN 107-51-7). An additional analysis was conducted to determine modelled BCF values for PTS and L5, and a modeled BAF value for M4Q, using a three-trophic level version of the Arnot-Gobas kinetic mass-balance approach (Arnot and Gobas 2003). Using this approach, BCFs of 1096 and 1445 were determined for PTS and L5, respectively. The kinetic model was re-parameterized using a normalized metabolic rate constant (k_M) based on analysis of kinetics of both the BCF and BMF test data. The BAF model was further parameterized to account for the low dietary assimilation efficiency reported in the BMF study. BAF (uptake from all sources) is expected to be the most relevant metric for M4Q because 93% of the total exposure in the aquatic environment is expected to come via the diet and 7% from water (using log Kow as the bioavailability parameter). If log Koc is considered, bioavailability in the water is higher. Based on the kinetic analysis, the BAF is estimated to be ~263,000. Model predictions are considered to be in all relevant model applicability domains and reliable. Therefore, based on the BCF, BAF and BMF data, M4Q is expected to bioaccumulate in the environment, but is not expected to biomagnify in food webs.

The following acute and chronic aquatic toxicity data are available for M4Q:

Acute

Fish

96-hour LC₅₀

> 0.000182 mg/L (empirical; flow-through)*

	0.031 mg/L (ECOSAR 2008)**
	33.11 mg/L (AIEPS 2003-2007) ***
14-day LC ₅₀	0.034 mg/L (ECOSAR 2008)**
14-day NOEC	≥ 0.000159 mg/L (empirical; flow-through)*
Daphnid	
48-hour LC ₅₀	0.034 mg/L (ECOSAR 2008)**
	10.93 mg/L (AIEPS 2003-2007)***
Mysid	
96-hour LC ₅₀	0.001 mg/L (ECOSAR 2008)**
Algae	
72-hour EC ₅₀	4.95 mg/L (AIEPS 2003-2007)***
<i>Chronic</i>	
Fish	
30-d ChV	0.004 mg/L (ECOSAR 2008)**
Daphnid	
21-day EC ₅₀ (survival)	> 0.000191 mg/L (empirical; flow-through)*
21-day NOEC (growth, reproduction)	≥ 0.000191 mg/L*

* These results reflect the highest measured concentration tested and the functional limit of solubility under the conditions of administration.

** M4Q falls within the ECOSAR model's mechanistic domain (neutral organic) and water solubility domain, however, maximum log K_{ow} limits were exceeded for all acute toxicity estimates (i.e., fish, daphnid, mysid and algae). Chronic values (ChV) were within the domain of the model.

*** For the AIEPS model, similarity with the training set was relatively low for Si-O (60-67%).

For all experimental studies on M4Q, no adverse effects were observed at test concentrations up to and slightly above the reported water solubility of 0.00015 mg/L (at 23 °C). Modelled values (ECOSAR 2008, v1.00; AIEPS 2003-2007, v2.05) also predict no effects at saturation. This lack of effects may reflect limited bioavailability of M4Q, due possibly to physical and chemical properties such as very low water solubility as well as steric hindrance from the large and complex molecular structure. Based on the available acute and chronic data, it is considered unlikely that M4Q will cause adverse effects in pelagic organisms at or near the limit of water solubility. While adverse effects to sediment organisms have been reported for another siloxane (L3), no sediment toxicity data are available for M4Q.

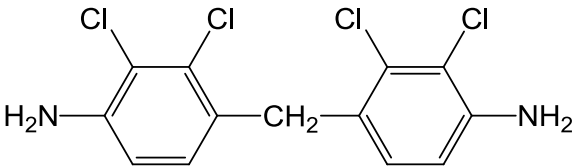
M4Q does not possess properties indicating an acute hazard for the environment (based on acute toxicity to pelagic organisms up to its water solubility limit.). However, it is expected to bioaccumulate and not to be readily biodegradable.

Exposure

M4Q is an organic substance that occurs as a reaction by-product or impurity in a wide range of silicon-based products, including those found in adhesives, sealants, processing intermediates, lubricants, antifoaming agents, paints and coatings. The substance does not occur naturally in the environment. In 2006, M4Q was not manufactured in Canada in quantities equal to or greater than the reporting threshold of 100 kg; however, total imports of M4Q into Canada in that year were in the range of 1000–10 000 kg.

A life cycle analysis designed to estimate losses of M4Q during different stages of industrial and commercial applications confirmed that the substance may be released into the Canadian environment (estimated losses were 35% to wastewater, 62% to landfill and 2% to incineration, with 1% exported in end-use products). However, it has also been reported that during processing operations M4Q becomes physically contained within products, thereby reducing the potential for migration out of the finished product with subsequent release into the environment. No monitoring data were identified for M4Q.

INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	42240-73-3
Chemical Name	4-[(4-Amino-2,3-dichlorophenyl)methyl]-2,3-dichloroaniline (ADCA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address only the following endpoint(s): [Human Health: acute toxicity, repeated dose toxicity and *in vitro* mutagenicity]. It cannot be considered as a full SIDS Initial Assessment. Nevertheless, the conclusions for the endpoints addressed have been agreed by member countries and may be used for hazard and risk assessment. Results on other endpoints may be relevant for hazard and risk assessment but have not been addressed in the assessment.

Rationale for targeting the assessment

Under the Japanese Chemical Substances Control Law, hazard assessment of existing chemical substances has been conducted. If a chemical substance is evaluated as “not biodegradable (persistent)” and “not highly bioaccumulative”, at least, a 28-day repeated dose toxicity and two *in vitro* mutagenicity studies are required as screening studies for hazard evaluation regarding human health. If a chemical is evaluated as having potential of long-term toxicity for human health, the chemical is classified as a Type II Monitoring Chemical Substance. If not, the chemical is of low priority for further action. Type II Monitoring Chemical Substances undergo risk-based management; at first, annual production volumes of those substances are monitored.

ADCA was evaluated as “not biodegradable (persistent)” and “moderately bioaccumulative” by METI (Ministry of Economy, Trade and Industry, Japan). Biodegradation and bioaccumulation are not part of the targeted assessment and therefore not presented in this ITAP. In order to determine whether this chemical is classified as a Type II Monitoring Chemical Substance, the initial hazard assessment of ADCA was conducted for the repeated dose toxicity and mutagenicity by MHLW (Ministry of Health, Labour and Welfare, Japan) in December 2009.

This targeted assessment document was originally based on the material from the chemical assessment council of MHLW, and we reassessed the toxicological profile for the OECD HPV chemical programme.

Physical-chemical properties

ADCA is a brown powder at standard temperature and pressure. Melting point and boiling point are 186.75 °C and 444.66 °C respectively by MPBPWIN. Vapour pressure is calculated to be 1.81×10^{-6} Pa at 25 °C by MPBPWIN. Measured values of partition coefficient between octanol and water ($\log K_{ow}$) are 5.39 at pH 12 and 3.9 at pH 7. Water solubility is 0.227–0.788 mg/L at 25 °C by WATERNT and WSKOWWIN. The dissociation constant (pK_a) in water is 1.20 and 2.01 by SPARC, ADCA is un-dissociated in environmental water.

Human Health

No information was found on the acute toxicity of ADCA. However, as no treatment related mortality or no clinical signs of toxicity were found up to 1000 mg/kg bw/day at the beginning of dosing in 28-day repeated oral

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gavage toxicity study, it is assumed LD50 value is more than 1000 mg/kg bw.

A repeated dose oral toxicity study in rats was conducted following OECD Test Guideline 407. In this study, ADCA was administered daily via gavage at 0 (vehicle control: 0.5 w/v% methylcellulose), 100, 300, or 1000 mg/kg bw/day for 28 days. Two additional groups were given 0 or 1000 mg/kg bw/day of ADCA for 28 days and were allowed to recover for two weeks after the administration period. No treatment-related deaths or clinical signs of toxicity were observed in ADCA-treated animals. There were no differences in body weight between the control and ADCA-treated groups. Serum total protein, and the percentage and concentration of α -1 globulin fraction decreased in males at 300 mg/kg bw/day and more. Serum triglyceride level increased in females at 1000 mg/kg bw/day. Relative liver weight increased in females at 1000 mg/kg bw/day. Histopathologically, hypertrophy of centrilobular hepatocytes was observed in both sexes at 300 mg/kg bw/day and more. All effects observed in this study were reversible after exposure. Based on the hypertrophic changes in the liver with altered blood biochemistry, the NOAEL of repeated dose oral toxicity was 100 mg/kg bw/day in both sexes.

In a bacterial reverse mutation study using four strains of *Salmonella typhimurium* and an *Escherichia coli* WP2 *uvrA* strain (OECD TG 471), ADCA was negative with or without metabolic activation. In an *in vitro* chromosome aberration test using Chinese hamster lung (CHL/IU) cells (OECD TG 473), ADCA was also negative with or without metabolic activation. No information was identified regarding *in vivo* genotoxicity.

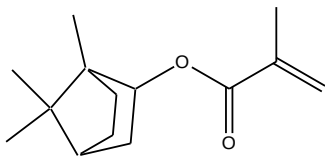
Agreed hazard conclusions

This chemical does not possess properties indicating a hazard for the human health endpoints targeted in this assessment (acute toxicity, repeated dose toxicity and *in vitro* mutagenicity) targeted in this assessment.

Available Exposure information

According to the national survey in Japan, sponsor country, no production or import of ADCA was reported in fiscal year 2007. Although reporting is obligatory for manufactures/importers dealing the substance at more than 1 tonne/year, the production volume and/or import volume of ADCA in Japan seems to be very limited. Information on the production volume in other countries is not available. ADCA is used as a reagent for high-performance polymer research.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7534-94-3
Chemical Name	Isobornyl Methacrylate (IBOMA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physicochemical Properties**

Isobornyl methacrylate (**IBOMA**) is liquid at room temperature. In a melting point study, the measured melting point was not detected, but a relaxation peak and an endothermic Specific heat capacity (C_p)-step was shown at -94°C , characteristics for a glass transition (i.e., the test item solidifies amorphously in the glassy state). The measured boiling point value is 258°C ; measured vapor pressure is 0.012 hPa at 25°C ; measured water solubility is 5.44 mg/L at 20°C ; measured octanol log K_{ow} values is 5.09. Estimated and measured values are highly concordant.

Human Health

No toxicokinetic, metabolism or distribution studies were identified for **IBOMA**. However, in general, methacrylates are known to be metabolized to methacrylic acid and the corresponding alcohols.

In rats, the oral LD_{50} value was 3,100 mg/kg bw (males) and 6,670 mg/kg bw (females) in an oral gavage study [pre-guideline]. The clinical signs included depression, hunched appearance, ataxia, excessive urination, and labored respiration. Animals that died during the study showed gastrointestinal inflammation and/or congestion of the lung lobes at the two highest dose levels (i.e., approximately 4,547 and 9,800 mg/kg bw for males and 9,800 and 21,070 mg/kg bw for females). **IBOMA** is not considered to be an acutely toxic substance via the oral route. No reliable acute toxicity studies were identified for the inhalation or dermal routes of exposure. Based on its low vapor pressure, **IBOMA** is unlikely to be hazardous via the inhalation route.

No guideline, or reliable, skin or eye irritation studies were identified for **IBOMA**. Following intracutaneous induction in a guinea pig maximization test [OECD TG 406], **IBOMA** did not evoke a skin reaction during challenge exposure when applied undiluted under occlusive conditions. As such, **IBOMA** was not sensitizing to skin under the conditions of the test.

Repeated-dose toxicity of **IBOMA** has been investigated in two subchronic dietary toxicity studies using rats and dogs, and in one oral gavage study [OECD TG 421] in rats. In the subchronic dietary rat study [Pre-guideline; similar to OECD TG 408], **IBOMA** was administered to 15 rats/sex/group, in the diet, *ad libitum*, at concentrations of 0, 1000, 3000, or 10,000 ppm (approximately 0, 50, 150, or 500 mg/kg bw/day) for 3 months. No deaths were reported at any concentration. Treatment-related effects included significantly decreased growth rate, food consumption and mean terminal body weights in males and females at 10,000 ppm compared to the controls. Increased liver weight relative to body weight (both sexes), and increased kidney and testis weight relative to body weight (males), was observed at 10,000

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ppm. Histopathological findings in the liver at all concentrations ranged from biliary epithelial hyperplasia at 1000 ppm to severe bile duct hyperplasia at 10,000 ppm in both sexes. Histopathological changes in the kidneys of male and female rats were observed at all concentrations. At 10,000 ppm, hypertrophy of the deep proximal convoluted tubules was seen, while at 3000 and 1000 ppm, varying degrees of protein imbibition, slightly more severe than controls, was considered to be related to treatment. In addition, hypercellularity of the bone marrow was noted in animals at 10,000 ppm. A NOAEL could not be established because histopathologic changes were noted at all concentrations. The LOAEL for 3 months of dietary exposure to **IBOMA** was 1000 ppm (approximately 50 mg/kg bw/day) based on histopathologic changes in the kidneys and liver at all doses.

In the subchronic dietary dog study [Pre-guideline; similar to OECD TG 409], **IBOMA** was administered daily to 4 dogs/sex/group in the diet at concentrations of 0, 1000, 3000, or 10,000 ppm (approximately 0, 31, 95, or 352 mg/kg bw/day) for 13 weeks. No deaths were reported at any concentration. Toxicologically-significant effects were limited to the animals at 10,000 ppm and included slightly increased blood urea nitrogen (BUN), increased liver to body weight ratio, and minimal to slight degenerative changes in the epithelial cells of the kidney proximal convoluted tubules. The NOAEL for 13-weeks of dietary exposure to **IBOMA** in dogs was 3000 ppm (approximately 95 mg/kg bw/day). The LOAEL was based on clinical pathology (BUN), organ weights (liver), and histopathologic findings (kidney) at 10,000 ppm (approximately 352 mg/kg bw/day).

In a reproduction/developmental toxicity screening study (OECD TG 421), three groups of 10 male and 10 female rats received **IBOMA** by daily oral gavage at 0 (corn oil), 25, 100, and 500 mg/kg bw/day. The males were dosed for 29 days and the females were dosed for up to 55 days. Hypersalivation was observed in a dose-related manner in males and females given 100 or 500 mg/kg bw/day. During the first week of the pre-mating period, males given 500 mg/kg bw/day gained less weight than controls. There were no other treatment-related effects on body weight, weight gain or food consumption during the study for males or females. There was a statistically significant increase in liver weight (males and females) and kidney weight (males only) at 500 mg/kg bw/day. No treatment-related findings were found in the reproductive organs examined. Microscopic findings in the liver included biliary proliferation/hypertrophy associated with fibrosis and macrophages infiltration (100 and 500 mg/kg bw/day, both sexes); disorganization of the hepatic cords (500 mg/kg bw/day, both sexes); and necrosis in the parenchyma (500 mg/kg bw/day, males). No treatment-related microscopic findings were observed at 25 mg/kg bw/day. In the kidneys, acidophilic globules were observed in the cortical tubular epithelium with a higher severity in males at 100 and 500 mg/kg bw/day, relative to controls. Based on the experimental conditions of the study, the NOAEL for systemic (parental) toxicity was 25 mg/kg bw/day.

In an Ames test [OECD TG 471], with multiple strains of *Salmonella typhimurium* and *Escherichia coli* WP2 uvrA, **IBOMA** was negative both with and without metabolic activation. In an *in vitro* chromosomal aberration test [OECD TG 473] using cultured human lymphocytes, **IBOMA** was negative with or without metabolic activation. Based on these results, **IBOMA** is not considered genotoxic under *in vitro* conditions.

No *in vivo* genetic toxicity studies were identified for **IBOMA**.

No data are available for the carcinogenicity of **IBOMA**.

In a reproduction/developmental toxicity screening test [OECD TG 421], three groups of 10 rats/sex/dose were administered **IBOMA** daily via oral gavage for 15 days prior to mating, during mating and gestation, and through lactation day (LD) 5. The dose levels were 0 (corn oil), 25, 100, or 500 mg/kg bw/day. The males were dosed for 29 days and the females were dosed for up to 55 days. The systemic toxicity effects for parental animals are described above. No treatment-related findings were noted in the reproductive organs examined. The male and female fertility indices were unaffected by treatment. All pregnant females had live pups, and the duration of gestation was similar in the control and **IBOMA** groups. There was no effect of treatment on the mean number of live born pups or on pup death after birth. There were no gross external pup abnormalities in the control or **IBOMA** groups. No significant differences were noted in the male and female pup body weight gain. No relevant findings were noted in pups sacrificed at PND 6. No treatment-related findings were found in the reproductive organs examined. Based on the experimental conditions of the study, the NOAEL for systemic toxicity was 25 mg/kg bw/day and the NOAEL for reproductive/developmental toxicity was 500 mg/kg bw/day (highest dose tested).

IBOMA possesses properties indicating a hazard for human health (repeated-dose toxicity), and the liver and kidney appear to be the main target organs. Adequate screening level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The predicted atmospheric half-life (AOP v.1.92) is 5.0 hours (12-hr day; 1.5×10^6 OH/cm³). In general, methacrylates do not contain photolytically active groups (i.e., direct photolysis by absorption of light > 290 nm will not occur). Methacrylates are hydrolytically stable at acidic and neutral pH levels. For environments at a pH range between 5-7, hydrolysis is not expected to be a significant route of degradation for **IBOMA**; however, at higher pH levels (i.e., 9-11), methacrylates rapidly hydrolyze.

The level III fugacity model (EpiSuite 4.00) calculation for **IBOMA** with equal and continuous release (1000 kg/hr) to air, water, and soil suggests that **IBOMA** will distribute mainly to the soil (86.7%) with minor distribution to other compartments (11.9% to water, 0.8% to sediment, and 0.6% to air). With 100% release of 1,000 kg **IBOMA**/hr to water, 92.1% would remain in the water, 6.5% would distribute to sediment, 1.4% to air and <0.1% would enter the soil. Similarly, with 100% release of the same amount to soil, 99.7% is expected to remain in the soil with virtually no distribution to air, water or sediment.

