

Unclassified

ENV/JM/MONO(2012)4/PART5

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

27-Feb-2012

English - Or. English

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

Cancels & replaces the same document of 13 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.

JT03316630

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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.

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**OECD Environment Directorate,
Environment, Health and Safety Division
2 rue André-Pascal
75775 Paris Cedex 16
France**

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org

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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).

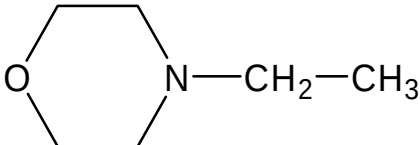
The collection of SIAPs has been divided in six parts, following a chronological order, to keep individual parts to a manageable size. For each part of the document, the corresponding SIDS Initial Assessment Meeting (SIAM) number and the year of the meeting have been indicated below.

		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.	100-74-3
Chemical Name	Morpholine, 4-ethyl-
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

There is no available information of morpholine, 4-ethyl- on toxicokinetics, metabolism or distribution.

In the acute oral toxicity study [OECD TG401], rats (5 animals/sex/dose) were given morpholine, 4-ethyl- by gavage at 0, 500, 1000, 1500 or 2000 mg/kg bw. Death was observed in three males and two females at 2000 mg/kg bw, one male at 1500 mg/kg bw, and one female at 1000 mg/kg bw. Most of males and females at 1000 mg/kg bw and higher showed tonic and/or clonic convulsions and decreased locomotor activity. The body weight gain of both sexes was suppressed at 1500 mg/kg bw and higher. No abnormalities were found at necropsy in surviving animals, although edema and red area in the glandular stomach were found in the dead animals. The LD₅₀ values are considered to be approximately 2000 mg/kg bw in rats. Groups of 6 rats were exposed to atmospheres saturated with this chemical. Strong irritation of the eyes and mucous membranes were observed during exposure, and 5 of the 6 rats died after 30-minutes exposure.

This chemical is an irritant to the eye and respiratory tract in humans, and skin and eye in rabbits. No information is available regarding sensitisation.

In a repeated dose toxicity study [OECD TG407], male and female rats were given this chemical by gavage at 0, 50, 200 or 800 mg/kg bw/day for 28 days. The initial numbers of rats were 10/sex at 0 and 800 mg/kg bw/day, and 5/sex at other doses. Five rats/sex from each group were killed on day 29, and the remaining 5 rats/sex at 0 and 800 mg/kg bw/day were kept without treatment for 14 days (recovery period). No death was observed in any group. Cage-licking and chewing were observed at 200 and 800 mg/kg bw/day in both sexes. The following toxicological changes were noted at 800 mg/kg bw/day with action tremors, decrease in movement, crouching position, eyelid closure, salivation, and suppression of body weight gain accompanied by reduced food consumption were observed in males and females. In urinalysis, increased level of ketone bodies and urobilinogen and decreased specific gravity in females were found. Blood biochemical examinations revealed increased levels of inorganic phosphate and decreased levels of chloride in both sexes, increased levels of calcium and blood urea nitrogen and decreased level of albumin in males, and increased levels of glucose and triglyceride and decreased level of total bilirubin in females. Increases in relative weights of the liver and kidney in both sexes and of brain, adrenal glands and testes in males were observed. Histopathological examinations revealed hypertrophy of the centrilobular hepatocytes and vacuolation of the epithelium in distal and Henle's loop. Based on clinical signs, the LOAEL and NOAEL for repeated dose toxicity are considered to be 200 and 50 mg/kg bw/day, respectively, in male and female rats.

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This chemical was not mutagenic at concentrations up to 5000 ug/plate in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA with or without metabolic activation [OECD TG471]. Even at the highest concentration tested (10 mmol/L), there was no effect on growth, polyploidy or the incidence of chromosome aberrations after 6- or 24-hr incubation, with or without metabolic activation [OECD TG473].

No information is available for carcinogenicity.

In a reproductive/developmental toxicity screening study [OECD TG421], rats (13 animals/sex/dose) were given this chemical by gavage at 0, 50, 150 or 500 mg/kg bw/day. Males were dosed for a total of 42 days beginning 14 days before mating. Females were dosed from 14 days before mating to day 3 of lactation throughout the mating and pregnancy period. No death was found in males. One female at 500 mg/kg bw/day died on day 2 of lactation. Tremors were noted in dead females. Salivation was observed in surviving males and females at 150 mg/kg bw/day. Decrease in body weight gain accompanied by a reduced food consumption was detected in males at 500 mg/kg bw/day and females at 150 mg/kg bw/day and higher. No effect on absolute and relative weights of the testes and epididymides was found. Necropsy and histopathological examinations revealed no changes related to this chemical. Histopathological examinations of the testes, epididymides and ovaries revealed no toxicological changes. There were no adverse effects on estrous cyclicity, copulation index, fertility index, precoital interval, gestation length, gestation index or number of corpora lutea. No significant changes were observed in numbers of implantations and pups or live pups, or in indexes for implantation, delivery, birth or live birth. No treatment-related changes in body weight, external appearance or necropsy findings were found in offspring. Based on clinical signs and decreased body weight gain and food consumption, the LOAEL and NOAEL for general toxicity are considered to be 50 mg/kg bw/day in males and females. The NOAEL for reproductive and developmental toxicity is considered to be 500 mg/kg bw/day.

Environment

Morpholine, 4-ethyl- is a transparent and flammable liquid with a slight ammonia-like odour. Water solubility is 303 g/L at 20 °C, a melting point of – 68.4 °C, a boiling point of 138.6 °C at 1013 hPa, a vapour pressure of 1.12 hPa at 25 °C and a relative density of 0.8996 at 20/20 °C are reported. Based on the measured log Kow value of 0.08 (non-ionised form, pH at 11.9) bio- or geoaccumulation of this chemical is unlikely. Environmental distribution using Mackey level III suggests that when morpholine, 4-ethyl- is released into the environment, it distributes mainly into water and soil. A calculated Henry's Law constant of 4.3×10^{-7} atm.m³/mole indicates that only limited volatilisation of morpholine, 4-ethyl- from water may occur. Morpholine, 4-ethyl- is not readily biodegradable and no abiotic degradation is expected. A measured dissociation constant value of 7.57 suggests that some portion of the substance is present as an ionized form in the environment. In the atmosphere morpholine, 4-ethyl- is indirectly photodegraded by reaction with OH radicals with a half-life of 0.1 days.