In a recent biodegradation study [OECD 301 D], **IBOMA** reached the 60% pass level within the 10-day window and 70% after 28 days. **IBOMA** is considered to be readily biodegradable. The calculated Henry's law constant (HENRYWIN v. 3.0) for **IBOMA** is 36.6 Pa-m³/mole (3.61×10^{-4} atm-m³/mole), which suggests that volatilization from the water phase is expected to be moderate. Based on the measured log K_{ow} of 5.09 and the relatively low measured water solubility (5.44 mg/L at 20°C and 6.35 mg/L at 30°C), there is a potential for bioaccumulation (estimated BCF = 1060, regression-based method; BCFBAF v. 3.00). An estimated Log K_{oc} value of 3.4 indicates that **IBOMA** has a moderate sorption to soil and sediment.

The following aquatic acute toxicity results have been determined for **IBOMA**:

An acute toxicity to fish [OECD TG 203] study yielded a 96-hour LC₅₀ for zebrafish, *Danio rerio*, of 1.79 mg/L (measured);

An acute toxicity to *Daphnia magna* [OECD TG 202] study indicated that the 48-hour **IBOMA** EC₅₀ was 1.1 mg/L (nominal). A more recent *D. magna* study [OECD TG 202] reported a measured 48-hour EC₅₀ of > 2.57 mg/L. A saturated solution of 2.57 mg/L was the maximum dissolved concentration of **IBOMA** that could be achieved under the test conditions in the test medium;

An aquatic plant toxicity to *Pseudokirchneriella subcapitata* [OECD TG 201] study produced 72- and 96-hour E_rC₅₀ (algal growth) values of 2.28 and 2.66 mg/L, respectively, and E_bC₅₀ (biomass) values of 0.835 and 0.913 mg/L, respectively; the NOEC at 72- and 96-hours was 0.251 and 0.254 mg/L, respectively, based on both the growth rate and biomass.

IBOMA possesses properties indicating a hazard for the environment (acute toxicity to fish, daphnia, and algae from less than 1 to 10 mg/L). IBOMA has some potential for bioaccumulation. IBOMA is readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

The world-wide estimated total annual production volume of **IBOMA** is 1000 to 10,000 metric tons. The percentage breakdown by country/region is considered confidential. **IBOMA** is manufactured using only closed systems. On a commercial scale, **IBOMA** is produced by the reaction of camphene and methacrylic acid. **IBOMA** may also be made through the reaction of isobornyl alcohol and methacrylic acid; however, this is a secondary method and is not used on a commercial scale. **IBOMA** is purified through distillation.

With respect to the impurities in the commercial-scale material, it is normal to have both camphene and isobornyl alcohol impurities. Although isobornyl alcohol is not used as a reactant on a commercial scale, the alcohol impurity results from the hydrolysis of camphene with water.

IBOMA is manufactured and processed in closed systems which limit environmental exposure. Waste streams containing

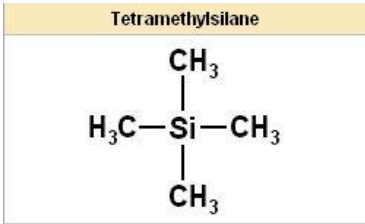
IBOMA are typically treated as hazardous waste through incineration or, for aqueous waste streams, at on-site biological treatment facilities. For other uses (e.g., providing properties of abrasion and/or water and chemical resistance), **IBOMA** may enter the environment in small quantities.

IBOMA is used as a reactive monomer intermediate in the manufacture of resins. Nearly all (>95%) of the monomer is polymerized by large industrial paint and coatings companies. The polymers made with **IBOMA** are used in paints and coatings for industrial applications in metal, glass, and plastics; the polymers are not used in consumer paints or coatings. Very small amounts of polymers are used in other industrial or commercial applications: adhesives, polymer concrete, and optical products. After initial manufacture of the resin, the material is washed to remove residual monomers. Typical residual monomer levels of **IBOMA** in finished resins are 10-20 ppm. Therefore, consumer exposure to **IBOMA** is expected to be negligible.

The majority of **IBOMA** is shipped in bulk containers (e.g., IBCs, tank trucks, rail cars) rather than in drums. As a result, the material is transferred/pumped directly from bulk containers to process equipment using closed piping with vapor recovery systems. Exposure and release are generally limited to fugitive emissions.

The general public and consumers are not expected to ever be exposed to **IBOMA** in monomer form. The only people that may be exposed to **IBOMA** would be a very limited number of workers either producing the monomer or workers in coatings and adhesive resins facilities that use the **IBOMA** to make acrylate resins.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-76-3
Chemical Name	Tetramethylsilane
Structural Formula	 The image shows the chemical structure of Tetramethylsilane (TMS). It consists of a central silicon atom (Si) bonded to four methyl groups (CH₃). The structure is represented as H₃C-Si-CH₃ with two additional CH₃ groups attached to the silicon atom, one above and one below the central bond.

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

Tetramethylsilane is a liquid with a measured melting point of -99.1°C and a measured boiling point of 26.7°C at 1013 hPa. The extrapolated vapor pressure value from measured data is 957 hPa at 25 °C. The measured water solubility is 19.6 mg/L at 25 °C. The estimated log K_{ow} of tetramethylsilane is 3.24.

Human Health

No toxicokinetics data were available for tetramethylsilane. Based on acute toxicity studies, systemic absorption following inhalation or dermal exposure appears to be low, while there appears to be some absorption and systemic distribution following oral (gavage) exposure. Repeated inhalation exposures suggest tetramethylsilane may be distributed to the liver.

The 4-hour inhalation LC_{50} in rats was $> 21.3 \text{ g/m}^3$ (21.3 mg/L) [OECD TG 403]. There were no clinical signs but macroscopic findings were noted in the lungs (discoloration, petechiae and/or hyaline spot/areas on one or more lobes) and intestines (tightened) at necropsy. The 7-hour inhalation LC_{50} in male rats is $> 2130 \text{ ppm}$ (7.7 mg/L) [no guideline specified]. There were no clinical signs of toxicity or macroscopic findings at necropsy. The dermal LD_{50} value is $> 2000 \text{ mg/kg-bw}$ [OECD TG 402] in rats. There were no clinical signs of toxicity or macroscopic findings at necropsy. The oral LD_{50} was $> 2000 \text{ mg/kg-bw}$ [OECD TG 401]. The clinical signs noted at 30 minutes to 6 hours after treatment included abnormal gait, squatting and abdominal position, sedation, paddling movements, piloerection, diarrhea, and diuresis. In another study, the oral LD_{50} in male rats was ca. 2000 mg/kg bw [no guideline specified]. There was one death at this dose level, but there were no clinical signs of toxicity and abdominal distension was noted at necropsy. Tetramethylsilane was not irritating to the rabbit skin [OECD TG 404] or eyes [OECD TG 405], and is not expected to be irritating to the respiratory tract based on acute inhalation studies in rats, and was not sensitizing to the skin of the guinea pig [OECD TG 406].

In a combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], rats were exposed via whole-body vapor inhalation to 0, 200, 1000 or 5000 ppm (0, approximately 0.72, 3.6 or 18 mg/L, respectively) tetramethylsilane, for 6 hours/day, 7 days/week, for up to 29 days. No treatment-related effects were observed at any exposure concentration. The NOAEC for systemic toxicity was 5000 ppm (18 mg/L/day), the highest concentration tested.

Tetramethylsilane did not induce gene mutations in *Salmonella typhimurium* strains (TA 98, TA 100, TA 102, TA 1535 and TA 1537) in an *in vitro* test [OECD TG 471] in the presence and absence of metabolic activation. Tetramethylsilane did not induce gene mutations [OECD TG 476] and chromosomal aberrations [OECD TG 473] in mammalian cells *in vitro*. Tetramethylsilane is not considered genotoxic *in vitro*. Carcinogenicity data are not available.

In the combined repeated-dose/reproductive/developmental toxicity screening test [OECD TG 422], described above, rats were exposed to tetramethylsilane via whole-body inhalation, two weeks prior to mating, during mating and up to gestation day 19. Dams and pups were euthanized on post-natal day 4. There were no treatment-related effects observed on fertility or

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developmental toxicity parameters. The NOAEC for reproductive and developmental toxicity was 5000 ppm (18 mg/L/day), the highest concentration tested.

Tetramethylsilane has a low hazard profile for human health. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The EPISuite program developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although measured data are included in some of the training sets); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

The Si-C bond in tetramethylsilane is expected to be hydrolytically stable under conditions typically found in the environment for very long periods of time; a hydrolysis study has not been conducted. Measured photodegradation data are available for tetramethylsilane. Based on measured OH radical rate constants, the calculated lifetime of tetramethylsilane for indirect photo-oxidation (reaction with OH radicals) ranges from 9 to 30 days. Level III Fugacity modeling, using equal releases to air, soil, and water (loading rates of 1000 kg/hour to each medium), shows the following percent distribution of tetramethylsilane: Air = 50.9%, Water = 48.4%, Soil = <1%, and Sediment = <1%. Tetramethylsilane was not readily biodegradable (8 % after 28 days) under the conditions of a ready biodegradability test conducted following EC Directive 92/69/EEC C.4-C and ISO/DIS 14593 (Modified Sturm test). The biodegradation results may be conservative as the substance will partition to the headspace during the test. The estimated Henry's Law constant of 2.24×10^4 Pa-m³/mole (0.22 atm-m³/mole) suggests that volatilization from the water phase for tetramethylsilane is expected to be high.

The BCF for tetramethylsilane cannot be predicted accurately, however, the regression-based estimated BCF value is 63.79 L/kg wet-wt (BCFBAF Program, v3.00).

Due to the physical chemical properties of the test substance, volatilization during the conduct of the reported algal and daphnia studies occurred, such that the reported concentration may be uncertain. Modelled data are provided to supplement the measured data.

The following acute toxicity test results with tetramethylsilane have been determined for aquatic species:

Fish [<i>Oncorhynchus mykiss</i>]	96 h LC50 = 1.9 mg/L (OECD TG 203; WAF, flow-through, closed system; measured)
	96 h LC50 = 15.9 mg/L (estimated)
Invertebrate [<i>Daphnia magna</i>]	48 h EC50 > 103 mg/L (OECD TG 202; static; closed system, measured by headspace analysis)
	48 h EC50 = 9.9 mg/L (estimated)
Algae [<i>Scenedesmus subspicatus</i>]	72-hour ErC50, EbC50 > 0.0079 mg/L; NOEC ≥ 0.0079 (OECD TG 201; WAF, closed system, measured). Where: EbC50 =
	EC50 based on biomass; ErC50 = EC50 based on growth rate.
	96 h EC50 = 6.5 mg/L (estimated)

Tetramethylsilane possesses properties indicating a hazard for the environment (acute toxicity to fish and *Daphnia* from 1 to 10 mg/L). Tetramethylsilane is not readily biodegradable. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

The North American production and import volume in 2005 was 106,594 tonnes (235 million lbs), the European production and import volume in 2005 was 90,718 tonnes (200 million lbs), and the Japanese production and import volume in 2005 was 2268 tonnes (5 million lbs). Tetramethylsilane is used as a precursor for chemical vapor deposition of SiO and SiC layers in the production of integrated circuits, as an analytical reference standard for Nuclear Magnetic Resonance Spectroscopy method, and is used in coatings and sealants. These uses are the same in North America, Europe and Japan.

Tetramethylsilane is produced in closed systems [hard-piped]; it is shipped by road in tanks, trailers and drums. Engineering controls such as local ventilation are used during packaging and sampling. Worker exposure due to non-accidental releases at the facility level is expected to be minimal.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7786-30-3
Chemical Name	Magnesium chloride
Structural Formula	$\begin{array}{cc} \text{Cl}^- & \text{Cl}^- \\ & \text{Mg}^{2+} \end{array}$

SUMMARY CONCLUSIONS OF THE SIAR**Physical and chemical properties**

Magnesium chloride is a colourless crystalline powder with a melting point of 714 °C, a boiling point of 1412 °C. It has a density of 2.32 g/cm³ and water solubility of 560 g/L at 25 °C. The vapour pressure, dissociation constants and partition coefficients are not applicable to inorganic salt.

Human Health

Magnesium is absorbed mainly in the small intestine after oral exposure; the colon also absorbs some. Magnesium absorption following oral ingestion is reported to range from 40 to 60%, with a lower percentage of absorption at higher daily intakes. Magnesium decreases the absorption of fluoride, and excess calcium may partially inhibit the absorption of magnesium. In the plasma, the level of magnesium is about 65% in ionic form, with the remainder bound to plasma proteins. Of the approximately 20 g body burden of magnesium, most is stored primarily in bone and muscle following absorption. Magnesium is excreted into the digestive tract by bile and pancreatic and intestinal juices. A small amount of radiomagnesium given intravenously appears in the gastrointestinal tract. The serum levels are remarkably constant. There is an apparent obligatory urinary loss of magnesium, which amounts to about 12 mg/day and the urine is the major route of excretion under normal conditions. Unabsorbed magnesium is excreted in the feces. Magnesium excretion can also occur via the sweat and breast milk.

The acute oral LD₅₀ value for female rats lay between 300 and 2,000 mg/kg bw/day and was estimated to be 1,085 mg/kg bw/day. Dead animals had gastric filling with the test substance. At 300 mg/kg bw/day no treatment related clinical signs and no mortality were observed. There were normal body weight gains in all animals. At the end of the study, necropsy was conducted on all animals and no abnormal gross findings were observed. The 24-hour dermal LD₅₀ value was in excess of 2,000 mg/kg bw/day in male and female rats. Signs of toxicity such as diarrhea and watery diarrhea were observed at 2,000 mg/kg bw/day.

The skin sensitization of magnesium chloride has been investigated in female of guinea pig (5weeks) following the study [OECD TG 406] and there was no evidence of skin sensitization.

The repeated dose toxicity of magnesium chloride has been investigated in two studies. In a repeated dose oral toxicity study [OECD TG 407], the substance was administered via gavage to rats(5/sex/dose) at 0, 250, 500 and 1,000 mg/kg bw/day for 28 days. No death were observed in either sex. The sporadically increased respiration was observed from day 7 in three females at 1,000 mg/kg bw/day. However, treatment related effects on body weight gain, food consumption, haematology, clinical biochemistry, organ weight changes, macroscopical/histopathological findings) were not observed at any dose. Based on these results, the NOAEL for repeated dose oral toxicity was considered to be 1,000 (males) and 500 (females) mg/kg bw/day.

Sprague-Dawley Rats were treated by gavage at doses of 0, 250, 500, or 1,000 mg/kg bw/day [OECD TG 421].

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Males in the main group were administered for a total of 42 days, and females in the main group were administered for two weeks. In males and females dosed with 500 and 1,000 mg/kg bw/day, soft stool, diarrhea and salivation were observed and shown to be dose-dependent during the dosing period. These were considered to be overdoses of the test substance since diarrhea and digestive disorders can be caused by overdoses of mineral such as magnesium. There were no differences on food consumption in all the dosed groups compared to the control. In males dosed with 500 and 1,000 mg/kg bw/day and in females dosed with 1,000 mg/kg bw/day, body weights showed a decreasing tendency compared to the control group. These were considered to be indirect effects by soft stool and diarrhea with overdoses of the test substance. In the 250 mg/kg bw/day dosed group, soft stool was observed occasionally, but body weights were not changed. The LOAEL was 500 mg/kg bw/day, based on a dose-dependent decrease in male bodyweight and a dose-dependent increase in salivation in both males and females. The NOAEL was 250 mg/kg bw/day.

In a bacterial reverse mutation assay [OECD TG 471] with multiple strains of *Salmonella typhimurium* and *Escherichia coli* WP2uvrA, magnesium chloride was negative with and without metabolic activation. An *in vitro* chromosomal aberration test [OECD TG 473] was negative with and without metabolic activation. An *in vivo* micronucleus test [OECD TG 474] was performed with mice. The incidence of micronuclei was evaluated in polychromatic erythrocytes of bone marrow. In the main test, mice were administered by intraperitoneally (i.p) two times with the test substance at dose levels of 30, 60 or 120 mg/kg bw/day and negative and positive control groups were treated with distilled water and mitomycin C, respectively. According to the results, magnesium chloride did not form micronucleus in bone marrow cells. Based on these results, magnesium chloride is considered to be non genotoxic *in vitro* and *in vivo*.

The carcinogenic potential of magnesium chloride has been investigated in one study. In an oral carcinogenicity study [no guideline followed], the substance was administered via the diet to mice (50/sex/dose) at 0, 570 or 2,810 mg/kg bw/day for males and 0, 730 or 3,930 mg/kg bw/day for females, for 104 weeks. Survival rates did not differ between the treatment and control groups for males or females. In females of the high-dose group a decrease in body weight was observed. Clinical signs and urinary, haematological or serum clinical chemistry parameters showed no treatment related toxic effects. On histological examination, tumours were mainly found in the skin and subcutis, liver and lymphatic system. With the exception of a significant decrease in the incidence of liver tumours among males of the high dose group, no differences were noted in the tumour incidence between the treated and control animals. Based on these results, magnesium chloride is considered to have no carcinogenic-potential.