Eco-toxicity data of this chemical are available in aquatic species. For fish a 96 h LC₅₀ of > 100 mg/L (OECD TG 203, *Oryzias latipes*, semi-static), and a 96 h LC₅₀ of 280 mg/L (DIN 38412, Part 15, *Leuciscus idus*, static) are available. For daphnids, a 48 h EC₅₀ of > 92 mg/L (OECD TG 202, *Daphnia magna*, semi-static) and a 48 h EC₅₀ of > 580 mg/L (DIN 38412, Part 11, *Daphnia magna*, static) were reported. For algae, two reliable test results are available. For *Pseudokirchneriella subcapitata* (OECD TG 201, open system), the (0-72 h) ErC₅₀ and the (0-72 h) EbC₅₀ were > 53 mg/L and 52 mg/L, respectively. In addition, for *Scenedesmus subspicatus* (DIN 38412, Part 9), a (0-72 h) ErC₅₀ of 580 mg/L and a (0-72 h) EbC₅₀ of 270 mg/L were reported.

In a chronic study, for daphnids, a 21 d EC₅₀ of > 100 mg/L and a 21 d NOEC of 99 mg/L on reproduction were reported (OECD TG 211, *Daphnia magna*, semi-static). For algae, the (0-72 h)

NOECs were 23 mg/L by both growth rate and biomass methods (OECD TG 201, *Pseudokirchneriella subcapitata*, open system).

Regarding the toxicity towards microorganisms of morpholine, 4-ethyl- the EC₅₀ for *Pseudomonas putida* was > 1800 mg/L, and the EC50 for activated sludge (OECD TG 209, a limit test) was > 600 mg/L.

Exposure

Morpholine, 4-ethyl- is commercially produced by at least three manufactures in Japan with an annual production volume of approximately 110-115 tonnes (2002-2004). Worldwide production capacity outside Japan is not known. In Japan whole production process is operated in a closed system and all the residual non-reacted raw materials and bi-products are recovered from the reactor tank and applied for re-distillation and/or incineration.

Although no exposure scenario outside Japan is available, it is known that morpholine, 4-ethyl- is used as an intermediate (indirect use) for dyestuffs, pharmaceuticals, rubber accelerators, emulsifying agents and as a solvent (direct use) for dyes and resin oils. In some facilities, morpholine, 4-ethyl- is used to adjust pH values of industrial water which also affects rust preventer.

Under certain use conditions, e.g. pH adjustment and/or solvents, morpholine, 4-ethyl- is expected to be released mainly into the water compartment.

Morpholine, 4-ethyl- is liquid with moderate vapour pressure, occupational exposure through inhalation and dermal route is possible at production sites and user sites. An occupational exposure standard of 5 ppm is adopted in many countries. An OEL for this chemical is not established in Japan. In one production site personal protective equipments are used to prevent exposure. Based on the limited information available, it can be considered that the exposure to workers is not significant in the sponsor country.

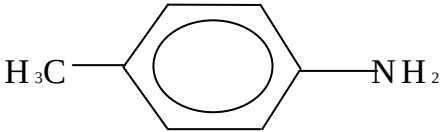
The general population may be exposed through dermal contact via industrial water contaminated with morpholine, 4-ethyl-. Another route would be the inhalation of vapour under conditions where morpholine, 4-ethyl- is used as a solvent in certain applications. In addition multiple applications including end use products also suggest that direct exposure to consumers are possible to some extent in the sponsor country.

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, irritation). Exposure to general public is expected through dermal contact and inhalation. This chemical is produced in a closed system in a company in Japan, but used to formulate various products. Occupational exposure through inhalation and dermal route is possible in both production and user sites. Therefore, an exposure assessment and, if necessary, risk assessment for workers and consumers are recommended.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity in algae). Although these hazards do not warrant further work as they are related to aquatic acute toxicity which may become evident only at high exposure level, they should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-49-0
Chemical Name	p-Toluidine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

There are no specific studies available which evaluate the possible potential of p-toluidine to affect fertility or to cause developmental toxicity. Information from m-toluidine is used to fill the data gap. Therefore the SIAR contains a short comparison of p-toluidine and m-toluidine for all endpoints. The isomer m-toluidine was already discussed and concluded in SIAM 11, 2001; the data are published by UNEP in 2003. A comparison of the intrinsic toxicological properties of m-toluidine with these properties of p-toluidine showed that m-toluidine is more potent in methemoglobin forming than the p-isomer. Taking into account that methemoglobinemia in pregnant rats is causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Furthermore developmental toxicity data from the structurally related p-isopropylaniline were included in the assessment. This seems to be justified due to the structural similarity of both substances as both aniline derivatives have substituents in para position of nearly the same influence on the reactivity of the respective molecule. This could be demonstrated with the data on acute toxicity as well as with repeated toxicity data. For all three substances methemoglobinemia and/or erythrocyte toxicity seem to be the most relevant mechanism for systemic toxicity. In addition, with respect to mutagenicity, the comparison of results of the respective tests with these substances demonstrates the inconsistency, which is typical for aromatic amines.

p-Toluidine is absorbed via gastrointestinal tract and is distributed, metabolized and excreted via urine and feces. The identification of 2-amino-5-methylphenol indicates that the metabolism in rat proceeds through ring hydroxylation with subsequent conjugation. There are no specific toxicokinetic data on absorption via skin and respiratory tract; absorption via these administration routes can be reasonably be predicted due to the molecular size of p-toluidine.

m-Toluidine (SIAM 11) is rapidly absorbed via gastrointestinal tract, via skin and is metabolized by ring hydroxylation. Although 2-amino-4-methylphenol and 4-amino-2-methylphenol were identified in the rat urine with a small amount of the parent compound, there is no sufficient information on quantitative metabolism of m-toluidine or on toxicokinetics. **Overall conclusion:** Both isomers, p- and m-toluidine are absorbed via gastrointestinal tract and via skin and distributed. They are metabolized by ring hydroxylation with subsequent conjugation and excreted via urine and feces.