Magnesium chloride has been investigated in a reproductive and developmental toxicity screening test in rats [OECD TG 421]. Rats were treated by gavage at doses of 0, 250, 500 or 1,000 mg/kg bw/day. Males were dosed once daily for a total of 42 days (two weeks each prior to, during and post mating), and females once daily for two weeks prior to mating, throughout gestation and four days after delivery. During the study, no necropsy findings and histopathological changes in lungs were found in one dead male and three dead females dosed with 1,000 mg/kg bw/day. The mating and gestation periods, mating index, fertility index and gestation index did not show statistically significant differences between the dosed groups and the control group. Normal parturition, mean litter size, pre- and post-implantation loss rate, live birth index and viability index on postnatal Days 0 and 4 were observed in all the dosed groups compared to the control group. There were no effects on the sex ratio, external findings, body weights and clinical signs of pups. Moreover, no differences were noted in absolute and relative organ weights of testes, epididymis, uterus, and ovaries, and no histopathological changes were observed. No adverse effects were noted in reproduction parameters of parents or the development of the pups in any of the dosed groups. In conclusion, the NOAEL for reproductive and developmental toxicity was 1000 mg/kg bw/day.

Magnesium chloride does not present a hazard to human health due to its low hazard profile. Adequate screening-level data are available to characterize a human health hazard for the purposes of the OECD HPV Programme.

Environment

Given its high solubility in water, magnesium chloride will dissociate and release Mg^{2+} and Cl^- ions. The dissociated Mg^{2+} cation can then transform and form complexes with dissolved ligands present in natural

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waters. Magnesium is widespread in living cells and does not bioconcentrate in aquatic organisms. Environmental fate analysis based on log Kow and log Koc and typical fugacity modelling is not applicable to magnesium chloride as it is an inorganic compound. Photodegradation and biodegradation are also not applicable to inorganic metal salts such as magnesium chloride.

The following acute toxicity test results have been determined for aquatic species:

Fish [<i>Oryzias latipes</i>]	96 h-LC ₅₀ > 95.2 mg/L (OECD TG 203, measured)
[<i>Pimephales promelas</i>]	96 h-LC ₅₀ = 2,120 mg/L (EPA guidance, nominal)
Invertebrate [<i>Daphnia magna</i>]	48 h-EC ₅₀ > 88.7 mg/L (OECD TG 202, measured)
[<i>Daphnia magna</i>]	48 h-LC ₅₀ = 1,330 mg/L (EPA guidance, nominal)
[<i>Ceriodaphnia dubia</i>]	48 h-LC ₅₀ = 880 mg/L (EPA guidance, nominal)
Algae [<i>Pseudokirchneriella subcapitata</i>]	72 h-E _r C ₅₀ > 82.7 mg/L (OECD TG 201, growth rate) (measured)
	72 h-E _y C ₅₀ > 82.7 mg/L (OECD TG 201, yield) (measured)

Chloride (Cl⁻) and magnesium (Mg⁺²) are both essential nutrients important for normal plant growth. High concentrations of MgCl₂ ions in the soil may be toxic or change water relationship in the plant resulting in diminished accumulation of water and nutrients. Once inside the plant, chloride moves through the water-conducting system and accumulates at the margins of leaves or needles, where dieback occurs first. Leaves are weakened or killed, which can lead to the death of the tree.

Magnesium chloride does not present a hazard to the environment due to its low hazard profile. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

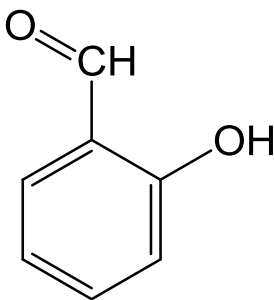
In the Republic of Korea, [sponsor country], the import and export volumes of magnesium chloride were 463 and 19 tonnes in 2006, respectively. At present, magnesium chloride is not produced in the sponsor country and the volume of use was 38,100 tonnes. The volumes of the import and export in the US were 6,914 and 4,763 tonnes in 1990, respectively. In European Nordic countries estimated use amounts of magnesium chloride were approx. 3,100, 3,080 and 3,390 tonnes in 2006, 2007 and 2008, respectively. The annual demand for magnesium chloride in Canada was 9 kilotonnes in 2005 and projected to be 10 kilotonnes in 2010.

Magnesium chloride is used as thickening agent in the production of synthetic detergents, intermediates, surface-active agents, anti-condensation agents, flame retardants and fire preventing agents, catalyser and flux agents for casting in the sponsor country. It is also used for a source of magnesium metal, magnesium oxychloride cement, refrigerating brines, ceramics, cooling drill tools, textiles, paper manufacture, road dust-laying compounds, road anti-icer and de-icing additive. It is estimated that 90% of Canadian consumption of magnesium chloride is for use as a dust suppressant and the remainder is for ice control. Magnesium chloride is used in pills as supplemental sources of magnesium, an important coagulant used in the preparation of tofu from soy milk and an ingredient in baby formula milk. Magnesium chloride is the main component of seawater bittern and used as firming agent, colour fixing agent and fortifying nutrient (food additive). The consumer may be exposed to small quantities of magnesium chloride by the consumption of food and drink.

In the manufacturing facilities of synthetic detergents, magnesium chloride is handled in a continuous closed system in the sponsor country. Occupational exposure is managed with local ventilation systems and personal protective equipments such as dust masks, gloves and goggles. According to the monitoring data, the 8hr-TWA (Time Weighted Average) concentrations of hazard materials for workplaces were not detected. Wastewater of each process is well controlled by physical and chemical treatment (e.g., floatation, sedimentation, sand filtration), consequently producing lower values than control standards. Occupational exposure is considered to be negligible in the sponsor country.

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SIDS INITIAL ASSESSMENT PROFILE

CAS No.	90-02-8
Chemical Name	2-Hydroxybenzaldehyde
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

2-Hydroxybenzaldehyde is a colourless oily liquid at standard temperature and pressure with almond like odour. Melting point and boiling point are -7 °C and 197 °C respectively. Vapour pressure is 75 Pa at 25 °C and partition coefficient between octanol and water ($\log K_{ow}$) is 1.66 at pH 6.2 – 6.3. Water solubility is 4.9 g/L at 25 °C. As a dissociation constant (pK_a) in water is 8.28, 2-hydroxybenzaldehyde is partially dissociated in environmental water. However, the un-dissociated form is dominant between pH 6 and pH 8.

Human Health

After administration of a single oral dose of 400 mg/kg bw of 2-hydroxybenzaldehyde to a fasted rabbit, 75% of the dose was excreted as ether-soluble acids in urine within 24 hrs, indicating that this substance was well absorbed via the gastrointestinal tract. Urine analysis revealed that 27% and 3% of the dose was excreted as glucuronic acid and sulphate conjugates, respectively.

In an acute oral study conducted according to OECD TG 423, the approximate lethal dose in female rats was estimated to be 500 mg/kg bw. No deaths occurred at 300 mg/kg bw, and all (3/3) died at 2000 mg/kg bw. The substance caused decreased locomotor activity, deep respiration, diarrhea and a soiled perineal region in dead animals. No abnormality was found at necropsy. Reliable acute toxicity studies with dermal or inhalation exposure were not available.

In a skin irritation test conducted in accordance with OECD TG 404, undiluted 2-hydroxybenzaldehyde caused a very slight to well defined erythema and very slight to severe oedema after a 4-hour semi-occlusive application to the skin of rabbits. These changes remained for 7 days after application, and desquamation from the skin was found in some animals. Primary Irritation Index was calculated to be 2.54. Reliable studies on skin irritation in human are not available. No information was identified regarding the eye and respiratory tract irritancy of 2-hydroxybenzaldehyde.

With regard to skin sensitization, reliable data on animal studies are not available. In humans, some skin sensitization studies and case reports demonstrated positive reactions to 2-hydroxybenzaldehyde in patch tests conducted in patients with contact dermatitis. Therefore, 2-hydroxybenzaldehyde is considered to have a sensitizing potential in humans.

One study investigated repeated dose toxicity of 2-hydroxybenzaldehyde. This study was conducted according to the procedures of OECD TG 422, except for the limited haematological and clinical chemistry examination in

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only male. The substance was administered via gavage to 12 rats/sex/dose at 0, 2.5, 10, 40 or 160 mg/kg bw/day for 49 days (starting from 14 days before mating) in males and 41-46 days (starting from 14 days before mating to day 3 of lactation) in females. No treatment-related changes were found in the clinical signs, body weight, food consumption, and haematological and blood biochemical parameters. Increased absolute and relative liver weights and decreased absolute and relative ovary weights were observed in the female 160 mg/kg bw/day group. A decrease in the degree and incidence of cytoplasmic lipid droplets in the liver was observed in the males of the groups treated with 40 and 160 mg/kg bw/day and a slight increase in glycogen deposits in the liver was observed in females treated with 40 and 160 mg/kg bw/day. Based on effects on liver histopathology, the NOAEL for repeated dose oral toxicity was considered to be 10 mg/kg bw/day.

In an Ames test with multiple strains of *Salmonella typhimurium* and *Escherichia coli* [OECD TG 471 and 472], 2-hydroxybenzaldehyde was negative both with and without metabolic activation. An *in vitro* chromosome aberration test using cultured Chinese hamster lung (CHL/IU) cells [OECD TG 473] was positive with and without metabolic activation. However, an *in vivo* bone marrow micronucleus assay [OECD TG 474], in which 2-hydroxybenzaldehyde was administered orally to male rats at up to 400 mg/kg bw/day and to female rats at up to 200 mg/kg bw/day for 2 days, was negative. In this study, body weight was lowered at 400 mg/kg bw/day in males, but no dose-related change was found in the incidence of polychromatic erythrocytes. Doses were selected based on the results of the dose-finding study, in which deaths occurred at 800 mg/kg bw/day in males and 400 mg/kg bw/day and above in females. Based on these results, 2-hydroxybenzaldehyde is considered non genotoxic *in vivo*.

No data are available for the carcinogenicity of 2-hydroxybenzaldehyde.

In a combined repeated dose toxicity study with the reproductive/developmental toxicity screening test in rats [the modified OECD TG 422, repeated-dose portion described above], 2-hydroxybenzaldehyde was administered orally via gavage to 12 animals/sex/dose at 0, 2.5, 10, 40 or 160 mg/kg bw/day for 49 days (starting from 14 days before mating) in males and 41-46 days (starting from 14 days before mating to day 3 of lactation through mating and pregnancy period) in females. No adverse effects on reproductive parameters (i.e. estrous cycle, copulation index, precoital interval, fertility and gestation index, gestation length, and the number of corpora lutea and implantations) were observed up to the highest dose tested; however, two dams at 160 mg/kg bw/day had undeveloped nipples and all pups of the two dams died. At the end of the administration period, there was a decrease in absolute and relative weight of the right ovary at 160 mg/kg bw/day. Based on the effect on nipple development and the ovary weight, the NOAEL for reproductive toxicity was considered to be 160 mg/kg bw/day for males and 40 mg/kg bw/day for females. As for the developmental effects, trends of decreases (not significant) in newborn viability index on postnatal day 4 were observed at 160 mg/kg bw/day. This change was attributed to deaths of all pups from the two dams with undeveloped nipple. Two litters from two of the twelve dams died between postnatal day 0 and day 4. No dose-related changes were observed in any group for the number of stillborn and live born, delivery index, live birth index, sex ratio and external and necropsy findings of pups on postnatal day 4. Therefore, a plausible explanation for the pup death from the two dams is mainly due to a failure of lactation caused by physically undeveloped nipple. The NOAEL on developmental effects was considered to be 160 mg/kg bw/day in this study.

2-Hydroxybenzaldehyde may present a hazard to human health (skin irritation, skin sensitization, repeated dose toxicity and reproductive toxicity). Adequate screening level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

In the atmosphere, 2-hydroxybenzaldehyde is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.38 days is obtained by AOPWIN (version 1.92) for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

2-Hydroxybenzaldehyde is not hydrolysed due to the lack of hydrolysable functional groups. A hydrolysis test according to OECD test guideline 111 showed that 2-hydroxybenzaldehyde was stable in water at pH 4, pH 7 and pH 9 at 50 °C for five days.

An OECD test guideline 301C test was conducted with 2-hydroxybenzaldehyde with activated sludge for four weeks. The concentration of the test substance was 100 mg/L and the concentration of the activated sludge was 30 mg/L as suspended solid matters. The test result showed 2 % degradation by BOD. However,

2-hydroxybenzaldehyde was not detected in the test system and whole amount of the chemical was converted to 2-hydroxybenzoic acid (salicylic acid) after the cultivation period.

After the main test, an additional biodegradation test with 2-hydroxybenzaldehyde was conducted under the condition of OECD test guideline 302C without measurement of BOD. The concentration of 2-hydroxybenzaldehyde was 30 mg/L and the concentration of activated sludge was 100 mg/L as suspended solid matters. After four weeks cultivation period, neither 2-hydroxybenzaldehyde nor 2-hydroxybenzoic acid was detected in the test system, which means 2-hydroxybenzaldehyde was biodegraded. Based on the results of algae test and other available eco-toxicity tests, it is likely that 2-hydroxybenzaldehyde may be toxic to microbial inoculums used in the test-guideline 301 C at relatively high concentration of 100 mg/L.

An independent biodegradation study with 2-hydroxybenzoic acid with an equivalent protocol with OECD test-guideline 301C showed 88.1 % degradation by BOD after two weeks.

BIOWIN estimation (version 4.10) predicts that 2-hydroxybenzaldehyde is classified as ready biodegradable. Based on the weight of evidence consideration, 2-hydroxybenzaldehyde is considered to be biodegradable.

No information was available on the bio-concentration of 2-hydroxybenzaldehyde. Using an octanol-water partition coefficient ($\log K_{ow}$) of 1.66, a bio-concentration factor of 5.8 was calculated with BCFBAF (version 3.00). This chemical is not expected to bioaccumulate.

Fugacity level III calculations show that 2-hydroxybenzaldehyde is mainly distributed to the soil compartment (69.2 %) and the water compartment (29.8 %) if equally and continuously released to the air, soil and water. These results have to be treated with caution because partial dissociation of the substance is possible under particular environmental conditions ($pK_a = 8.28$). A Henry's law constant of 0.178 Pa.m³/mole at 25 °C suggests that volatilization of 2-hydroxybenzaldehyde from water is slow. A soil adsorption coefficient of $\log K_{oc} = 1.8$ indicates 2-hydroxybenzaldehyde has low adsorption to soil and sediment.

The following acute toxicity test results have been determined for aquatic species;

Fish [<i>Oryzias latipes</i> OECD-TG 203]:	96 h LC50 = 1.6 mg/L (measured)
[<i>Pimephales promelas</i>]	96 h LC50 = 2.3 mg/L (measured)
Daphnid [<i>Daphnia magna</i> OECD-TG 202]:	48 h EC50 = 2.6 mg/L (measured)
Algae[<i>Pseudokirchneriella subcapitata</i> OECD-TG 201]:	72 h ErC50 = 4.8 mg/L (measured, growth rate)
	72 h EbC50 = 1.6 mg/L (measured, biomass)

The following chronic toxicity test results have been determined for aquatic species:

Daphnid [<i>Daphnia magna</i> OECD-TG 211]:	21 d LOEC = 0.23 mg/L (measured)
	21 d NOEC = 0.13 mg/L (measured)
Algae[<i>Pseudokirchneriella subcapitata</i> OECD-TG 201]:	72 h NOErC = 0.55 mg/L (measured; growth rate)
	72 h NOEbC = 0.55 mg/L (measured; biomass)

2-Hydroxybenzaldehyde possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 10 mg/L for fish, invertebrate and algae, and chronic toxicity values less than 1mg/L for invertebrate and algae). This chemical is considered biodegradable and is not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

Production volume and/or import volume of hydroxybenzaldehyde in Japan (sponsor country) was between 100 and 1,000 tonnes in fiscal year 2007. This figure includes amounts of 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde and 4-hydroxybenzaldehyde. Production and/or import volume of 2-hydroxybenzaldehyde in the United States was less than 500,000 pounds (227 tonnes) during 2006 according to Inventory Updated Reporting. Production volume in the world was not available.

According to the Japanese pollution release transfer register system, 19 kg of 2-hydroxybenzaldehyde were released in the air compartment and 2 kg of 2-hydroxybenzaldehyde were released to the public water body in the

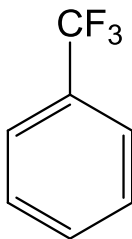
fiscal year of 2008. Release to the soil compartment was not reported. Based on this reporting results, environmental release of 2-hydroxybenzaldehyde from manufacturing and processing sites is thought to be not significant.

2-Hydroxybenzaldehyde is produced from phenol, chloroform and alkali according to Reimer-Tieman reaction. 2-Hydroxybenzaldehyde is used in perfume, coumarin synthesis and as an intermediate for pharmaceutical products and pesticides. This chemical is also used as an auxiliary fumigant, flavour ingredient in foods, medical chemicals, reagent in analytical chemistry, and gasoline additive.

Occupational exposure to 2-hydroxybenzaldehyde through inhalation of vapor and via the dermal route is anticipated from its physical properties. No OEL's for 2-hydroxybenzaldehyde are established.

As 2-hydroxybenzaldehyde is used as an ingredient of perfume, a flavour ingredient in foods and gasoline additive, consumer exposure is anticipated. Daily intakes of 2-hydroxybenzaldehyde as a food flavouring agent were estimated to be 1.6 µg/kg bw/day in Europe and 0.3 µg/kg bw/day in the United States. The Joint FAO/WHO Expert Committee on Food Additives evaluated that no safety concern of 2-hydroxybenzaldehyde as a food flavouring agent would be expected at current estimated levels of intakes. No other information on the consumer exposure is obtained.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-08-8
Chemical Name	Trifluoromethylbenzene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Physical-chemical properties**

Trifluoromethylbenzene is a colourless liquid at standard temperature and pressure with aromatic odour. Melting point and boiling point are -28.95 °C and 102.1 °C respectively. Vapour pressure is 5.14 kPa at 25 °C and a partition coefficient between octanol and water (Log K_{ow}) is 3.01. Water solubility is 192 mg/L at 20 °C. Trifluoromethylbenzene is highly flammable.