For **p-toluidine**, the LC₅₀ (inhalative, rat) is > 0.64 mg/l, and LD₅₀ (dermal, rabbit) is 890 mg/kg bw. LD₅₀ (oral, rat) was determined 656 mg/kg bw and 620 mg/kg bw. Signs of intoxication include hypoactivity, muscular weakness,

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convulsions, cyanosis and narcosis. p-Toluidine is a methemoglobin forming chemical in rats. Levels up to 21.7 % following oral application to rats and up to 40 % following dermal application to rats were measured. p-Toluidine is a methemoglobin forming chemical in humans as it produces the same toxic effects as aniline from 22 mg/m³ onwards with less cyanosis but more stranguria and hemoglobinuria.

For **m-toluidine**, LD₅₀ values are from 450 to 1430 mg/kg bw by oral route to rats and 3250 mg/kg bw by dermal route to rabbits (no information on study quality available). Severe methemoglobin formation is reported following single exposure to m-toluidine ranging up to 36.4 % in rats after oral application and 40 % in rats after dermal application (these data as well as those given above for p-toluidine are derived from a study which examined the methemoglobin formation of m- and p-toluidine in parallel) and up to 60.2 % in cats (i.v.). For **p-isopropylaniline**, LD₅₀ values of 985 mg/kg bw and 757 mg/kg bw were reported of rats following single oral application. Single oral application of 25 mg/kg bw to cats resulted in elevated methemoglobin level and an increase in Heinz bodies. **Overall conclusion:** Based on the available data, p- and m-toluidine are of moderate acute toxicity. Main toxic signs result from the methemoglobin formation in rats as well as in humans. m-Toluidine is considerably more active in methemoglobin formation than p-toluidine when tested at equal dosages and under similar experimental conditions. p-Isopropylaniline led to an increase in methemoglobin after oral application of 25 mg/kg bw to cats (no quantitative data available).

p-Toluidine causes irritation to the eyes of rabbits which recovered within 7 days. No irritational effects were observed when applied to the rabbit's ear for 24 hours under occlusive conditions. **p-Toluidine** is a sensitizer by skin contact as shown in a patch test with guinea pigs. There is no valid human data available.

There are no adequate repeated dose toxicity studies available for **p-toluidine**. There are a number of limited studies sufficient to support a weight of evidence approach. Limitations include documentation of the experiments in general, number of animals under test, treatment time as well as the lack of necessary investigations. Nevertheless, the overall weight of evidence indicates low systemic toxicity with liver and blood as target organs. Based on increased liver to body weight ratio in the available subacute feeding study a NOAEL of 165 ppm (corresponding to 13.8 mg/kg bw/day) can be derived for rats. In studies over a period of 6 months dose-related (40 - 160 mg/kg bw/day) increases in methemoglobin level up to ≥ 10 % are reported for rats. In addition, it is demonstrated that prolongation of treatment time up to 12 months does not result in further increase in methemoglobin levels in rats. Treatment of rats and mice with p-toluidine in feed for 18 months resulted in a NOAEL (systemic toxicity) of 2000 ppm in rats (highest dose tested, approximately 150 mg/kg bw/day). In mice treated with 500 ppm (approximately 75 mg/kg bw/day) no influence on body weight and/or mortality rate was reported, however hepatomas occurred in males.

With **m-toluidine** there has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 on rats with gavage application of the structurally closely related isomer m-toluidine which has been assessed during OECD-ICCA SIAM 11 in 2001. In this study m-toluidine leads to deposit pigmentations and extramedullary hematopoiesis in spleen starting already at the lowest dose of 30 mg/kg bw/day representing the LOAEL. There are sufficient evidences that this chemical induces methemoglobinemia, but methemoglobin content was not determined in this study. With **p-isopropylaniline** there has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 on rats with gavage application resulting in a NOEL (systemic toxicity) of 6 mg/kg bw/day based on erythrocyte toxicity including secondary effects. **Overall conclusion:** Following repeated dosing both toluidine isomers as well as p-isopropylaniline reveal as main targets the erythrocytes (methemoglobin formation) and liver (increased liver weight/m-toluidine and p-isopropylaniline and slight hepatocyte swelling/p-toluidine in rats; liver tumors in mice/m- and p-toluidine). The NOELs in rats for all three substances are roughly in the same dose range; main toxic principle of all three substances is the methemoglobin formation with accompanying symptoms.

p-Toluidine does not induce point mutations in the vast majority of *in vitro* Ames tests. In Chinese hamster lung cells p-toluidine is clastogenic in the presence but not in the absence of S9-mix. *In vivo*, DNA single strand breaks are detected in liver and kidneys of mice using alkaline-elution technique after single intraperitoneal injection of 2/3 of the respective LD₅₀ (35 mg/kg bw), therefore it cannot be decided definitely whether the effects occurred due to cytotoxicity or real genotoxic mechanisms. Overall, there is some indication for clastogenic activity *in vitro* and some residual suspicion for such action *in vivo*.

There are no adequate studies with **p-toluidine** to evaluate carcinogenicity in rats and mice. There are a number of limited studies sufficient to support a weight of evidence approach. The limitations include e.g. only one dose in the dermal study, limited number of animals, treatment time too short and are only reported in brief. Following oral and dermal (one dose only) application to rats no tumors can be identified at any dose level. In mice, hepatomas are identified in males in all dose groups whereas females showed liver tumors only in the high dose group. In a study with subcutaneous injection of p-toluidine to rats only a slight, not significant increase in the number of tumors at the injection site and in the liver are reported.

There are no specific data on toxicity for reproduction for **p-toluidine**. Data from repeated dose toxicity studies give no evidence for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available.