Human Health

Although no toxicokinetic information was identified for absorption, metabolism, distribution or excretion, trifluoromethylbenzene is considered to be absorbed from the gastrointestinal tract and well distributed throughout the rat body based on observations in the combined repeated dose toxicity and reproductive/developmental toxicity test by oral administration of this chemical.

The dermal LD₅₀ value was above 2000 mg/kg bw for male and female rats in the acute study following OECD TG 402 (exposure time: not specified but 24 hr in the guideline). No toxic effects were observed at 2000 mg/kg bw. No reliable studies were available for acute oral and inhalation toxicity. Although the quality of data is not robust, trifluoromethylbenzene seems to be slightly toxic after single exposure via oral and inhalation routes. Indeed, the inhalation LC₅₀ values were reported to be 70.81 mg/l (4 hrs) for rats and 92.24 mg/l (2 hrs) for mice, and the oral LD₅₀ to be 15000 mg/kg bw for rats and 10000 mg/kg bw for mice.

In the skin irritation test conducted in accordance with OECD TG 404, undiluted trifluoromethylbenzene caused very mild edema and mild to moderate erythema up to 72 hrs after 4-hr application to the rabbit skin. While the erythema and edema had almost completely disappeared by the end of the 14-day observation period, the skin surface remained dry and rough, and was parchment-like and flaky in parts. The average irritation value was 2.0 for erythema and eschar formation and 0.2 for edema formation. In the eye irritation test conducted according to OECD TG 405, trifluoromethylbenzene exerts some irritating effects (injected vessels, and carmine-colored and slightly swollen conjunctivae) one hour after instillation into the eye of rabbits, but these effects were no longer observed at other examination times. Therefore, trifluoromethylbenzene was considered to be a skin irritant but not an eye irritant in rabbits. No information regarding the respiratory tract irritancy of trifluoromethylbenzene was available.

No information was available for sensitisation.

The repeated toxicity of trifluoromethylbenzene has been investigated in a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [according to the procedures of OECD TG 422, except for limited haematological and clinical chemistry examination in only male]. The substance was

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administered via gavage to male and female rats at 0, 20, 100 or 500 mg/kg bw/day. The duration of treatment in males was 49 days including a 14-day pre-mating period. Females were dosed for a 14-day pre-mating period, during mating and gestation periods, and until day 3 of lactation. One female died after delivery on day 23 of gestation in the 500 mg/kg bw/day group. No other treatment-related clinical signs of toxicity were observed. No effects were found on body weight and food consumption. Hematological and blood biochemical examination performed in males only revealed a decrease in glucose and increases in total protein, albumin, total cholesterol, phospholipid and calcium at 500 mg/kg bw/day. The absolute and/or relative liver weight increased in males in the 100 mg/kg bw/day group and in both sexes in the 500 mg/kg bw/day group, and histopathological examination revealed centrilobular hypertrophy of hepatocytes at 100 and 500 mg/kg bw/day in both sexes. In males, increased absolute and relative kidney weights were also found in the 500 mg/kg bw/day group, and microscopic changes in the kidney (hyaline droplets, epithelial necrosis, dilatation and basophilic changes in the epithelium of proximal tubules) were observed at 100 and 500 mg/kg bw/day. Based on histopathological changes in the liver and kidneys, the NOAEL for repeated dose oral toxicity was considered to be 20 mg/kg bw/day for both sexes.

In an Ames test conducted in accordance with OECD TG 471 and 472, trifluoromethylbenzene was negative in multiple strains of *Salmonella typhimurium* (TA100, TA1535, TA1537, TA98) and *Escherichia coli* (WP2 uvrA) both with and without metabolic activation. Other bacterial reverse mutation studies with *Salmonella typhimurium* (TA100, TA1535, TA1537, TA97, TA98) and *Escherichia coli* (pkM101) also showed negative results with and without metabolic activation. An *in vitro* chromosome aberration test (OECD TG 473) using cultured Chinese hamster lung (CHL/IU) cells with 24-hr and 48-hr continuous exposures without metabolic activation, and 6-hr short term exposure with and without metabolic activation was negative. Negative results were also obtained in a rec assay for DNA damage with *Bacillus subtilis* and mitotic crossover and the gene conversion assay with *Saccharomyces cerevisiae*. Based on these results, trifluoromethylbenzene is considered to be non genotoxic *in vitro*. There was no *in vivo* study on mutagenicity.

No information on carcinogenicity for trifluoromethylbenzene was identified.

In a combined repeated dose toxicity study with the reproductive/developmental toxicity screening test [the modified OECD TG 422, repeated-dose portion described above], trifluoromethylbenzene was administered via gavage to male and female rats at 0, 20, 100 or 500 mg/kg bw/day. The duration of treatment for males was 49 days including a 14-day pre-mating period. Females were dosed for a 14-day pre-mating period, during mating and gestation periods, and until day 3 of lactation. In the 500 mg/kg bw/day group, one dam died after delivery on day 23 of gestation, which was considered due to dystocia. No adverse effects on reproductive parameters (estrous cycle, copulation, fertility and gestation index, precoital and gestational days, and the number of corpora lutea, implantation sites, live newborns and stillborns) were observed up to the highest dose tested. There were also no changes in the weight and histopathology of reproductive organs in either sex. Therefore, the NOAEL for reproductive toxicity was considered to be 100 mg/kg bw/day. For developmental effects, there were no treatment-related changes in the number of live pups born, nor in the sex ratio. No dose-related abnormality was found in gross external and internal findings in pups. In all treatment groups lower body weights of pups were found at day 0 (<10%), which did not recover at day 4 (16% maximum). The toxicological relevance of this observation is unclear as no other signs of developmental toxicity were observed. Therefore, the substance is not considered to be a developmental toxicant. Nevertheless as the body weight reduction was statistically significantly different at the lowest dose tested the overall LOEL of this study is considered to be 20 mg/kg bw/day. The NOAEL for maternal toxicity was 20mg/kg bw/day.

Trifluoromethylbenzene may present a hazard to human health (skin irritation, repeated dose toxicity). Adequate screening level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

In the atmosphere, trifluoromethylbenzene is expected to be degraded by hydroxyl radicals. A calculated half-life time of 27.3 days is obtained by AOPWIN (version 1.92) for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

Trifluoromethylbenzene is not hydrolysed due to the lack of hydrolysable functional groups. A hydrolysis test according to OECD test guideline 111 showed that trifluoromethylbenzene was stable in water at pH 4, pH 7 and

pH 9 at 50 °C for five days.

An OECD Guideline 301D test was conducted with trifluoromethylbenzene with sludge for four weeks. The concentrations of trifluoromethylbenzene in the test system were 2.4 mg/L and 11.9 mg/L. The test result showed 0 % degradation by BOD after four weeks cultivation period for both treatments. BIOWIN estimation (version 4.10) predicts that trifluoromethylbenzene is not readily biodegradable. According to these results, trifluoromethylbenzene is considered to be not-readily biodegradable.

In a study performed according to a protocol equivalent to OECD Guideline 305 with carp exposed to trifluoromethylbenzene, bio-concentration factors of 26–54 were obtained for the concentration of 100 µg/L and 31–58 for the concentration of 10 µg/L for six weeks exposure period. In this test, the lipid content value of the test fish was 4.9 %. Taking into account the octanol-water partition coefficient, a bio-concentration factor can be calculated as 45 according to a log K_{ow} of 3.01 by BCFBAF (version 3.00). Trifluoromethylbenzene is not expected to bioaccumulate.

Fugacity level III calculations show that trifluoromethylbenzene is mainly distributed to the water compartment (45.0 %) and air compartment (43.6 %) if equally and continuously released to the air, soil and water. A Henry's law constant of 4.74×10^3 Pa.m³/mole at 25 °C suggests that volatilization of trifluoromethylbenzene from water is rapid. A soil adsorption coefficient of Log K_{oc} = 2.6 indicates trifluoromethylbenzene has moderate sorption to soil and sediment.

The following acute toxicity test results have been determined for aquatic species;

Fish [<i>Oryzias latipes</i> , OECD-TG 203]:	96 h LC ₅₀ = 19 mg/L (measured)
Daphnid [<i>Daphnia magna</i> , OECD-TG 202]:	48 h EC ₅₀ = 3.1 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i> , OECD-TG 201]:	72 h ErC ₅₀ = 5.4 mg/L (measured, growth rate)
	72 h EbC ₅₀ = 3.0 mg/L (measured, area under growth curve)

The following chronic toxicity test results have been determined for aquatic species:

Daphnid [<i>Daphnia magna</i> , OECD-TG 211]:	21 d LOEC = 1.9 mg/L (measured)
	21 d NOEC = 0.59 mg/L (measured)
Algae [<i>Pseudokirchneriella subcapitata</i> OECD-TG 201]:	
	72 h NOErC and 72 h NOEbC 1.5 mg/L (measured)

Trifluoromethylbenzene possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L for fish, invertebrate and algae and chronic toxicity less than 1 mg/L for invertebrate). This chemical is considered not readily biodegradable and is not expected to have bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

According to the notification obligation of the amount of manufacture/import based on the Chemical Substances Control Law in Japan (sponsor country), no production was reported and import was less than 1 tonne/year in fiscal year 2007. Although the reporting is obligatory to manufacturers/importers dealing with the substance at more than 1 kg/year, the production volume and/or import volume of trifluoromethylbenzene in Japan seems to be almost zero. Information of the production volume in other areas is not obtained.

As trifluoromethylbenzene seems not to be manufactured in Japan, no detailed information is available on the production method and use patterns. Trifluoromethylbenzene is produced by the reaction of hydrogen fluoride on benzotrichloride, or reaction of antimony trifluoride on benzotrichloride. Trifluoromethylbenzene is used as an intermediate for pharmaceutical products and pesticides. This chemical is also used in dye chemistry, in the manufacturing of substituted trifluoromethylbenzene containing an ethylenic group, in high polymer chemistry,

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and in dielectric fluids, such as transformer oils. Other uses are solvent, vulcanizing agents and insecticides.

Occupational exposure to trifluoromethylbenzene through inhalation of vapour and via the dermal route is anticipated from its physical properties. No OEL's are established for this chemical.

As trifluoromethylbenzene is not used in the general consumer products, no consumer exposure is expected. No more detailed information is available for the consumer exposure.

SIDS INITIAL ASSESSMENT PROFILE

CAS No. and Chemical Name	106-98-9 107-01-7 590-18-1 624-64-6 115-11-7 25167-67-3	1-Butene 2-Butene <i>cis</i> -2-Butene <i>trans</i> -2-Butene Isobutylene (2-Methylpropene) Butene, mixed isomers
CAS Numbers with Structural Formula	106-98-9 107-01-7 590-18-1 624-64-6 115-11-7 25167-67-3	$\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_3$ $\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_3$ (contains <i>cis</i> - and <i>trans</i> - forms) $\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_3$ (<i>cis</i> - form) $\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_3$ (<i>trans</i> - form) $\text{CH}_2=\text{C}(\text{CH}_3)_2$ Contains all butene structures above

SUMMARY CONCLUSIONS OF THE SIAR**Category/Analogue Rationale (if appropriate)**

The Butenes Category includes six CAS numbers that are similar from a process and toxicology perspective. Each substance within this category is a C4 olefin or contains a mixture of selected C4 olefins that are produced from a reaction and/or separation activity in an olefins chemical plant. Four CAS numbers describe different C4 isomers, each is a hydrocarbon with the same chemical formula and one double bond between two carbon atoms. Two CAS numbers describe mixtures of C4 olefins that contain either two or all four different isomers. The six substances share relatively similar physico-chemical properties, which suggests that their environmental fate will be similar. The chemicals are expected to have similar kinetic properties because of similar physical-chemical properties. No specific target organ was identified and no or minimal changes in body weight were found at the highest dose only for all the butenes. Therefore the butenes can be treated as a category.

Physical-chemical properties

The physical properties of Butenes Category members are given in ranges as the substance differ minimally in these properties. Melting Point (°C) ranges from -105.5 to -185.3, boiling point (°C) ranges from -6.9 to 3.7, relative Density (g/cm³ at 25°C) ranges from 0.588 to 0.6213, vapor pressure (hPa at 25°C) ranges from 2,106 to 3,080 (determined experimentally), water solubility (mg/L at 25°C) ranges from 222 – 700 and the log Kow (at 25°C) ranges from 2.31 - 2.4.

Human Health

The acute toxicity data on members of the Butenes Category is limited. Only acute inhalation studies are available. Overall, these limited data suggest that the members of this category have a low order of acute toxicity. The 4-hr LC₅₀ value of 2-butene was found to be higher than 10,000 ppm (23,100 mg/m³). The 2-hour LC₅₀ of isobutylene in mice was 180,000 ppm (415,000 mg/m³) and the 4-hour LC₅₀ in rats was 270,000 ppm (620,000 mg/m³). At concentrations exceeding the lower explosion limit (LEL > 8000 ppm (18,400 mg/m³)), the butenes have the potential to produce narcosis or cause asphyxia by reducing the available concentration of oxygen.

There are no data to evaluate the dermal or ocular irritation potential of butenes. However, should skin or eye contact occur to this chemical in its liquid state, tissue freezing, severe cold burn, and/or frostbite may result. This is likely to be a function of the temperature as the boiling point is around 0°C. There are no data to evaluate the skin or respiratory tract sensitization potential of butenes in either animals or humans.

Based on the results of the repeated-dose studies conducted in animals, the members of the Butenes Category appear to have a low order of sub-chronic toxicity. The NOAEL for 1-butene in an inhalation OECD 422 guideline study (combined repeated dose toxicity and reproductive/developmental toxicity test) was > 8000 ppm (18,400 mg/m³). In a repeated- dose study conducted with 2-butene, exposure of animals to 2500 ppm (5700 mg/m³) and 5000 ppm (11,500 mg/m³) did not induce significant systemic toxicity in male rats exposed for up to 46 days, or in pregnant

female rats exposed for 2 weeks pre-mating, through mating and gestation to day 19. The only statistically significant effects were effects on body weight and body weight gain. However, as these effects were not dose-related and not consistently present during the study, it was concluded that the NOAEC for butene-2 in this study was ≥ 5000 ppm (11,500 mg/m³). Isobutylene was not toxic to rats or mice exposed to concentrations up to 8,000 ppm (18,400 mg/m³) for 14 weeks or 2,000 ppm (4,600 mg/m³) for 105 weeks. The NOAEC of 2,000 ppm (4,600 mg/m³) is based on minimal effects in the nasal cavity at the highest dose.

None of the members of the butenes category that have been tested produced mutagenic responses either *in vitro* or *in vivo*. 1-butene, 2-butene and isobutylene did not induce gene mutations in reverse mutation assays conducted in *S. typhimurium* and/or *E. coli* either in the presence or absence of metabolic activation. 2-butene was not clastogenic to rat lymphocytes *in vitro*. Isobutylene tested negative in an *in vitro* cell transformation assay using a mouse embryo fibroblast derived cell line and in a mouse lymphoma assay both in the presence or absence of metabolic activation. In addition, neither 1-butene nor isobutylene induced micronuclei formation in mouse bone marrow cells from animals exposed up to 22,000 ppm (50,600 mg/m³) or 10,000 ppm (23,000 mg/m³), respectively.

A carcinogenicity study on isobutylene (the only available study on this endpoint, in both rats and mice) is used to assess the potential of all Butenes Category members to cause cancer. Although isobutylene produced an increase in follicular cell carcinomas of the thyroid in male rats exposed for 105 weeks, this was observed only at the highest exposure concentration (i.e., 8000 ppm) and did not occur in female rats nor male or female mice. In addition, the follicular cell carcinomas in the thyroid were reported to be morphologically similar to spontaneously developing follicular cell carcinomas and there was no concurrent increase in the incidence of follicular cell hyperplasia or adenoma in male rats. It should also be noted that there was no evidence of any carcinogenic activity in female rats or mice up to 8000 ppm. As isobutylene is not genotoxic and as the thyroid tumors only occurred in male rats at the highest dose, i.e., 8000 ppm (18,400 mg/m³), the mechanism for the formation of the thyroid tumors most likely has a threshold. Overall, these data suggests that isobutylene as well as the other members of the Butenes Category have a potential for carcinogenicity, although the relevance for humans is unclear. The NOAEC in a chronic carcinogenicity study of isobutylene was 2,000 ppm (4,600 mg/m³).

Based on the reproductive/developmental toxicity studies conducted with 1-butene, 2-butene and isobutylene, it appears that the members of the Butenes Category are neither reproductive nor developmental toxicants.

The NOAEL for parental and F1 offspring was 8000 ppm (18400 mg/m³) in a combined repeated dose toxicity and reproduction/development toxicity study of 1-butene in rats conducted according to OECD guideline 422.

In a 422 guideline study of 2-butene, the parental NOAEL and the NOAEC for the F1 offspring were both ≥ 5000 ppm (11,500 mg/m³). The only statistically significant effects were effects on parental body weight and body weight gain. However, these effects were not dose-related and not consistently present during the study, therefore considered not toxicologically relevant.

In a prenatal developmental toxicity study of isobutylene conducted to OECD 414 guidelines, the NOAEL was 8,000 ppm (18,400 mg/m³) for maternal and foetal effects. There was no effect of isobutylene on the number, growth or survival of the foetuses in utero and no adverse effects on foetal development. These findings, along with the findings of no biologically significant effects on male or female reproductive organs attributed to isobutylene exposure in 14-week repeat dose inhalation studies in two rodent species, leads to a conclusion of low concern for reproductive toxicity for members of this category.

Environment

Results of distribution modelling show that butenes will partition primarily to the air compartment, with a negligible amount partitioning to water. In spite of their water solubility, wet deposition of butenes is not likely to play a significant role in their atmospheric fate because of rapid photodegradation. Volatilisation to the air will contribute to the rapid loss of butenes from aqueous and terrestrial habitats. In the air, butenes have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals and ozone with calculated degradation half-lives ranging from approximately 1.38 to 24.32 hours, respectively, depending on hydroxyl radical and ozone concentrations. Because of the relatively short half-life of selected butenes in the atmosphere and the low environmental concentrations typically found, their contribution to potential global warming can be considered minor. Aqueous photolysis and hydrolysis will not contribute to the transformation of butenes in aquatic environments because they are either poorly or not susceptible to these reactions.