In an OECD TG 422 guideline study with **m-toluidine** on rats it is shown that an impairment of reproductive function as well as adverse effects on development might occur after applying systemically toxic doses to the parents leading to methemoglobin formation. The NOEL for reproductive toxicity of m-toluidine in rats is 30 mg/kg bw/day. At this dose there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOEL for developmental toxicity for m-toluidine in rats is considered to be 100 mg/kg bw/day. In an OECD TG 422 guideline study with **p-isopropylaniline** on rats there is no impairment of reproductive ability until the highest dose tested (60 mg/kg bw/day) although indications for methemoglobinemia has been detected already at 20 mg/kg bw/day. The NOEL for developmental toxicity for p-isopropylaniline in rats is considered to be 20 mg/kg bw/day. **Overall Conclusion:** There are no specific data on toxicity for reproduction for p-toluidine. Data from repeated dose toxicity studies give no evidence for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available. But taking into account the results from an OECD TG 422 guideline study performed with the structurally closely related isomer m-toluidine as well as with the structurally related p-isopropylaniline on rats it can be deduced that an impairment of reproductive function as well as adverse effects on development might occur after applying systemically toxic doses to the parents leading to methemoglobin formation. The NOELs for reproductive toxicity in rats are 30 mg/kg bw/day for m-toluidine and 60 mg/kg bw/day for p-isopropylaniline. At these doses there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOELs for developmental toxicity for m-toluidine in rats are considered to be 100 mg/kg bw/day for m-toluidine and 20 mg/kg bw/day for p-isopropylaniline.

In view of the fact that m-toluidine is more potent in methemoglobin formation than p-toluidine and taking into account that methemoglobinemia in pregnant rats may be causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Since there is no evidence for adverse effects on reproduction or developmental effects for m-toluidine or p-toluidine through a direct mechanism of action further testing of p-toluidine is not regarded to be necessary.

Environment

p-Toluidine consists of lustrous plates or leaflets with a melting point of 44 °C, and a boiling point of 200.5 °C. The density is 0.9619 g/cm³ at 20 °C. The interpolated vapor pressure at 25 °C is 38.1 Pa. The measured log K_{ow} is 1.39. The solubility in water is 7.4 g/l at 25 °C. The flash point is 87 °C, the auto-ignition temperature 482 °C.

In the atmosphere, p-toluidine is degraded by photochemically produced OH radicals. The half-life is calculated to be ca. 2.9 hours.

With regard to the chemical structure, p-toluidine is not expected to hydrolyze due to the lack of hydrolysable functions.

p-Toluidine is inherently biodegradable (MITI test OECD TG 301 C: > 30 % after 14 days; OECD TG 302 B: 94 % after 8 days (industrial sludge), OECD TG 302 B: 94 % after both 10 and 13 days, OECD TG 302 B: 97.7 % after 5 days (adapted sludge), study similar to OECD TG 301 D: biodegradation 68 % after 20 days (study poorly documented)).

According to the Mackay fugacity model level I, the favorite target compartment of p-toluidine is water with 83.7 %,

followed by air with 16.0 %. The experimentally determined Henry's law constant ($0.20 \text{ Pa m}^3/\text{mol}$ at 25°C) proves a low to moderate potential for volatilization from surface waters.

In a sparsely documented study with fish, bioconcentration factors of < 1.3 were obtained at $100 \mu\text{g/l}$ and < 13 at $10 \mu\text{g/l}$. The bioconcentration factor $\text{BCF} = 2.35$ for p-toluidine, calculated from the octanol-water partition coefficient, indicates that there is a low potential for bioaccumulation of p-toluidine in fish. The available experimental data concerning uptake and elimination of p-toluidine in *Mytilus edulis*, indicates its low potential for bioaccumulation in mussels: 85 % elimination of the steady state body burden after 4 hours.

Experimentally obtained adsorption coefficients (K_{oc}) revealed a low to high sorption potential of p-toluidine. The experimentally achieved K_{oc} values were in the range of 102.2 to 1903.4 depending on soil properties. In addition, K_{oc} values were calculated with PCKOCWIN v. 1.66 ($K_{oc} = 72.5$) and with the TGD equation for the anilines ($K_{oc} = 52$). These results indicate a low sorption potential of p-toluidine onto the organic phase of soil or sediments. It can be assumed that at low pH the protonated form of p-toluidine with its electrostatic forces may play an important role in soil sorption processes.

Concerning the toxicity of p-toluidine to aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The tests were performed according to standard procedures or similar methods. The lowest effect values from short-term tests, as well as from a prolonged fish toxicity test are:

<i>Danio rerio</i> :	96 h- LC_{50} = 115 mg/l (m)
<i>Poecilia reticulata</i> :	14 d- LC_{50} = 10.7 mg/l (n)
<i>Daphnia magna</i> :	48 h- EC_{50} = 0.12 mg/l (m)
<i>Scenedesmus obliquus</i> :	48 h- E_rC_{50} = 62.9 mg/l (n)
<i>Scenedesmus quadricauda</i> :	96 h- E_bC_3 = 8.0 mg/l (n)

Data for algal toxicity (*S. capricornutum*, 72 h- E_bC_{50}) of m-toluidine (SIAM 11) and o-toluidine (SIAM 19) is 17.7 and 30.9 mg/l, respectively. For *Chlorella pyrenoidosa* the 96 h- E_rC_{50} for o-toluidine is 55 mg/l.

Tests on chronic toxicity of p-toluidine to aquatic species are not available.

Concerning the effects on terrestrial organisms the following data was obtained for plants in a root elongation test with a duration of 5 days:

<i>Brassica campestris</i> :	5 d- LC_{50} = 102.2 mg/l (n).

The lowest toxicity of p-toluidine to microorganisms measured in a test according to OECD TG 209. A 3h- EC_{50} value of 100 mg/l was obtained with predominantly domestic sewage.

As acute test results of p-toluidine for three trophic levels are available, an assessment factor of 1000 was applied for the derivation of the $\text{PNEC}_{\text{aquatic}}$ according to the EU Technical Guidance Document. The lowest of the available L(E)C_{50} values was obtained for *Daphnia magna*, 48 h- $\text{EC}_{50} = 0.12 \text{ mg/l}$, therefore resulting in a $\text{PNEC}_{\text{aquatic}} = 0.12 \mu\text{g/l}$.