A butene isomer has been detected in air samples. Isobutylene concentrations have been reported to range in urban air samples ranging from 1 to 10 ppb. Butene-2 has been detected directly over diesel exhausts to a lesser extent than butene-1. The more highly reactive trans-2-butene occurs at a much lower frequency in the atmosphere than other comparable hydrocarbons.

Although the biodegradability of the butene isomers have not been evaluated with standard 28-day test guidelines, research studies designed largely to evaluate the metabolic pathways involved in the degradation of butenes have demonstrated that selected isomers can be degraded by bacteria isolated from soil and surface water samples. The results from these studies suggest that the butenes are subject to microbial degradation. However, biodegradation is unlikely to contribute to the overall degradation of butene isomers in the environment because they are gaseous and the primary environmental compartment to which they will partition is the air. Additionally, data from the BIOWIN model, a biodegradation structure-activity relationship model, suggest that category members are biodegradable.

The butene isomers are not expected to sorb significantly to organic matter in soil, sediment, and wastewater solids based on a log K_{oc} range of 1.5 to 1.6.

Due to the fact that substances in the Butenes Category are gaseous at ambient temperature and pressure, and are expected to partition predominantly to the atmosphere, no aquatic toxicity testing has been conducted. The ECOSAR model was used to predict the aquatic toxicity of butene isomers using the equation for neutral organics, a reliable estimation method for this class of substances. Calculated acute toxicity values for fish and invertebrates range from 18 to 23 mg/L. For algae, the calculated 96-hr EC₅₀ ranges from 12 to 15 mg/L. Chronic toxicity values range from 1.2 to 2.8 mg/L for the three trophic levels; 30-day fish chronic values of 2.4 to 2.8 mg/L, 16-day invertebrate EC₅₀ values of 1.2 to 1.4 mg/L, and 96-hour alga chronic values of 1.6 to 1.8 mg/L. The butene isomers have a low potential to bioaccumulate in aquatic species based on a calculated log bioconcentration factor range of 1.08 to 1.15 for category member constituents.

Exposure

Fuel markets account for about 90% of butenes produced world-wide. The major fuel application is in the manufacture of gasoline blending components, such as gasoline alkylate, polymer gasoline, and dimersol. Isobutylene serves as a raw material for the oxygenates methyl tert-butyl ether (MTBE) and ethyl tert-butyl ether (ETBE). Butenes may also be blended directly into gasoline for volatility control. They are also marketed with propane and butane as liquefied petroleum gas (LPG). In chemicals applications, n-Butenes are used as a precursor for sec-butyl alcohol, butadiene, butene-1, and other smaller applications. Isobutylene is used to produce butyl rubber and polybutenes.

Estimated US production of various butene isomers totalled 49,000 Mlbs (22.2×10^3 ktonne) in 2001, of which 11,770 Mlbs (5.3×10^3 ktonne) was 1-butene, 18,990 Mlbs (8.6×10^3 ktonne) was 2-butene, and 18,250 Mlbs (8.3×10^3 ktonne) was isobutylene. Use in fuel applications, predominantly alkylation (34,000 Mlbs) and production of MTBE (12,245 Mlbs) consumed most of the butenes produced in the US. Western European production in 2001 was 2,125 kilotonnes (995 kilotonnes of isobutylene and 1,130 kilotonnes n-butenes), and Japanese production for 2000 (latest data available) was 3,190 kilotonnes (1,300 kilotonnes isobutylene and 1,890 kilotonnes n-butenes). Butenes are also produced in South America and Saudi Arabia.

Exposure to substances in the Butenes Category may occur at workplaces where they are manufactured. Based on physical properties, the primary workplace exposure would be by inhalation. Extensive consumer exposure is not foreseen because there are no direct sales to consumers; however, butenes have been reported in the vapor from gasoline refueling of passenger vehicles. Exposure to butenes in the environment can also occur from motor vehicle exhaust.

**RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION
AND NATURE OF FURTHER WORK RECOMMENDED**

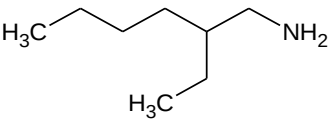
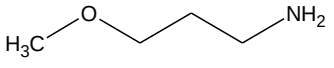
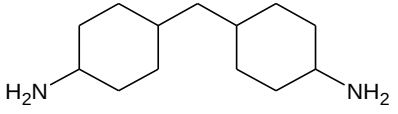
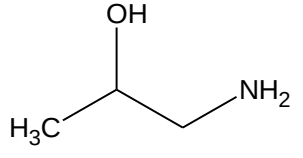
Human Health: The chemicals in this category are currently of low priority for further work. One chemical in this category may possess properties indicating a hazard for human health (carcinogenicity, although it is unknown if the findings related to isobutylene carcinogenicity are of relevance to humans). Based on data presented by the sponsor country, exposure to humans is anticipated to be low, and therefore, this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by Sponsor Countries.

Environment: The chemicals in this category are currently of low priority for further work. The chemicals in this category possess properties indicating a hazard for the environment. This does not warrant further work as it is related to acute aquatic toxicity which may become evident only at high exposure levels. It should nevertheless be noted by chemical safety professionals and other users.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	C1 -13 Primary Amines	
Category Members: CAS Registry Numbers, Chemical Names	74-89-5 Methylamine 75-04-7 Ethylamine 75-31-0 Isopropylamine 109-73-9 Butylamine 13952-84-6 sec-Butylamine 75-64-9 tert-Butylamine 111-86-4 Octylamine 104-75-6 Hexylamine, 2-ethyl 5332-73-0 Propylamine, 3-methoxy- 1761-71-3 Cyclohexylamine, 4,4'-methylenebis 78-96-6 2-Propanol, 1-amino-	
Structural Formula	Methylamine	$\text{H}_3\text{C}-\text{NH}_2$
	Ethylamine	$\text{H}_3\text{C}-\text{CH}_2-\text{NH}_2$
	Isopropylamine	$\text{H}_3\text{C}-\text{CH}(\text{NH}_2)-\text{CH}_3$
	Butylamine	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$
	sec-Butylamine	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}(\text{NH}_2)-\text{CH}_3$
	tert-Butylamine	$\text{H}_3\text{C}-\text{C}(\text{CH}_3)_2-\text{NH}_2$
	Octylamine	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$

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		Hexylamine, 2-ethyl	
		Propylamine, 3-methoxy-	
		Cyclohexylamine, 4,4'-methylenebis	
		2-Propanol, amino-	

SUMMARY CONCLUSIONS OF THE SIAR

Category rationale

The C10-C13 primary amines category is limited to the eleven sponsored substances as mentioned above. It excludes C12-C16 primary fat amines.

The C10-C13 Primary Amines category is represented by the structure with a single and primary amino-group R-NH₂, where R is an alkyl group that may be linear, branched or alicyclic; the alkyl group may include an atom or group that will not react with or substantially affect the properties of the amine function. The tendency to share the nonbonded electron pair on the nitrogen underlies the chemical behavior of amines as a group.

The C10-C13 Primary Amines category members are structurally similar showing trend in physical-chemical properties and ecotoxicity and similar toxicological properties. This category is defined as below:

- A structure that contains only aliphatic organic substituents that are linear, branched or cyclic;
- Molecular weights from approximately 30 to 250 Dalton, classifying these primary amines as low molecular weight aliphatic amines.
- Incremental structural change across the group consisting of an increasing number of atoms in the molecular backbone; moderate branching is acceptable. The change is restricted to adding elements that do not greatly change the physicochemical properties of the amino moiety, as evidenced by the consistency of pKa values within the narrow range of 9.86 to 10.87.

Observed corrosive properties overwhelm the systemic toxicity of the primary amines in most cases, including acute toxicity; the known acute oral and dermal effects are generally related to the alkaline properties and are expected to be a general feature of the category. Structure-activity similarities for mammalian toxicity and structure-activity relationships (SAR) shown for aquatic toxicity endpoints lend support to the category.

In general, members of the C10-C13 primary amines can be considered to be comparable in metabolism. However,

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there are known outliers for which own data are available to cover the endpoints (due to structural differences, methylamine, tert-butylamine may be metabolized by different pathways than the rest of the category). Read-across approach has been used for addressing the mammalian toxicity endpoints where no data were available on individual substances (as indicated in the table below).

In the case of ecotoxicity read-across approach was not used as sufficient data for the individual chemicals are available.

Substance	Skin irritation	Eye Irritation	Skin sensitization	Repeated dose toxicity	Effects on Fertility	Developmental toxicity	Genetic toxicity (Chrom. Aberration)
Methylamine	X	READ-ACROSS	READ-ACROSS	X	X	X	X
Ethylamine	X	X	READ-ACROSS	X	X	READ-ACROSS	READ-ACROSS
Isopropylamine	X	X	X	X	X	X	READ-ACROSS
Butylamine	X	X	X	X	READ-ACROSS	X	X
sec-Butylamine	X	READ-ACROSS	READ-ACROSS	READ-ACROSS	READ-ACROSS	READ-ACROSS	READ-ACROSS
tert-Butylamine	X	X	READ-ACROSS	X	X	READ-ACROSS	READ-ACROSS
Octylamine	X	X	X	X	X	X	X
Hexylamine, 2-ethyl	X	X	READ-ACROSS	READ-ACROSS	READ-ACROSS	READ-ACROSS	READ-ACROSS
Propylamine, 3-methoxy-	X	READ-ACROSS	X	X	X	X	X
Cyclohexylamine, 4,4'-methylenebis	READ-ACROSS	X	READ-ACROSS	X	X	X	X
2-Propanol, 1-amino-	X	X	X	X	X	X	X

X = data available

Using the category approach, read across has been performed from the tested members to those without available data. For those substances where data exist for developmental toxicity, the results indicate a lack of effect with the exception of butylamine, which was negative by inhalation but positive when administered as the hydrochloride salt by the oral route (gavage). Taking a precautionary approach, all those category members without developmental toxicity data are regarded as potential developmental toxicants when administered by the oral (gavage) route.

In some cases, the tested substance was the salts of amines to avoid damage to the gastrointestinal tract following gavage administration due to the caustic mode of action. Testing the salt also provides the ability to distinguish between symptoms caused by local effects such as irritation or corrosion and symptoms that are due to systemic toxicity as follows:

Substance	Repeated dose toxicity	Effects on Fertility	Developmental toxicity
Methylamine	Tested as the hydrochloride	Tested as the	Tested as the hydrochloride (CAS

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	(CAS no 593-57-1)	hydrochloride (CAS no 593-57-1)	no 593-57-1)
Octylamine	Tested as the hydrochloride (CAS no 142-95-0)	Tested as the hydrochloride (CAS no 142-95-0)	Tested as the hydrochloride (CAS no 142-95-0)
Propylamine, 3-methoxy-	Tested as the hydrochloride (CAS no 18600-41-4)	Tested as the hydrochloride (CAS no 18600-41-4)	Tested as the hydrochloride (CAS no 18600-41-4)
2-Propanol, 1-amino-	Tested as the hydrochloride (CAS no 7780-04-3)	Tested as the hydrochloride (CAS no 7780-04-3)	Tested as the hydrochloride (CAS no 7780-04-3)

Physical-chemical properties

The substances are gases (methylamine and ethylamine only) or liquids, with measured melting points that range from -104 °C (sec-butylamine) to 1 °C (2-propanol, 1-amino-). The measured boiling points range from -6.5 °C at 1013 hPa (methylamine) to 159°C (1013 hPa; 2-propanol, 1-amino-). Measured and estimated vapor pressures range from 0.63 hPa at 25 °C (2-propanol, 1-amino-) to 3140 hPa at 20 °C (methylamine). Water solubility correlates well with structure; longer chain or cyclic functionalities result in lower water solubility values. Water solubility values range from miscible (1000 g/l) for methylamine, ethylamine and 2-propanol, 1-amino- to 0.2 g/L for octylamine. Measured data on the log K_{ow} are available for all members except hexylamine, 2-ethyl and propylamine, 3-methoxy-; modeling was used to fill this endpoint. The log K_{ow} are <3 for the category members and when indicated, generally were not pH adjusted. The pKa values are similar for the primary amines with measured and estimated values between 9.87 and 10.8.

Human Health

Toxicokinetics

The C10-C13 primary amines may be absorbed through the skin up to chain length of about six carbon atoms. The charged form will hinder absorption across biological membranes, and the corrosive properties of the substances may also affect absorption. Dermal exposures to dilute solutions, aerosols and vapors might not have sufficient base capacity to overwhelm the skin's natural acidity and only a few of these molecules exist as the uncharged free base. In situations where the majority of the molecules would exist as the free base on the skin, the individual would experience a chemical burn. At the pH of the GI tract, only limited, non-ionized compound would be absorbed. Following inhalation, the C10-C13 primary amines will be removed by dissolution in the upper respiratory tract and swallowed. Vapors or particulates that get to the deep lungs will be primarily in the charged form which is expected to slow absorption somewhat and contribute to the local metabolism of these C10-C13 primary amines by alveolar and bronchiolar tissues. The major routes of metabolism of C10-C13 primary amines involve various processes including oxidation, conjugation, and other enzyme-catalyzed reactions leading to detoxification and excretion. Additionally, N-acetylation may occur, but represents only a very minor pathway in the metabolism of aliphatic amines. Methylamine, which has the amino group is attached to a methyl group rather than a methylene group, is not a substrate for monoamine oxidase. Pharmacokinetic studies have indicated that a substantial amount of methylamine is oxidized to carbon dioxide, even though some is excreted unchanged in expired air and urine. Although metabolic pathways have not been identified for tert-butylamine, it is expected, based on its structure, to have a different metabolic pathway than the other members of the category.

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Human health effects data are available for the C10-C13 primary amines. In some cases (repeated dose and reproductive toxicity), the tested substance was the salt of amines to avoid damage to the gastrointestinal tract following gavage administration due to the caustic mode of action. Testing the salt also provides the ability to distinguish between symptoms caused by local effects such as irritation or corrosion and symptoms that are due to systemic toxicity.

Acute toxicity

Acute inhalation toxicity studies are available for all members except sec-butylamine, propylamine, 3-methoxy-, and cyclohexylamine, 4,4'-methylenebis. Four hour vapor LC₅₀ values (rat) range from <1548 mg/m³ (hexylamine, 2-ethyl-) to 9,800 mg/m³ (males, ethylamine). Clinical signs and findings at gross necropsy were consistent with generally severe local effects of eye and respiratory irritation, respiratory distress and lung damage; similar effects of irritation were not seen following a 6-hour exposure to 2460 mg/m³ 2-propanol, 1-amino-. The effects observed in most cases were quite severe due to the corrosive nature of the substances tested. Dermal LD₅₀ values (rat or rabbit) are available for all members except methylamine, tert-butylamine, hexylamine, 2-ethyl- and 2-propanol, 1-amino-. Dermal LD₅₀ values (for 24-hour covered contact) ranged from around 200 mg/kg bw (sec-butyl and octylamine) to 2000 mg/kg bw (propylamine, 3-methoxy-). Severe skin necrosis at the site of application was noted in most studies. Similar results including severe skin necrosis would be expected for all substances based on structural similarities. Acute oral LD₅₀ values in rats range between 122 mg/kg bw (isopropylamine) and approximately 2813 mg/kg bw (2-propanol, 1-amino-). In the acute oral studies, most deaths occurred on day 1; clinical signs generally included salivation, breathing abnormalities, oral-nasal staining, decreased defecation, diarrhea, polyuria, piloerection, decreased activity, convulsions, ataxia, rough hair coat, urine stains and dehydration. Site of contact effects (irritation) were noted in the gastrointestinal tract at gross necropsy in some studies.

Irritation

Reliable skin irritation studies are available for all category members except cyclohexylamine, 4,4'-methylenebis. All tested category members were corrosive to skin. Based on the available acute dermal toxicity study with cyclohexylamine, 4,4'-methylenebis and data from other category members, this substance is also considered to be corrosive to the skin. Based on the available data and known eye irritation potential of alkyl amines in general, it is expected that all the amines in the category are corrosive to the eye. The C10-C13 primary amines are known irritants of the human respiratory tract; supporting animal data confirm this finding.

Sensitization

There was no evidence of positive sensitization results at the concentrations tested in animal studies for isopropylamine, butylamine, octylamine, propylamine, 3-methoxy-, or 2-propanol, 1-amino-. There were no data located for methylamine, ethylamine, sec-butylamine, tert-butylamine, hexylamine, 2-ethyl, cyclohexylamine, 4,4'-methylenebis; a similar lack of skin sensitization potential is expected for these substances.

Repeated dose toxicity

Local effects (irritation of the respiratory tract and mucous membranes) are the major effects following repeated inhalation exposure (methylamine, ethylamine, isopropylamine and tert-butylamine). This occurred in rats exposed to 96 mg/m³ of methylamine for 10 days, or to 200 mg/m³ of tert-butylamine for 13 weeks, and at higher concentrations of ethylamine and isopropylamine. Systemic effects (changes in clinical chemistry parameters) were also noted following repeated dose inhalation of tert-butylamine at 200 mg/m³. The oral NOAELs in rats were 15 mg/kg bw/d for cyclohexylamine, 4,4'-methylenebis-, 500 mg/kg bw/day as methylamine hydrochloride; CAS No. 593-51-1; 100 mg/kg bw for octylamine (as the hydrochloride, CAS No 142-95-0), 300 mg/kg bw/d for 2-propanol, 1-amino (as the hydrochloride; CAS No. 7780-04-3) and 1000 mg/kg bw/day (females) for propylamine, 3-methoxy- (as the hydrochloride; CAS No. 18600-41-4). The effects observed in these studies included reductions in body weight, body weight gain, and food consumption; and/or changes in blood, urine and clinical chemistry parameters, as well as histopathological findings in various organs with cyclohexylamine, 4,4'-methylenebis-. Similar effects following repeated exposure are expected for the remaining members (sec-butylamine, butylamine and hexylamine, 2-ethyl) are expected. For those category members for which read-across is applied, the lowest NOAEC/NOAEL level is used.

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Genetic toxicity

All of the members of the category have been tested in the Ames test and no evidence of mutagenic potential was detected with the exception of 2-propanol, 1-amino-, which was positive in one bacterial mutagenicity assay with *Salmonella* TA1535 with activation; the second bacterial mutagenicity assay was negative. Of the five compounds evaluated in a mouse lymphoma assay, all but methylamine gave negative results. Four of these five, including methylamine, have been examined in micronucleus tests in rodents and none showed any evidence of clastogenic activity. 2-Propanol, 1-amino- was negative in a mammalian gene mutation assay and an *in vitro* chromosomal aberration assay. Cyclohexylamine, 4,4'-methylenebis- was negative in two *in vivo* micronucleus assays. A third micronucleus assay (with methodological limitations) was positive; data for clastogenicity are equivocal for this substance. The weight-of-evidence suggests the category members are not mutagenic.

Carcinogenicity

No data are available for the carcinogenicity of the C10-C13 Primary Amines.

Reproductive toxicity*Effects on fertility*

Reproductive toxicity has been directly investigated following inhalation or oral (gavage) exposure on eight members of the category. Following oral (gavage) exposure, no reproductive toxicological potential was detected for octylamine, propylamine, 3-methoxy or 2-propanol, 1-amino- (each tested as the hydrochloride). Cyclohexylamine, 4,4'-methylenebis- reduced the number of implantation sites in an OECD 422 study in rats at an oral dose of 50 mg/kg bw/day that also produced other indications of parental systemic toxicity. No reproductive or systemic toxicity occurred at 15 mg/kg bw/day. Methylamine (as the hydrochloride), in an oral (gavage) OECD 422 study did produce adverse reproductive effects at 1000 mg/kg bw/day, a dose that also produced overt indications of parental toxicity. The NOAEL for systemic and reproductive toxicity was considered to be 500 mg/kg bw/day. Following inhalation exposure, no reproductive toxicological potential was detected for isopropylamine in a one generation study with rats. Reproductive toxicity has also been investigated as part of repeated dose inhalation studies. In a 24-week repeated dose inhalation toxicity study, ethylamine did not adversely effect male and female gonads up to 922 mg/m³. In a 13-week repeated dose inhalation toxicity test, tert-butylamine produced no adverse effects on the testes up to 2000 mg/m³. Substances that have not been tested for reproductive toxicity (butylamine, sec-butylamine, and hexylamine, 2-ethylhexyl) are not expected to be reproductive toxicants based on read across to other category members.

Developmental toxicity

Developmental toxicity has been investigated following inhalation and oral (gavage) exposures in rats. An inhalation study found isopropylamine not to be fetotoxic in rats at test concentrations that also produced maternal toxicity; administration of butylamine by the inhalation route was associated with significant respiratory tract (portal of entry) irritation of the dams at even the lowest tested concentration of 50 mg/m³, while fetal effects were not observed at the highest test concentration of 450 mg/m³. Rat studies involving repeated oral exposures to methylamine, octylamine, propylamine, 3-methoxy and 2-propanol, 1-amino- (each tested as the hydrochloride) or cyclohexylamine, 4,4'-methylenebis during pregnancy identified no evidence of developmental toxicity potential. Butylamine (tested as the hydrochloride, CAS 3858-78-4) produced fetal malformations in rats at an oral gavage dose of 400 mg/kg bw/day that was not overtly toxic to the dams. Rat studies involving repeated inhalation exposures to isopropylamine, or butylamine during pregnancy identified no evidence of developmental toxic potential. The reported developmental effects of butylamine (as the hydrochloride salt) are therefore expected to be route specific occurring only after oral exposure. For those substances where data exist for developmental toxicity, the results indicate a lack of effect with the exception of butylamine, which was negative by inhalation but positive when administered as the hydrochloride salt by oral (gavage). Taking a precautionary approach, ethylamine, sec-butylamine, tert-butylamine and hexylamine, 2-ethyl, are regarded as potential developmental toxicants when administered by the oral (gavage) route.

The C10-C13 Primary Amines possess properties indicating a hazard for human health (acute toxicity,

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irritating/corrosive properties). Cyclohexylamine, 4,4'-methylenebis (oral gavage) and tert-butylamine (inhalation) may exhibit additional potential hazardous properties for human health (repeated dose toxicity). Butylamine may exhibit additional potential hazardous properties for human health (developmental effects when tested as the salt by the oral route); based on read-across, ethylamine, sec-butylamine, tert-butylamine and hexylamine, 2-ethyl may also cause similar developmental effects by the oral route. Adequate screening-level data are available to characterize the hazard to human health for the purposes of the OECD HPV Chemicals Programme.

Environment

Most aliphatic amines are considered stable to hydrolysis, as the molecules do not contain any functional group sensitive to hydrolysis. Tert-butylamine was resistant to hydrolysis at pH 4, 7, or 9 at 50°C up to 125 hours (OECD TG 111). In water solution, all of the simple alkyl amines share the property of forming ammonium ions. This is due to the ability of the free electron pair on the amine nitrogen to pick up a proton from water and form a hydroxide ion raising the solution pH. Estimated pKa values of >9.5 indicate that the C10-C13 primary amines will exist primarily as cations in the environment (relevant pH 5.0 – 9.0). However, the EPIWIN modeling program predicts environmental fate endpoints for C10-C13 primary amines in their uncharged form.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of <1 day. For the C10-C13 primary amines, EPIWIN Level III fugacity modeling predicts that, when distributed equally to air, water and soil, for most of the amines, the substances will partition more towards the soil compartment relative to the water compartment; the favored distribution towards soil increases proportionally with molecular weight of the C10-C13 primary amines. Most of the C10-C13 primary amines are readily biodegradable (methylamine, ethylamine, isopropylamine, butylamine, sec-butylamine, octylamine, hexylamine, 2-ethyl, and 2-propanol, 1-amino-). Tert-butylamine, propylamine, 3-methoxy- are not readily biodegradable; however, they are inherently biodegradable. Cyclohexylamine, 4,4'-methylenebis- showed <10% biodegradation in 28 days, and is considered to be not readily biodegradable. Predicted BCF values, from BCFBAF Program v3.00 in EPIWIN v4.0, range from 3.162 to 38.06 indicating that they have low bioconcentration potential and are not expected to be bioaccumulative. The measured BCF was 2.7-3.6 for 2-propanol, 1-amino (OECD TG 305C) indicating it is not expected to be bioaccumulative.

The following acute aquatic toxicity test results using buffered/unbuffered conditions have been determined for the C10-C13 primary amines (key and supporting studies are presented; the supporting studies are used to illustrate pH effects). "Estimated" values are from the ECOSAR Program (v1.00).

Fish:

Substance	Species	LC50 (96 hr; mg/L)	Remark	Estimated values (ECOSAR 1.0) (96 hr, mg/L) ⁸
Methylamine	<i>Brachydanio rerio</i>	711	pH 8.0; nominal/measured not specified ¹	210
	<i>Leuciscus idus</i>	16	48 hr; unbuffered, nominal	
		970	48 hr; buffered, nominal	
Ethylamine	<i>Pimephales promelas</i>	227	pH not specified; nominal/measured not specified	155
Isopropylamine	<i>Oncorhynchus mykiss</i>	40	maximum pH 10.2 at 100 mg/L ² ; nominal	114
Butylamine	<i>Pimephales promelas</i>	268	Buffered pH; measured	64.5
sec-Butylamine	<i>Leuciscus idus</i>	>46 - <68	Unbuffered pH; nominal	71.5

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		>100	Buffered pH; nominal ³	
tert-Butylamine	<i>Oncorhynchus mykiss</i>	28 (soft water); 270 (hard water)	pH not specified; nominal	75.3
Octylamine	<i>Pimephales promelas</i>	5.19	pH not specified; measured	7.5
Hexylamine, 2-ethyl-	<i>Leuciscus idus</i>	> 46.4 - < 68.1	Unbuffered; nominal	8.3
		> 100 - < 500	Buffered; nominal ⁴	
Propylamine, 3-methoxy-	<i>Leuciscus idus</i>	148	Unbuffered; nominal	448
		>1000	Buffered; nominal ⁵	
Cyclohexylamine, 4,4'-methylenebis-	<i>Leuciscus idus</i>	67.8	Unbuffered; nominal	6.41
		>100	Buffered; nominal ⁶	
2-Propanol, 1-amino-	<i>Leuciscus idus</i>	>215-<464	Unbuffered; nominal	1102
		>1000	Buffered; nominal ⁷	

¹ test method: development of zebrafish eggs was observed microscopically for 96 hr beginning with the 8 cell stage.

² The pH normalised during the test period and was in the range of the control values by the end of the test.

³ no effects at 100 mg/L

⁴ no effects at 100 mg/L (buffered, nominal); 100% mortality at 500 mg/L (buffered, nominal)

⁵ no effects at 1000 mg/L (buffered; nominal)

⁶ at 100 mg/L (buffered, nominal): observed mortality: 10 % (1 of 10 fish)

⁷ no effects at 1000 mg/L (buffered; nominal)

⁸ ECOSAR Class used was Aliphatic Amines; all predicted values fall within the applicability domain

Aquatic invertebrates:

Substance	Species	EC50 (48 hr; mg/L)	Remark	Estimated values (ECOSAR 1.0) (48 hr, mg/L) ¹¹
Methylamine	<i>Daphnia magna</i>	163	Unbuffered; nominal	12.3
		702	Buffered; nominal	
Ethylamine	<i>Ceriodaphnia dubia</i>	7.9	pH 8.0-9.0; measured	10.0
Isopropylamine	<i>Daphnia magna</i>	47.4	Unbuffered; nominal ⁹	8.0
Butylamine	<i>Ceriodaphnia dubia</i>	8.2	pH 7.8; measured	5.1
sec-Butylamine	<i>Daphnia magna</i>	40	Unbuffered; nominal ¹⁰	5.5
tert-Butylamine	Daphnid	-	-	5.8
Octylamine	<i>Daphnia magna</i>	1.9	Not specified; measured	0.89
Hexylamine, 2-ethyl-	Daphnid	-	-	0.974
Propylamine, 3-methoxy-	Daphnid	-	-	27.2

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Cyclohexylamine, 4,4'-methylenebis-	<i>Daphnia magna</i>	6.84	pH not specified; nominal	0.84
2-Propanol, 1-amino-	<i>Daphnia magna</i>	109	Unbuffered; nominal	57.47

⁹ observed effects at higher test item concentrations may be due to high pH (up to 11.95)

¹⁰ observed effects at higher test item concentrations may be due to high pH (up to 10.46)

¹¹ ECOSAR Class used was Aliphatic Amines; all predicted values fall within the applicability domain

Algae:

Substance	Species	EC50 (72 hr; mg/L)	Remark	Estimated values (ECOSAR 1.0) (96 hr, mg/L) ¹²
Methylamine	<i>Pseudokirchnerella subcapitata</i>	21% ErC50 at 31 mg/L	pH not specified; duration not specified; measured	2.25
Ethylamine	<i>Green algae</i>	-	-	2.14
Isopropylamine	<i>Desmodesmus subspicatus</i>	18.9 ErC50; 4.13 yield	pH 8.0-9.7; nominal	1.97
Butylamine	<i>Green algae</i>	-	-	1.5
sec-Butylamine	<i>Desmodesmus subspicatus</i>	0.520 (EyC50); 2.03 (ErC50); 0.716 (EbC50)	pH 8.0 – 10.0; nominal	1.6
tert-Butylamine	<i>Pseudokirchnerella subcapitata</i>	16	96 hr; pH not specified; measured	1.65
Octylamine	<i>Desmodesmus subspicatus</i>	0.23 (ErC50); 0.12 (EbC50)	pH not specified; nominal	0.50
Hexylamine, 2-ethyl-	<i>Desmodesmus subspicatus</i>	10 (ErC50); 4.5 (EbC50)	pH 7.4 – 8.0; measured	0.53
Propylamine, 3-methoxy-	<i>Green algae</i>	-	-	5.36
Cyclohexylamine, 4,4'-methylenebis-	<i>Desmodesmus subspicatus</i>	141.42 - 200(ErC50 and EbC50)	pH not specified; nominal	0.54
2-Propanol, 1-amino-	<i>Desmodesmus subspicatus</i>	25.4 (EbC50); 32.7 (ErC50)	pH 8.68 – 10.24; nominal	8.74

¹² ECOSAR Class used was Aliphatic Amines; all predicted values fall within the applicability domain

Observed effects in acute toxicity tests for fish appear to be due to an increase in pH at higher test item concentrations, as demonstrated in the tests with fish, where unbuffered and buffered test solutions were tested in parallel.

The C10-C13 Primary Amines possess properties indicating a hazard for the environment (acute aquatic toxicity values < 1 and up to 100 mg/L). These C10-C13 Primary amines are readily or inherently

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biodegradable except for cyclohexylamine, 4,4'-methylenebis- which is not readily biodegradable. The C10-C13 primary amines are not bioaccumulative. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

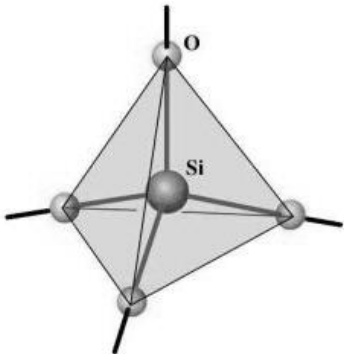
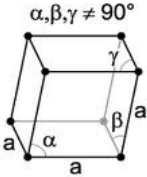
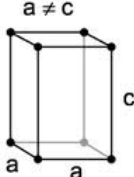
The estimated production volumes (metric tons) of the primary amines from 2007 are provided for the United States and globally. Data from 2003 are provided when 2007 data was not available:

	<u>United States; Global</u> (2007)
Methylamine	52,000; 742,900
Ethylamine	16,000; 64,800
Isopropylamine	43,000; 95,800
Butylamine	2,100; 17,300
sec-Butylamine	1000- 2,000 (2003); 2,000 - 4,000 (2003)
tert-Butylamine	0; 10,600
Octylamine	500 - 1,500 (2003); 1,000 - 3,000(2003)
Hexylamine, 2-ethyl-	500 - 1,500 (2003); 1,000 - 3,000 (2003)
Propylamine, 3-methoxy-	0 - 6,000 (2003); 3,000 - 10,000 (2003)
Cyclohexylamine, 4,4'-methylenebis	5,000 - 15,000 (2003); 15,000 - 30,000 (2003)
2-Propanol, 1-amino-	1,000 - 3,000 (2003); 3,000 - 6,000 (2003)

Primary amines can be synthesized in various ways including reaction of ammonia with alkyl halides or alcohols, reduction of nitriles or amides, or reductive amination of aldehydes. The reaction between ammonia and alcohol forms the basis for most of the present commercial processes for making primary amines. No monitoring data are available. The most likely route of human occupational exposure is either via dermal contact or inhalation; most of these materials are highly irritating or corrosive to the skin and adequate protective equipment is required if any splash hazard is present. In addition, employee health and safety training provides employees with an understanding of the potential for skin and eye damage from direct contact with these materials. There are no known direct consumer exposures with the exception of home-use herbicides containing glyphosate isopropylamine salt. This exposure would be primarily dermal as the salt form is non-volatile. In production, these materials are handled in closed systems. Transfer of these materials is in closed pipe systems rather than in open systems to minimize loss. There may be low level losses in process waters, which are discharged to a waste water treatment system. Limited potential exists for release of material to a publicly-owned treatment works (POTW) or a body of water after primary biological treatment on site. All of these materials are stored in closed tanks or pressurized cylinders and transported in tank cars and tank trucks, and smaller amounts are transported in drums, pressurized cylinders or Intermediate Bulk Containers (IBCs). The possibility of a release to air varies from material to material as a function of vapor pressure, ranging from certain for anhydrous methylamine to minimal for the higher molecular weight amines.

Intentional environmental release occurs for the glyphosate salt of isopropylamine that is used as an herbicide. During the approximate period 1972 to 1987, sec-butylamine was registered as a fungicide and was thus permitted to be released in the environment.

INITIAL TARGETED ASSESSMENT PROFILE (Human Health)

CAS No.	Quartz: CAS RN 14808-60-7 Cristobalite: CAS RN 14464-46-1	
Chemical Name	Quartz and Cristobalite	
Structural Formula	Molecular Formula: SiO ₂ 	
	Unit Cell: Trigonal symmetry $\alpha, \beta, \gamma \neq 90^\circ$  Quartz: CAS RN 14808-60-7	Unit Cell: Tetragonal symmetry $a \neq c$  Cristobalite: CAS RN 14464-46-1
SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT NOTE: The present assessment is targeted to address the following human health endpoints: repeated dose toxicity and carcinogenicity via the inhalation route of exposure, and genotoxicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment included in the Canadian screening assessment but have not been presented to OECD member countries, and thus are not included in this profile. The final screening assessment will be published under the responsibility of the Government of Canada. Rationale for Targeting the Assessment The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its <i>Canadian Environmental Protection Act, 1999</i> (CEPA 1999). Additional details may be found at http://www.chemicalsubstanceschimiques.gc.ca/about-apropos/categor/index-eng.php. Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: inherently toxic to humans or to the environment and that might be persistent and/or bioaccumulative; and substances to which people might have greatest potential for exposure. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000		

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chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release. Quartz and cristobalite were identified at that time, applying the categorization criteria, as high priorities for human health risk because they were considered to pose greatest potential for exposure and their respirable forms are classified by the International Agency for Research on Cancer as carcinogenic to humans (quartz and cristobalite) and by the National Toxicology Program as known human carcinogens (crystalline silica). These substances did not meet the ecological categorization criteria for bioaccumulation potential or inherent toxicity to aquatic organisms.