Exposure

p-Toluidine is commercially manufactured by reduction of p-nitrotoluene. In 2000, the global production volume of p-toluidine was estimated to be 19 600 tonnes by 23 producers: Western Europe 8000 tonnes/a, USA 3000 tonnes/a, Japan 1200 tonnes/a, South Korea 2400 tonnes/a, China 3800 tonnes/a, and India 1200 tonnes/a. In the Sponsor country, one company has a total production volume of 2000 -10 000 tonnes/a. The total production of this company is used as an intermediate in chemical synthesis, either onsite or offsite by customers. The total end use volume of Western Europe (approximately 5700 tonnes/a of p-toluidine) is used as an intermediate in chemical synthesis as well.

In the Sponsor company, p-toluidine is manufactured and processed in closed systems. The effluent concentration from the wastewater treatment plant was below the detection limit of $20 \mu\text{g/l}$ (With a dilution factor of 700 at that site the concentration in the receiving river is below $0.03 \mu\text{g/l}$). p-Toluidine is transported in rolling channel drums and also in rail or road tankers. The transported goods are classified and labeled according to the relevant national and international transport regulations. There are 2 other companies which produce p-toluidine in the Sponsor country. However, no information is available from these companies.

p-Toluidine is used exclusively as an intermediate in chemical processes, e.g. for the manufacturing of 4B acid

(intermediate for pigments) and of other pigments, dyestuff, pesticides, and pharmaceuticals. No consumer use is known for p-toluidine. p-Toluidine is listed in the Danish and Norwegian Product Registers as an industrial product. It is not listed in the Finnish and Swedish Product Registers. In the Swiss Product Register p-toluidine is registered to occur in a consumer product (acrylate glue) with a p-toluidine concentration of 0.01 %. Thus, an exposure of consumers and of the environment due to releases from (consumer) products appears to be negligible.

Toluidine (isomers not specified) was detected in certain vegetables and liquid fuels. p-Toluidine was identified in gasoline. It is released from *Penicillium viridicatum* and from *Methylobacterium mesophilicum* biofilm interlaced with *Penicillium viridicatum*. p-Toluidine is an intermediate in the biodegradation of p-nitrotoluene, e.g. at former munitions sites. p-Toluidine is formed during pyrolysis.

In 1979, p-toluidine was detected in the river Rhine, with the highest p-toluidine concentration of 1 µg/l. In 1991, p-toluidine was not detected in several rivers in North Rhine-Westfalia in Germany (detection limit: 0.1 - 1 µg/l). In 2001, p-toluidine could also not be detected in 3 Indian water samples (detection limit: 23 ng/l). p-Toluidine occurs in air and tobacco smoke with emissions of up to 2.4 µg/cigarette.

Measurements at the workplaces have been performed according to German Technical Guidance TRGS 402. In Germany up to 2004, for occupational settings, a legally binding maximum admissible concentration (technical based) of 1.0 mg/m³ was set for p-toluidine. With the new German Ordinance on hazardous substances at January 1, 2005, this limit value was officially withdrawn by the German Ministry of Labour. In the Sponsor country, as also confirmed by one company, the exposure of workers is below this limit. p-Toluidine has a TWA (Time-weighted average) value of 2 ppm and is also classified in the TLV list A3 as a confirmed animal carcinogen with unknown relevance to humans.

Concentrations of p-toluidine in urine of occupationally exposed workers were similar to these of the general population. Prominent differences were found between males and females. 3 out of 4 studies found elevated levels of p-toluidine hemoglobin adducts in blood of smokers, compared to non-smokers.

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

Human Health: The chemical possesses properties indicating a hazard for human health (acute and subacute toxicity, methemoglobin formation, skin sensitization, eye irritation, possible genotoxicity and carcinogenicity). Based on the data presented by the Sponsor country (relating to production by one producer in one country which accounts for 10 - 50 % of global production and relating to the use pattern in several OECD countries), exposure is controlled in occupational settings, and exposure of consumers appears to be negligible. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. The substance is currently of low priority for further work.

Environment: The chemical possesses properties indicating a hazard for the environment (acute aquatic toxicity to *Daphnia magna*). Based on data presented by the Sponsor country (relating to production by one producer in one country which accounts for 10 - 50 % of global production and relating to the use pattern in several OECD countries), exposure to the environment is anticipated to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. The substance is currently of low priority for further work.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-18-6
Chemical Name	2-Propen-1-ol
Structural Formula	$\text{CH}_2=\text{CH}-\text{CH}_2-\text{OH}$

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Animal studies demonstrate that 2-propen-1-ol appears to be oxidised readily in the liver, giving a variety of metabolic products, such as acrolein, acrylic acid, glycidaldehyde, and glyceraldehyde. Among these metabolites, the most reactive metabolite, acrolein may cause hepatotoxicity in the liver.

The inhalation LC_{50} is 140-150 mg/m^3 for 8 hours exposure in rats. The dermal LD_{50} (rabbit) is 89 mg/kg bw. The oral LD_{50} values are 70 and 99-105 in rats, 96 in mice and 71 mg/kg bw in rabbits. The intraperitoneal LD_{50} values are 37 and 42 in rats, and 60 mg/kg bw in mice. A 55-year old man died within 100 minutes of oral ingestion of 2-propen-1-ol. The amount ingested was assumed to be 212 g of 2-propen-1-ol at the maximum. Death was attributed to acrolein-induced cardiotoxicity.

2-Propen-1-ol is considered to be slightly irritating to the skin and irritating to eyes in animals. Moreover, 2-propen-1-ol may cause irritation of the eye and nasal mucosa in humans. 2-Propen-1-ol is considered not to be a skin sensitizer in guinea pigs [OECD TG 406].

In a repeat dose inhalation toxicity study, male rats were exposed to 2-propen-1-ol at nominal concentrations of 0, 2.4, 4.7, 12, 47, 95, 142, 237 or 355 mg/m^3 for 7 hours/day, 5 days/week for 12 weeks. Histopathology showed that there was slight congestion of the lungs and liver at the dose of 355 mg/m^3 (150 ppm). The NOAEL for inhalation toxicity in male rats is 12 mg/m^3 (5 ppm) based on a significant decrease in body weight gain in groups exposed to 47 mg/m^3 (20 ppm) and higher.