Under the Canadian legislation a determination of whether one or more of the criteria of the CANADIAN ENVIRONMENTAL PROTECTION ACT (CEPA) 1999, section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) Challenge is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of the regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use.

Physical-chemical properties

The silicon dioxide group represents a polymorphic category containing a large number of forms identical in composition but with different atomic arrangements which afford different chemical properties. There are two sub-categories within this group: crystalline silica, to which the present substances quartz and cristobalite belong, and non-crystalline or amorphous silica. The key distinction between these sub-categories is that in crystalline substances, the building blocks are arranged in regular, repeating 3-dimensional pattern having long range order, whereas amorphous materials do not display long range order. In all forms of silica, (crystalline and non-crystalline), the silicon atom is tetrahedral and bound to four neighbouring oxygen atoms.

Quartz and cristobalite are solid at room temperature, existing normally as colourless or white crystals. The melting points for quartz and cristobalite are 1400-2000 °C and 1713-1728 °C, respectively and for both compounds, the boiling point is 2230 °C. Even though no experimental data were available, their vapour pressure and Henry's Law constant are likely negligible. Log K_{ow} (octanol-water partition coefficient) and log K_{oc} (organic carbon-water partition coefficient) are not applicable to these substances. The densities range from 2500-2700 kg/m³ for quartz and 2300-2380 kg/m³ for cristobalite.

The very similar physico-chemical properties of quartz and cristobalite reflect their closely related crystal forms. The solubility of crystalline silicates decreases as a function of silica tetrahedral packing density and long-range crystal order. For example, cristobalite has a more open framework structure than quartz and its density is lower, therefore, its solubility is higher. The water solubility of these minerals is also function of temperature, pH, particle size, and the presence of a disrupted surface layer. This may explain the variability of solubility values reported by many authors. The most probable solubility value for quartz is approximately 3.8 mg Si/L, or 6.4 mg/L expressed as the SiO₂ species, while the solubility of cristobalite is approximately 8.7 mg Si/L, or 18 mg SiO₂/L. The kinetics of dissolution of these substances is slow due to the high activation energy required to hydrolyse the Si-O-Si bond.

Human Health Targeted Endpoints

The majority of the studies described here have been reviewed by the International Agency for Research on Cancer (IARC 1997). However, additional data relevant to the screening assessment were identified up to August 2010.

Repeated dose toxicity/non-neoplastic effects (development of silicosis).

Studies on animals

Significant short-term and subchronic studies have demonstrated adverse effects in the lungs, while one of the 6 studies showed effects on the spleen in mice. Rats were exposed to 0, 10 or 100 mg/m³ of cristobalite via inhalation for 6 hours/day during 3 days. Animals were observed 3 months after exposure. Elevated levels of granulocytes and elevated markers of cytotoxicity from the lung lavage fluid were noted in all exposed groups. Another study of similar duration (9 days) conducted in mice also identified a LOAEC of 10 mg/m³. Effects observed included minimal interstitial thickening, accumulations of mononuclear cells and slight lymphoid tissue hypertrophy in the lungs.

In a 4-week inhalation study, female rats were exposed to 0, 0.1, 1 or 10 mg/m³ of quartz 6 hours/day, 5 days/week. Bronchoalveolar lavage fluid was evaluated at 1, 8, and 24 weeks after exposure. Elevated levels of

granulocytes and significant elevation of markers of cytotoxicity (Lactate dehydrogenase [LDH] and β -glucuronidase [β -glu]) were observed at 1 mg/m^3 and higher. The increased levels of LDH and β -glu were only significant at 24 weeks after exposure. A LOAEC of 1 mg/m^3 was identified at 24 weeks.

Male rats (4 animals per dose) were exposed to 0 or 3 mg/m^3 of cristobalite via inhalation for 6 hours/day, 5 days/week during 13 weeks. Pulmonary inflammation and fibrosis were observed in the exposed group at the end of treatment. When mice were similarly exposed to 5 mg/m^3 of quartz for 6 hours/day, 5 days/week for 15 or 27 weeks, the authors observed increased spleen weight and formation of plaque in the spleen.

In two separate studies, in which rats or hamsters were exposed to quartz via inhalation for at least 6 months, LOAECs of 2 and 3 mg/m^3 were identified, respectively. All the effects observed were related to inflammation and fibrosis of the lung tissue.

Several chronic studies investigated exposure of the respirable forms (i.e. accumulated via inhalation in the lung tissues) of quartz and cristobalite to rats, mice and hamsters. The following is a description of the study in which the lowest non-neoplastic LOAEC was determined. Groups of 50 rats/sex were exposed 6 hr/day, 5 days/week for 24 months to filtered air or 1 mg/m^3 of DQ-12 quartz, containing 74% of respirable quartz, through whole-body inhalation. An additional 50 rats/sex were exposed to 5 mg/m^3 of titanium dioxide as positive controls. The mean mass of particle at the end of the exposure period was 0.91 mg/lung . The LOAEC identified was 0.74 mg/m^3 (adjusted for 74% respirable quartz) based on lipoproteinosis, multifocal, inflammatory cell infiltrate and alveolar hyperplasia.

Human epidemiology data

In humans, the lowest observed adverse effect level was identified in a U.S. cohort study. The study was conducted on 3330 gold miners (all are males), who had an average of 9 years underground exposure during the period 1940 to 1965. The cohort was followed up through 1990. Silicosis¹ was identified through death certificates or chest X-rays. A job-exposure matrix together with work history was used to estimate individual exposure. The total silica content in the respirable dust in the mine was estimated at 13% and the median crystalline silica exposure was 0.05 mg/m^3 . In this sub population of miners, 170 cases of silicosis were identified. The best predictor for risk of silicosis was cumulative exposure, which varied from less than 1% for a 0.5 mg/m^3 -year exposure to 68-84% when exposed to more than 4 mg/m^3 -year (based on the average daily dust exposure during the workday each year and summed over time for each miner). The main limitations identified by the authors include the limited number of radiographic surveys, the potential bias from death certificates

¹ Silicosis: Lung disease caused by inhalation of crystalline silica dust, and resulting in inflammation and scarring in forms of nodular lesions in the upper lobes of the lungs. By definition, clinically or pathologically diagnosed silicosis implies prior exposure to silica (Silicotics). It does not follow that a history of exposure to silica necessarily results in silicosis (Nonsilicotics). The typical "Silicotic" lung nodule is shown in Figure 1.

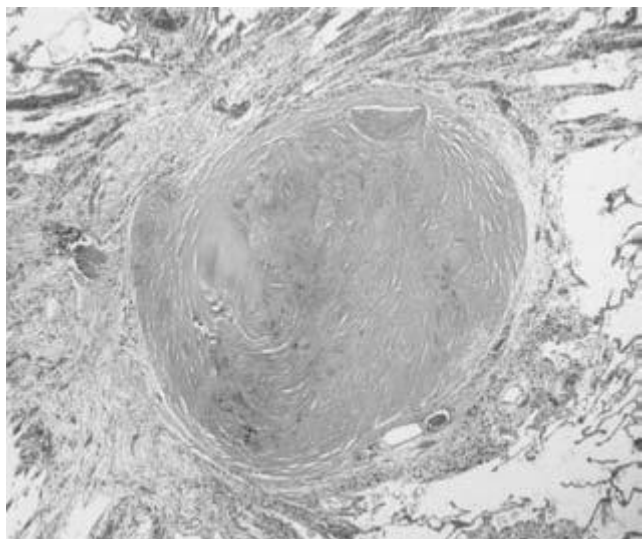


Figure 1. Silicotic nodule characterised by a central zone of hyalinised collagen with a whorled appearance and peripheral dust-containing macrophages (Rees and Murray, 2007).

(relying on death certificates instead of relying on repeated x-rays, which were lacking for each miner, may have underestimated the number of cases) and the fact that the conversion of dust counts to

gravimetric measurements may not be accurate based on the estimation of 13% silica content in the respirable dust (although based on a relatively large number of samples ($n = 82$) collected in two different surveys, there was broad range of content in these samples (1% to 48%, $SD = 9$), and the percentage of respirable quartz may have differed in earlier years, but data were lacking for these years).

Two other human studies have identified similar LOAECs based on the critical endpoint of radiographic confirmed silicosis. A LOAEC of 0.053 mg/m^3 (mean exposure) was identified in a cross sectional study of South African gold miners and a LOAEC of 0.064 mg/m^3 (mean exposure) was derived in a mining community population-based random sample survey in Colorado.

Carcinogenicity studies

Studies on animals

Experimental studies conducted in rats have shown clear and consistent increases in lung tumours after chronic inhalation exposure. In the nine rat studies identified, five were inhalation studies and four were intratracheal instillation studies. All studies except one inhalation study showed increased incidence of lung tumours. For the inhalation studies with treatment related tumours, concentrations ranged from 1 to 50 mg/m^3 (1, 6, and 30 mg/m^3 of DQ-12 quartz; 12 and 50 mg/m^3 of Min-U-Sil 5 quartz) and duration of exposure ranged from 29 days to 2 years. In the inhalation study with no treatment-related tumours, exposure was 60 mg/m^3 of Sikron F300 quartz for 13 weeks. The following is a description of the neoplastic results in the study also identified as the critical study for non-neoplastic results. Groups of 50 rats/sex were exposed 6 hr/day, 5 days/week for 24 months to filtered air or 1 mg/m^3 of DQ-12 quartz through whole-body inhalation. An additional 50 rats/sex were exposed to 5 mg/m^3 of titanium dioxide as positive controls. In the exposed group, 18 animals developed tumours (12 in females, 5 in males), as opposed to 3 and 2 for the control and positive control groups respectively. The majority (10/18) of the tumours observed were adenocarcinomas. The mean mass of particles in the lungs at the end of the exposure period was 0.91 mg/lung .

For the intratracheal instillation studies, doses ranged from 4 to 57 mg/kg-bw (based on 7, 12 or 20 mg/animal of Min-U-Sil (5) quartz or 20 mg/animal of novaculite quartz). Exposure regimes were diverse and included single instillation with observation for up to two years, to weekly instillation for 10 weeks. It is noteworthy that the single intratracheal administration of a 95% pure quartz particles ($<5 \mu\text{m}$) resulted in an increased incidence of silicotic granulomas after 3 weeks and lung tumours after 11 months. The most common tumours reported across the long term rat studies were adenocarcinomas, however other tumours such as squamous-cell carcinoma, alveolar carcinoma and bronchiole-alveolar adenoma were also reported, and all animals that developed tumours also showed some degree of fibrosis.

Of particular interest is the intratracheal instillation study, investigating the sequence of pathological events leading to lung tumors. An unspecified number of rats/sex/dose received a single intratracheal instillation of various crystalline silica dusts or ferric oxide, allowing direct administration into the bronchial tree. The doses were 12 or 20 mg of Min-U-Sil 5 quartz (MQZ), 12 mg of hydrofluoric-acid-etched Min-U-Sil 5 quartz (HFMQZ), 12 mg of cristobalite, 12 mg of tridymite and 12 mg of ferric oxide suspended in saline. All groups were observed until six months post exposure, except for both MQZ groups, the HFMQZ and the ferric oxide group which were observed up until 17 months post-exposure. Interim sacrifices were conducted at 6, 11 and 17 months. The rat lungs showed a clear progression of effects. The sequence of pathological events were, an initial inflammatory response leading to a marked hyperplasia and hypertrophy of alveolar cells after one month, and at six months hyperplasia was evident but no lung tumours were observed. In this study, lung tumours were observed starting at the 11 month sacrifice with a 17% and 42% incidence in males and females (based on 3/18 males and 8/19 females), respectively, and at 17 months incidences were 32% and 59% (based on 6/19 males and 10/17 females, respectively). No lung tumours were found in ferric oxide treated rats. Similar studies have also been conducted in hamsters and mice. Although treated mice and hamsters showed treatment related signs (inflammation or fibrosis), no tumours were observed in hamsters. No increase in the incidence of lung tumours was seen in mice treated with quartz; however silicotic granulomas and lymphoid cuffing around airways but no fibrosis were seen in the lungs of quartz-treated mice.

Human epidemiology data

There is an extensive dataset of human studies investigating the link between crystalline silica exposure and cancer. IARC (1997) identified over 50 epidemiological studies based on occupational exposure to dust containing respirable crystalline silica. Main industry sectors from which the human data is derived include gold mines, foundries, granite/stone industry, pottery workers and refractory brick workers. From the least confounded studies, it was noted that lung cancer tended to increase with the following parameters: cumulative

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exposure; duration of exposure; peak intensity of exposure; presence of radiographically defined silicosis; and length of follow-up time from date of silicosis diagnostic. By definition, clinically or pathologically diagnosed silicosis implies prior exposure to silica (Silicotics).

Since the 1997 IARC report, a large number of epidemiological studies have been published, with the more recent studies being updates from supplementary follow-up of results from previously assessed case-control studies cohorts, new results based on refined exposure assessments or adjustment for confounders or meta-analyses of the pooled data from these epidemiology studies

In a meta-analysis of the data from 10 cohort studies of gold, tin and tungsten miners, granite workers, industrial sand, diatomaceous earth and pottery workers with quantitative exposure estimates for crystalline silica were pooled in order to analyse the risk related to lung cancer. The pooled cohort standardized mortality ratio (SMR, against national rates) [See Appendix 1 for definition] was 1.2 (Confidence Interval [CI] 1.1-1.3). The results from the case-control analyses show a statistically significant trend with duration of exposure (odds ratios (ORs) [See Appendix 1] by quintile of cumulative exposure increased from 1.0 to 1.6 [CIs of 0.85 to 2.1] and by quintile of average concentration increased from 1.0 to 1.7 [CIs of 1.1 to 2.3]), supporting the importance of the increasing lung burden of silica in the occurrence of cancer. Overall, the authors concluded that the results support the carcinogenicity conclusion presented by IARC (1997).

To investigate the link between crystalline silica, silicosis and lung cancer, epidemiological data published between 1966 and 2001 were gathered. Over 50 studies were selected and pooled according to type of study and the parameter being linked to lung cancer (i.e. silica exposure, presence of silicosis in subjects). The quality of study, adjustment for confounding factors, co-exposure to other carcinogens and availability of a more recent analysis of a same cohort were taken into consideration in the final selection of the studies. Analysis of the relationship between exposure to silica and lung cancer included 17 cohort and 13 case-control studies. For the analysis of lung cancer versus silicosis, 11 cohort and 5 case-control studies were selected. The third analysis included 6 cohort and 2 case-control studies to evaluate the risk of lung cancer in non-silicotics. A random effect model was used to conduct each meta-analysis. Pooled cancer risk ratios (RRs) were 1.32 (CI 1.23-1.41) for crystalline silica exposure, 2.37 (CI 1.98-2.84) for individuals exposed to silica with confirmed silicosis (Silicotics) and 0.96 (CI 0.81-1.15) for individuals with no evidence of silicosis (non-silicotics) with confirmed exposure to silica, supporting the general observation that silicosis has a stronger temporal relationship with crystalline silica exposure and furthermore support the view that a human silicotic response could be a preliminary stage in the development of cancer.

A more recent meta-analysis included 28 cohort, 15 case-control and two proportionate mortality ratio (PMR) [See Appendix 1] studies from a variety of occupational settings conducted between 1996 and 2005. Risk ratios (RRs) were calculated based on type of study and silicosis status using fixed and random effect models (results presented here are from the random model). RRs for all cohort studies was 1.34 (CI 1.25-1.45), and were 1.69 (CI 1.32-2.16) for silicotics, 1.25 (CI 1.18-1.33) for those with undefined silicosis status and 1.19 (CI 0.87-1.57) for non-silicotics. In the case-control studies, the general RR was 1.41 (CI 1.18-1.67), and the same sub-groups as mentioned above resulted in RRs of 3.27 (CI 1.32-8.2), 1.41 (CI 1.18-1.70) and 0.97 (CI 0.68-1.38), respectively. The proportionate mortality ratio for the last two studies was 1.24 (CI 1.05-1.47). The authors noted that the association between lung cancer and exposure to crystalline silica was more consistent for silicotics, i.e., those diagnosed with silicosis and RR values split into type of occupational settings in which participants worked.

Based upon the above three meta-analysis studies and the epidemiology studies discussed in IARC (1997), the following can be concluded. Lung cancer rates are higher in workers confirmed to have silicosis versus similarly exposed workers that do not have silicosis. Cancer risk is often more significant in workers exposed to crystalline silica over a 20 year period or to higher cumulative exposure levels; however a consistent finding is that the onset of silicosis, requires a smaller lag period than that for the appearance of tumours. Similarly, cancer risk is often more significantly associated at higher quintiles of exposure compared to the lower quintiles.

There have been reports of tumours outside of the lungs in persons with high silica exposure; however, these reports are sparse and the data inconsistent and have not been unequivocally linked to exposure to either one of the crystalline forms (quartz or cristobalite). Some of the reported locations are: oesophagus, stomach, liver, skin and bone. Sufficient epidemiological or toxicological data do not currently exist for quantitative assessment of the exposure-response relationship on these other tissues or organs.

Genotoxicity

Potential genotoxicity has been assessed in multiple *in vitro* and *in vivo* assays. Table 1 below gives a brief summary of the positive results observed in each type of assay.

Table 1. Summary of positive results over total number of results for each assay and each category (all studies

conducted with crystalline silica: quartz, except where indicated).