In a repeated dose oral toxicity study, 2-propen-1-ol had adverse effects on kidney tissues in rats, administered in the drinking water continuously for 15 weeks at or above a level of 100 ppm (8.3 mg/kg bw/day in males and 6.9 mg/kg bw/day in females). The NOAEL was 50 ppm of 2-propen-1-ol in drinking water (equivalent to 4.8 mg/kg bw/day in male rats and 6.2 mg/kg bw/day in female rats) based on adverse effects on kidney tissues (increases in absolute kidney weight and relative kidney weight) for females and on an increase in relative stomach weight for male and females at 100 ppm.

The *in vitro* studies, including reverse mutation assays in bacteria (*S. Typhimurium*: positive in T1535 with S9, TA100 without S9; negative in TA97, TA98, TA100 and TA1535 without S9), microbial forward mutation and fungal point mutation assays (*Streptomyces coelicolor* and *Aspergillus nidulans*, respectively: negative) and gene mutation in mammalian cells (V79 cells: positive) gave conflicting results, , while the *in vivo* studies concerning micronucleus and the dominant lethal assay in rodents gave negative results. Based on these data *in vitro* and *in vivo*, there is equivocal evidence that 2-propen-1-ol may be genotoxic.

A carcinogenicity study was conducted with male and female Fischer 344 rats via drinking water (300 mg/L , total dose of 3.2 g) for 106 weeks, followed by observation until natural death (123-132 weeks). The study gave no clear evidence of carcinogenicity in male rats, but there was equivocal evidence of carcinogenicity in the liver of female rats.

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Reproductive/developmental toxicity was studied in SD rats by gavage at doses of 0, 2, 8 or 40 mg/kg bw/day [OECD TG 421]. Males were dosed from 14 days before mating for total of 42 days, and females were dosed from 14 days before mating throughout the mating and pregnancy period to day 3 of lactation. The autopsy was conducted on the day after the final administration. No deaths were found in any group. Clinical findings in parental animals at 40 mg/kg bw/day were salivation, decrease in locomotor activity, irregular respiration (male and female), lacrimation and loose stool (male). Histopathological examinations at 40 mg/kg bw/day revealed atrophy of the thymus and hyperplasia of luteal cells in the ovary in females, necrosis, fibrosis, proliferation of bile duct, hypertrophy, and brown pigment deposition in perlobular hepatocytes, and diffuse clear cell changes in males and females, and hyperplasia of squamous epithelium in the forestomach in males. In male rats, no changes in histopathological findings or weight of the testes and epididymis were found. In females, extension of mean oestrous cycle length and increase in females with irregular oestrous cycle were observed at 40 mg/kg/day group. There were no adverse effects on the other reproductive performance parameters (such as the mating index, fertility index, numbers of corpora lutea or implantations, implantation index, delivery index, gestation index, gestation length, parturition or maternal behaviour). In examination of offspring, decrease in viability index on day 4 and total litter loss (from one dam) were observed at 40 mg/kg bw/day group. There were no-treatment-related findings in the external appearance, general conditions and necropsy findings in the offspring. The NOAEL is considered to be 8 mg/kg bw/day for general toxicity and reproductive/developmental toxicity.

In a prenatal developmental study conducted in SD rats, 2-propen-1-ol was administered by gavage at doses of 0, 10, 35, or 50 mg/kg bw/day to pregnant rats on gestation days 9 to 19 [OECD TG 414]. At doses of 10 mg/kg bw/day and higher significant toxicity in dams was observed. Maternal toxicities at 35 and 50 mg/kg bw/day were mortalities, clinical findings, reductions in body weight gain and feed consumption, macroscopic liver findings and increased liver weights. One female at 10 mg/kg bw/day also had macroscopic liver findings. An increased frequency of total litter loss was observed at 35 and 50 mg/kg bw/day dose levels. In case of total litter loss, severe toxicities were observed in the dam (loss of body weight, severe decreases in feed consumption, and evidence of significant liver toxicity). Despite the severe maternal toxicity observed, there were no 2-propen-1-ol related increases in malformation rates or incidence of variations. 2-Propen-1-ol had no effects on intrauterine growth or survival in the fetuses from dams that survived to necropsy. Therefore, 10 mg/kg bw/day was considered to be the LOAEL for maternal toxicity, based on liver findings, and 10 mg/kg bw/day was considered to be the NOAEL for developmental toxicity, based on an increased frequency of total litter loss at 35 and 50 mg/kg bw/day, when 2-propen-1-ol was administered orally by gavage to pregnant rats.

Environment

2-Propen-1-ol is a colourless liquid and is miscible with water. Melting point, boiling point, vapour pressure and partition coefficient are -129 °C, 96.9 °C, 25 hPa (20 °C) and log Kow = 0.17, respectively. 2-Propen-1-ol is not expected to be hydrolyzed under normal environmental conditions. Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life of 4.32 hours. 2-Propen-1-ol is readily biodegradable under aerobic conditions within 14 days (BOD = 86 %). The estimated BCF is 3.2 and there is low potential for bioaccumulation. Fugacity Model Mackay level III calculations indicate that 2-propen-1-ol will be distributed mainly to air (67.6 %) water (25.1 %) and soil (7.3 %) compartment if released to air, while 2-propen-1-ol will stay exclusively in the water compartment (99.7 %) if released to water. If released to soil, 2-propen-1-ol will be distributed mainly to the water (19.4 %) and soil (80.4 %) compartment. If released simultaneously to air, soil and water, 2-propen-1-ol will be distributed mainly to water (62.1 %) and soil (36.7 %) compartment. Henry's Law constant is 4.99×10^{-6} atm.m³/mole.

Acute toxicities to fish (96-h LC₅₀) are 0.59 mg/L (Medaka) [OECD TG 203] and 0.32 mg/L (Fathead minnow). Acute toxicity to *Daphnia magna* (48-h EC₅₀) is 2.1 mg/L [OECD TG 202]. The 48-h LC₅₀ in Polychaete (*Ophryotrocha diadema*) is 0.33-1.0 mg/L. Acute toxicities to green algae (*Pseudokirchneriella subcapitata*) are 5.4 mg/L (72-h E_rC₅₀) and 2.3 mg/L (72-h E_bC₅₀) [OECD TG 201]. The NOEC of 21-d chronic toxicity in *Daphnia magna* is 0.92 mg/L [OECD TG 211]. The NOEC value in green algae (*Pseudokirchneriella subcapitata*) is 0.93 mg/L (72-h for growth rate and biomass) [OECD TG 201].

Exposure

The production volume of 2-propen-1-ol was estimated at 136,100 t/year worldwide in 2003 and 45,000 t/year in Japan in 2001. Two producers in Japan account for approx 30-40 % of global production. 2-Propen-1-ol is an important starting material, and is used in the manufacture of 1,4-butanediol, 2-methyl-1,3-propanediol, allyl diglycol carbonate, diallyl phthalate, diallyl isophthalate, allyl glycidyl ether, epichlorohydrin, allyl methacrylate, styrene 2-propen-1-ol and resins for coating applications, flavorings such as allyl hexanoate, contact herbicide, as an intermediate for manufacturing pharmaceuticals, fire retardants and herbicides.

2-Propen-1-ol is exclusively used as an intermediate in chemical synthesis. Occupational exposure is possible by the inhalation and dermal routes at the manufacturing and user sites. No consumer use is known for 2-propen-1-ol. However, monitoring data provided by the sponsor country indicate that potential indirect exposure via the environment is anticipated.

Consumers may be potentially exposed to 2-propen-1-ol from ingestion of foods. 2-Propen-1-ol has been detected in crab meat, mussels and garlic. 2-Propen-1-ol is rapidly formed in the body from the hydrolysis of allyl esters used as flavour agents in food. The estimated intake of 2-propen-1-ol from this route is 18 µg/kg bw/day in Europe and 5.8 µg/kg bw/day in the USA.

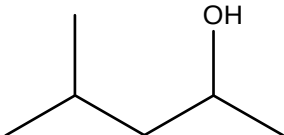
MOE, Japan monitored 2-propen-1-ol concentrations in the environment such as air, well water, sea water and river water throughout Japan. Based on these studies the estimated human exposure (EHE) is calculated to be 0.027 µg/kg bw/day under the standardised Japanese condition. A second Japanese monitoring study performed in the Kitakyushu-city area reported that no 2-propen-1-ol was detected in sea water, river water, reservoir water and effluent of sewage treatment plant in addition to well water, tap water and rain water at the limit of detection of 0.008 µg/L.

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, repeated dose toxicity, irritation, genotoxicity, carcinogenicity, reproductive/developmental toxicity). This chemical is manufactured in a closed system in Japan, but used to produce various products and occupational exposure through inhalation and dermal routes is possible in both production and user sites. Monitoring data provided by the sponsor country indicate that potential indirect exposure to consumers via the environment is anticipated. Therefore, an exposure assessment and, if necessary, risk assessment for workers and consumers should be performed.

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard to the environment (acute toxicity in algae, fish and daphnia and chronic toxicity in daphnia). Based on data presented by the sponsor country (relating to production by two producers which account for approx 30-40 % of global production and relating to the use, the total reported releases and the transfers in the sponsor country), potential environmental exposure is anticipated. Therefore, member countries are invited to perform an exposure assessment, and if necessary, a risk assessment for the environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-11-2
Chemical Name	4-Methylpentan-2-ol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

The metabolism and clearance of 4-methylpentan-2-ol (methyl isobutyl carbinol; MIBC) is rapid (C_{max} and $t_{1/2}$ approximately 30 min and 2 hr, respectively). MIBC is metabolized to 4-hydroxy-4-methyl-2-pentanone (HMP) through methyl isobutyl ketone (MIBK). Dosing with MIBC or MIBK results in similar internal exposure to MIBK and HMP and minimal exposure to MIBC. Thus, the data for MIBK and HMP adequately support the evaluation of MIBC systemic toxicity.

Human Health

Studies with experimental animals indicate that MIBC is of low toxicity by the oral, dermal and inhalation routes of exposure. MIBC has typical organic solvent effects in rats following acute inhalation exposures with anesthetic effects occurring at 10 mg/L (2360 ppm) and death following an 8-hour exposure to 8.4 mg/L (2000 ppm). The acute oral and dermal LD_{50} values for MIBC are 2260 - 2970 mg/kg and 2870 mg/kg, respectively.

In standard primary irritation studies, MIBC was slightly irritating to skin and moderately to severely irritating to the eye. Human volunteers exposed to MIBC vapors at 50 ppm experienced eye irritation in most subjects with nose and throat irritation experienced at higher concentrations. The maximum tolerable concentration was considered to be 25 ppm. A skin sensitization study in animals was negative and indicates that MIBC is not likely to be a sensitizer in humans.

Repeated dose studies with MIBC and its primary metabolites, MIBK and HMP, indicated that systemic toxicity is minimal. The NOAEC for subchronic inhalation exposure was 886 ppm (3.70 mg/L) for MIBC (6-weeks with rats) and 1000 ppm (4.09 mg/L) for MIBK (14-weeks with rats and mice). There were no organ-specific toxic effects for either chemical. The NOAEL for the ultimate metabolite, HMP, via gavage dosing for 45 days was 30 mg/kg/day for males (based on hyaline droplet nephropathy) and 100 mg/kg/day for females. The LOAEL for this study was 100 mg/kg/day for males and 300 mg/kg/day for females.

MIBC and HMP were not mutagenic to bacterial cells (bacterial reverse mutation assay) *in vitro* with or without metabolic activation. In a mammalian cell cytogenetic assay (rat liver cells), MIBC was negative with and without metabolic activation. HMP was negative in an *in vitro* chromosomal assay. Based on the negative results in the bacterial mutagenicity and mammalian cell cytogenetic assays with MIBC and bacterial mutagenicity and chromosomal aberration assays with HMP, MIBC is unlikely to be mutagenic in humans.