Assay	Animal data		Human data		Positives/Total	
	In vitro	In vivo	In vitro	In vivo ^d	In vitro	In vivo
Rec Assay	0/1				0/1	
DNA strand break	1/1	2/2	5/5 ^b	1/1	6/6	3/3
Sister chromatid exchange	0/1		0/1 ^c	1/1	0/2	1/1
Micronucleus	2/3	0/1	2/2 ^b	1/1	4/5	1/2
Chromosome aberration	0/1			1/1	0/1	1/1
Aneuploidy/polyploidy	0/3				0/3	
Cell transformation	4/4				4/4	
Hprt mutation	1/2	2/2 ^a	1/1 ^b		2/3	2/2
Oxidative DNA damage		4/5	2/2		2/2	4/5
DNA binding		1/1				1/1
p53 activation		0/1				0/1

a. one assay conducted with crystalline silica: cristobalite

b. one assay conducted with "ultrafine crystalline silicon dioxide".

c. crystalline silica: tridymite

d. crystalline silica dust (subtypes not provided).

All the *in vivo* human genotoxicity studies are based on three independent studies that used blood samples from workers from diverse occupational settings with confirmed exposures to crystalline silica dust; however, quantification of exposure was not provided. After stratification by smoking status, sister chromatid exchange remained statistically significant in both smokers and non-smokers although the frequency was higher in smokers. For the chromosome aberration assay conducted as part of the same study (blood samples from workers in the stone crusher industry), the increased frequency was no longer significant after stratification. In the DNA damage study of foundry and pottery workers and the micronucleus assay of workers involved in sandblasting and related jobs, results were positive when compared to controls. However, in both studies, smoking status influenced the results, contributing to the increased DNA damage observed since results were greater in smokers versus non-smokers, and the frequency of micronuclei in nasal epithelial cells was higher in smokers ($p=0.002$) but when using peripheral blood lymphocytes did not differ statistically between smokers and non-smokers who were similarly exposed to silica dust,

The role of *in situ* generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) has been well established in the following types of DNA damage: small scale insertions, DNA base pair deletion, base modification, chromosomal change/loss, microsatellite instability, DNA strand break, 8-hydroxydeoxyguanosine (8-OHdG) mutation and point mutations. ROS and RNS generation is postulated to be (a part of) the DNA damage mechanism for crystalline silica. Studies are described below to support this hypothesis.

DNA was exposed *in vitro* to various crystalline silica dusts, to H₂O₂, or to both. Results show that DNA damage was limited when dust or H₂O₂ were administered alone but increased with the co-exposure. When the reactive oxygen scavenger, dimethylsulfoxide, was added to the test system, DNA strand break was inhibited, data supporting the viewpoint that it is the presence of radicals generated in response to quartz and cristobalite that causes the DNA damage and not quartz or cristobalite themselves.

Hprt mutation assays in rat alveolar epithelial cells, both *in vitro* and *in vivo*, were positive in response to quartz. The positive results *in vivo* were seen only in the presence of significant inflammatory responses in the treated animals. Also, in a parallel *in vitro* experiment, rat alveolar epithelial cells were incubated with the bronchoalveolar lavage fluid from the rats exposed to quartz. Both macrophage and neutrophil enriched lavage cells induced mutation in the exposed alveolar epithelial cells. Addition of catalase (an enzyme which inactivates H₂O₂) before incubation inhibited the increase in *hprt* mutation.

Rats were exposed to either crystalline or amorphous silica in a manner to induce the same level of

inflammation in the lungs. The inflammatory response was assessed by measuring the proportion of neutrophils in the bronchiolar lavage fluid. The actual concentrations were 3 and 50 mg/m³ for crystalline and amorphous silica respectively. The animals were exposed for 13 weeks. *Hprt* mutation frequency was measured in the alveolar epithelial cells at the end of the exposure period. Mutation frequency was greatly increased only in the crystalline silica treated rats; no treatment related increase was found in the rats treated with the amorphous form.

In an 8-OHdG assay conducted to monitor DNA damage by reactive oxygen species, female rats were exposed to 0, 0.3, 1.5 and 7.5 mg/animal of quartz via intratracheal instillation. Effects were observed 90 days post-exposure. A clear dose-response relationship was identified between quartz exposure and various inflammation markers (differential cell count, protein, lung surfactant lipids and tumour necrosis factor alpha). Inflammation was present starting at the lowest dose. However, 8-OHdG showed a statistically significant increase starting at 1.5 mg/animal only. Similarly, in another study, 8-OHdG and DNA strand breaks were observed at concentrations of or above 10 ug/m³ in rat lung epithelial cells.

In the aim of investigating the role of ROS in lung carcinogenesis, rat lung epithelial cells were incubated with polymorphonuclear (PMN) leukocytes (involved in the inflammatory process and responsible for the release of certain ROS) or hydrogen peroxide. Statistically significant increases in 8-OHdG were observed in the presence of PMN or hydrogen peroxide in a dose-response manner.

In a series of experiments which used *in vitro* stimulation of macrophages with crystalline silica and *in vivo* intranasal instillation of crystalline silica in mice, it was demonstrated that the chronic fibrosis seen in a murine model of silicosis *in vivo* is dependent on the presence of adaptor molecule ASC and Nalp3 inflammasome. These data support a potential mode of action whereby silica triggers cellular responses that in turn activate alveolar macrophages, resulting in an inflammatory response and silicosis. In mice deficient in Nalp3 inflammasome, the development of inflammation and collagen deposition was significantly reduced compared with normal mice 3 months after the initial intranasal instillation of silica.

Analysis of Lung Tumour Data

The weight of evidence for both rats and humans indicates that fibrotic and silicotic lesions in the lung result from inhalation exposure to crystalline silica and that lung cancer is secondary to those lesions in the lung. Although the mechanism of induction for the lung tumours has not been fully elucidated, there is sufficient supportive mode of action evidence from the data presented to demonstrate that a threshold approach to risk assessment is appropriate based on an understanding of the key events in the pathogenesis of crystalline silica induced lung tumours. The body of evidence include the following:

- In experimental studies, all rats that developed tumours also showed fibrosis.
- Adenocarcinomas, the most common type of tumour identified in rats, are commonly associated with fibrosis and deeply scarred lung tissue.
- Experimental rat studies showed a clear progression of the effects from initially mild inflammation, followed by fibrosis over-time, leading eventually to lung tumours.
- Tumours are not present in all treated species dosed in the same way.
- The tumours, both in rats and humans, are concentrated in the lungs only, although other organs are indirectly exposed.
- In human studies, cancer risk is often more significant in workers exposed over a 20 year period or to higher cumulative exposure levels; however a consistent finding is that the onset of silicosis, requires a smaller lag period than that for the appearance of tumours.
- Similarly, cancer risk is often more significantly associated at higher quintiles of exposure compared to the lower quintiles
- Lung cancer rates are higher in workers confirmed to have silicosis versus similarly exposed workers that do not have silicosis.
- For genotoxicity, *in vitro* results were mostly mixed and *in vivo* results were mostly positive. However, the vast majority of the positive genotoxicity assay results can be explained by the generation of reactive oxygen species, as demonstrated experimentally, where ROS scavenging prevents the genotoxicity.
- *In vivo*, macrophage deficient mice (macrophages produce ROS in response to crystalline silica) do not develop silicosis nor do they develop tumours and the Nalp3 inflammasome, a key player in the macrophage initiated inflammatory response, is required for the development of pulmonary fibrosis after

inhalation of silica.

- Though inhalation exposure to crystalline silica in multiple occupational settings is clear, the increase in risk, based on the several recent meta-analyses of the multiple human epidemiological studies, remains low.

It is worth noting that where aggressive engineering controls have been made to reduce silica dust levels in the workplace (Sweden), silicosis has been eliminated. By corollary, existing exposures outside of the workplace in such areas do not pose a risk for silicosis to the general population.

The respirable forms of quartz and cristobalite possess properties indicating a hazard for human health (repeated dose toxicity, carcinogenicity and genotoxicity). The mode of action in the lungs involves irritation, inflammation and reactive species formation, leading to silicosis, and eventually to tumour formation.

Exposure

Uses

Consistent with oxygen and silicon being the two most abundant elements in the Earth's crust, silicon-oxide minerals, including quartz are ubiquitous in the natural environment. In particular, as a component of sand, quartz may find use in a diverse array of applications. Several high volume uses include, but are not limited to, the use of sand as a filling material for the construction of roads and in general building activities, the use of sand and gravel aggregates as abrasives on roads in winter and the use of fly-ash, which may contain 4-14% quartz and 0.5-1% cristobalite, as a cement additive. These abrasives when used on winter roads are usually mixed with road salts and may be sand only, stone dust, sand and gravel aggregates, or pre-treated sand. They are used mainly by rural municipalities or in areas where cold temperatures diminish the efficiency of salts for de-icing. Quantities of abrasives used in Canada were 5.73×10^9 kg, 4.59×10^9 kg, and 4.93×10^9 kg for 2007, 2008 and 2009, respectively.

Industrial sand, high purity silica sand products with closely controlled sizing are expected to contain quartz and cristobalite, include lump silica (2-3mm up to 15 cm or more), silica sand (75 μ m to 2-3mm) and silica flour (less than 75 μ m). Lump silica may be used in the production of silicon alloys, silica bricks, and the linings of certain types of pulverizers (eg. ball mills and tube mills).

Silica sand may be used in the manufacture of glass and glass fibres, silicate chemicals and silicon carbide, the hydraulic fracturing of wells, foundry moulding, and for sandblasting. Silica flour may find use in the ceramics and cement industries, as a filler and extender in rubber and coatings, and as an abrasive in soaps.

Natural clays, such as bentonite and fuller's earth, are used in cat litters for their high water absorbance capacities. Quartz is a natural component of these clays, and consequently, it may be present in cat litter products. High purity α -quartz is a piezoelectric material, which means that application of a voltage induces a distortion in the crystal shape and vice versa. This ability to interconvert electrical and mechanical energy has led to the use of quartz crystals in electronic devices requiring precise timing control, for example telephones, radios, watches and computers.

According to a survey conducted in Canada, quartz and cristobalite are also used in abrasives, adsorbents, filter products (diatomaceous earth), grout and cement. These substances reportedly also find use as fillers, which add bulk and improve wear resistance, in paints and coatings, adhesives, sealants, polymer films, caulking, epoxy resins and silicones. Also, quartz is listed as an ingredient in 60 cosmetic products in Canada. The types of products include anti-wrinkle preparation, eye and face makeup, lipstick, hair dyes, shampoos and grooming products, as well as skin cleansers, moisturizers and tanning preparations.

Natural Sources

In Canada, quartz naturally occurs in many types of rock formations. Those with high silicon dioxide content (95% SiO₂ or more) include vein and massive intrusion bodies, quartz pebbles, silica sand, sandstone and quartzite. Sandstone is a sedimentary rock mostly composed of quartz grains cemented by a bonding material such as clay, calcite or iron oxide. Quartzite is a hard, compact, metamorphosed sandstone made of grains of quartz firmly bonded with a siliceous cement. Mineral aggregates (e.g., sand and gravel) have variable silicon dioxide content. Quartz is also found as crystals, aggregates or discrete particles in certain igneous rocks (e.g., granites and pegmatites), soils, sediments, air and surface water. This omnipresence is consistent with the fact that silicon is the second most abundant chemical element on Earth.

Cristobalite is naturally produced in the ashes of volcanic eruptions, and by combustion metamorphism which is a local phenomenon of spontaneous combustion of naturally occurring substances such as bituminous rocks, coal or oil. It may be found in cavities in volcanic rocks and in thermally metamorphosed sandstones and may also be a transient stage in the diagenesis of diatomaceous shale with the result that soils made of these geologic formations may be rich in cristobalite. Unlike quartz, the natural occurrence of cristobalite is limited to specific geographic regions and mineral types.

Anthropogenic Sources

Natural quartz is isolated from ore via beneficiation, which involves milling or grinding the material into particles that are separated into desired mineral and waste. The materials obtained are either used directly or further purified. In Canada, in 2006, 2.146×10^9 kg of pure quartz were mined, and 2.385×10^{11} kg of sand and gravel aggregates were produced. The proportion of quartz in silica sand deposits and gravel aggregates will vary from one site to another.

Cristobalite can form from silica melts during the preparation of silica glass; quartz is not obtained from melts but is manufactured at elevated temperature and pressure via a hydrothermal process. Cristobalite also forms during the calcination² of diatomaceous earth.

Human Exposure Estimate

Ambient air

The exposure assessment is focussed on respirable quartz and cristobalite, which in ambient air comprises a component of total particulate matter (PM). In Canada, data on the concentrations of silicon in PM was available and used as a surrogate for quartz and cristobalite. This approach is conservative because the measured silicon includes all silicon-containing substances and therefore represents the upper limit for quartz and cristobalite in ambient air.

The National Air Pollution Surveillance (NAPS) Program measured concentrations in $\mu\text{g}/\text{m}^3$ of silicon in PM with aerodynamic radii less than $2.5 \mu\text{m}$ ($\text{PM}_{2.5}$ (dichot)), and from 2.5 to $10 \mu\text{m}$ (PM_{10} (dichot)) (the total particulate matter with aerodynamic radii less than $10 \mu\text{m}$ (PM_{10}) is obtained by adding these values) in Canada. In 2009, as part of the NAPS Program, silicon concentrations were determined on over 1600 samples of $\text{PM}_{2.5}$ (dichot) and over 1500 samples of PM_{10} (dichot) at 24 urban locations across Canada. An estimate of exposure to quartz and cristobalite can be obtained by assuming that all the silicon in the PM is represented stoichiometrically as SiO_2 , and multiplying the reported concentration of silicon by 2.14 to obtain a value for silica.

The intake of respirable quartz and cristobalite by the general population of Canada is estimated using a range covering the lowest 50th percentile SiO_2 concentration in PM_{10} , measured in Pt. Petre, ON, ($0.12 \mu\text{g}/\text{m}^3$) to the highest 50th percentile concentration in PM_{10} measured in Calgary, AB ($2.1 \mu\text{g}/\text{m}^3$). The 50th percentile SiO_2 concentrations ranged from 0.1 to $2.1 \mu\text{g}/\text{m}^3$ across the survey sites; the top of this range is quite close to the average of the maximum values for the 24 sites ($3.7 \mu\text{g}/\text{m}^3$). The outdoor data were used to represent the indoor levels, because information on indoor silicon concentrations was not available, and the range of PM_{10} measured indoors is generally lower than the outdoor range. Thus, this approach conservatively overestimates indoor exposure in homes.

The highest exposure group based on these calculations is children ages 0.5 to 4 years with an estimated daily intake ranging from 0.07 to $5.26 \mu\text{g}/\text{kg-bw}$ per day; the estimated daily intake decreases with age due to changes in the ratio of inhalation rates to body weights; the daily intake of adults, 20-59 years old, is estimated to range from 0.03 to $2.00 \mu\text{g}/\text{kg-bw}$ per day.

Consumer Products

Exposure to respirable quartz from the use of cosmetic products, which contained quartz as an ingredient, was considered low because they are not formulated for spray application, the loose powders were reported to contain less than 0.1% quartz, and in these products the substance is not expected to be associated with other components of the formulation and not available in a free form.

For consumer Do It Yourself (DIY) activities around the home, the highest mean breathing zone concentration of particles from sanding dry wall (median cut-point of $10 \mu\text{m}$) of $6.31 \text{ mg}/\text{m}^3$, was used to derive an upper-

² Calcinations: Heat treating a substance, but without fusion, to bring about change in its physical or chemical constitution.

bound exposure estimate ranging from 2 to 10 µg/kg-bw per event.

Quartz is used to formulate a large number of paints and coatings. To estimate potential inhalation exposure to quartz from these products, the spray painting of wall paints with an airless spray gun was considered appropriate as a conservative scenario. Exposure to respirable paint particles was estimated using data from controlled a laboratory study in which walls of poorly ventilated test rooms were painted by professional painters using an airless sprayer to apply interior latex paint. The maximum concentration of 13% quartz in paint in Canada was used to estimate exposure. The upper-bound estimate of exposure to quartz, based on the maximum concentration of 13% quartz in paint in the Canadian market and the maximum concentration of respirable paint particles measured in these controlled studies when recommended personal protective equipment is used, is 0.954 µg/kg-bw per event.

Inhalation of ambient air containing quartz and cristobalite is the dominant pathway of chronic exposure (excluding that from DIY activities) for the general population. Because SiO₂ makes up only approximately 5% of PM₁₀, silicon concentrations (expressed as SiO₂) measured in the Canadian NAPS survey of 24 urban locations were considered most relevant to the estimation of exposure by the general population. Quartz and cristobalite comprise only a portion of the total SiO₂ in PM₁₀, therefore, the use of the total silicon concentration to represent the upper bound crystalline silica concentrations results in an overestimation of exposure.

Appendix 1: Definitions of Epidemiological Terms in the ITAP

SMR (Standardized Mortality Ratio): The ratio (x 100) of observed to expected deaths in a study population. Expected deaths are calculated by applying a set of standard age-specific mortality rates to the age distribution of the study population. Standardized ratios are only useful for comparisons. They have no intrinsic meaning.

OR (Odds Ratio): In epidemiological case-control studies, a relative measure of disease occurrence. The odds in favour of a particular disease occurring in an exposed group are divided by the odds in favour of its occurring in an unexposed group. If the condition being studied is rare, the odds ratio is a close approximation to the relative risk.

RR (Risk Ratio): The probability of the occurrence of a disease in a group that has been exposed to some environmental, medicinal, microbial, or toxic influence, relative to its probability in a randomly selected population.

PMR (Proportionate Mortality Ratio): Proportionate mortality is the proportion of deaths in a specified population over a period of time attributable to different causes. Each cause is expressed as a percentage of all deaths, and the sum of the causes must add to 100%. These proportions are not mortality rates, since the denominator is all deaths, not the population in which the deaths occurred. Thus, proportionate mortality ratio is a measure of the frequency of occurrence of the proportionate mortality in a defined population during a specified interval of time.