MIBC showed no effects on reproductive organs following 6 weeks of inhalation exposure to concentrations as high as 3.70 mg/L (886 ppm). MIBK showed no reproductive effects in a two-generation study with inhalation exposures

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up to 8.18 mg/L (2000 ppm). Slight changes in reproductive performance (decreased fertility and implantations) and pup viability following high oral exposure to HMP (1000 mg/kg/day) in an OECD TG 422 study may have occurred in the presence of maternal toxicity (reduced weight gain, statistically significant changes in hematology, clinical biochemistry and relative organ weights; renal and hepatic histopathological lesions). No teratogenic effects were observed for rats or mice at MIBK inhalation concentrations as high as 3000 ppm (12.3 mg/L) and no fetal toxicity was observed without the presence of maternal toxicity; the NOAEC for maternal and fetal toxicity was 1000 ppm (4.09 mg/L) due to clinical signs of toxicity including neuromuscular effects (both species), and statistically significant changes in body weight, relative kidney weights and decreased food consumption (rats only) and increased liver weight (mice only), and decreased fetal body weight with evidence of delayed ossification. Based on the available animal data, MIBC is not expected to be a human reproductive or developmental toxicant.

Environment

The melting point of MIBC is -90°C and the boiling point is 131.7°C . The vapor pressure is 4.97 hPa at 20°C . The water solubility of MIBC is 16.4 g/L (20°C) and density is 0.81 g/cm^3 at 25°C . The calculated log Kow is 1.68. MIBC is predicted to be photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of approximately 10 hours (calculated). MIBC does not have hydrolyzable groups and therefore hydrolysis is not a degradation pathway. Distribution modeling using Mackay Level I indicated that partitioning will occur to air (37.8%), water (59.6%), and soil (2.5%) phases. Fugacity model Level III predicted greatest distribution ($\geq 86\%$) to the primary compartment of release. When equal releases were assumed, the predicted distribution was: 3.6% (air), 45% (water), 51% (soil) and $<1\%$ (sediment). A low bioaccumulation potential is expected based on the partition coefficient and other physical/chemical parameters. MIBC is readily biodegradable attaining 94% degradation within 20 days and meeting the "10-day window".

The 96-hour LC_{50} for rainbow trout (*Oncorhynchus mykiss*) is 359 mg/L (measured), the 48-hour EC_{50} for *Daphnia magna* is 337 mg/L (measured) and the 96-hour EC_{50} value for growth rate of algae (*Pseudokirchneriella subcapitata*) is 334 mg/L (measured) and for biomass is 147 mg/L (measured).

Exposure

The estimated total volume of MIBC production in North America in 1998 was 25,000 tonnes. MIBC is primarily used ($\sim 70\%$) in the production of lube oil additives. MIBC ($\sim 20\%$ of the total production) is used as a flotation frother for treating copper ores and coal with usual concentrations less than 1000 ppm and in many cases in the hundreds of ppm range (100 - 600 ppm). The remaining production is primarily for its use as an additive to surface coatings as a solvent to maintain binder softness until the binder fuses.

The use as a solvent and as flotation frothers result in environmental releases at very low concentrations. Human exposure to MIBC is very limited based on its use patterns. With the exception of tar sand mining frothers, MIBC is used in closed systems and only catastrophic failure results in any appreciable exposure. In tar sand mining, exposure (in the ppm range) is typically limited to the equipment operators. MIBC used as an intermediate in the manufacture of lube oil additives is blended with other alcohols and reacted. Normally these reactors are closed systems and exposure is limited to upsets or catastrophic failure of the reactor. In its primary use as an intermediate for corrosion inhibitor production, significant residual MIBC is not anticipated. As noted above, in mining operations, low ppm vapor exposure may occur in operators. Minimal exposure to vapors from the use of MIBC as a solvent in coating applications may also occur. The ACGIH TLV-TWA for MIBC is 25 ppm (104 mg/m^3) and the TLV-STEL is 40 ppm (167 mg/m^3). The German MAK value is 25 ppm.

Based on its pattern of use, consumer exposure to MIBC is expected to be negligible. Environmental exposure to MIBC can occur during mining processes or through accidental release.

RECOMMENDATION 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 potential hazard for human health (eye irritation, narcosis at high inhalation concentrations) These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure levels. They should nevertheless be noted by chemical safety professionals and users.

Environment: The chemical is currently a low priority for further work due to its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-62-3
Chemical Name	n-valeraldehyde
Structural Formula	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH=O

SUMMARY CONCLUSIONS OF THE SIAR**Analog Justification**

As a group, aliphatic aldehydes have similar structures, reactivities, and effects (e.g., respiratory irritation). As a result, their data can be used to assess the potential toxicity of valeraldehyde. *In vitro* and *in vivo* studies have demonstrated that aliphatic aldehydes are oxidized to their respective acids. Valeraldehyde is metabolized to valeric acid. Following the metabolic series approach, studies investigating the toxicity of valeric acid are considered useful in evaluating the potential systemic toxicity of valeraldehyde. Data from the supporting chemicals propionaldehyde (CAS# 123-38-6), butyraldehyde (CAS# 123-72-8), isobutyraldehyde (CAS# 78-84-2) and isovaleraldehyde (CAS# 590-86-3) are used to support and address the data gaps for the mammalian endpoints.

Human Health

Data for valeraldehyde are available for acute toxicity, skin and eye irritation, as well as skin sensitization. The acute oral LD₅₀ value for male rats was 4590 mg/kg. The dermal LD₅₀ in male rabbits was 4865 mg/kg; necrosis was observed at the application site. There was 50 percent mortality among rats exposed to 4000 ppm (11600 mg/m³) valeraldehyde vapor for 4 hours. Valeraldehyde is a corrosive liquid. Valeraldehyde causes severe skin and eye irritation and necrosis. Animal studies show it to be an upper respiratory tract irritant but not a skin sensitizer.

There are no repeated-dose toxicity studies for n-valeraldehyde. Repeated-dose toxicity studies with other aldehydes (n-butyraldehyde, isobutyraldehyde and propionaldehyde) have demonstrated mortality and localized lesions in response to irritation as well as some effects on hematology and clinical chemistry; however, systemic effects have not been observed. A similar toxicity profile is expected for n-valeraldehyde. Thirteen-week rat and 14-week dog inhalation studies at **n-butyraldehyde** concentrations of 125, 500, and 2000 ppm (363, 1450, and 5800 mg/m³) resulted in nasal lesions at all doses with LOAECs of 125 ppm for both species. A subsequent 12-week rat study determined a NOAEC for **n-butyraldehyde** vapor in rats of 50 ppm (145 mg/m³, the highest dose tested). A 13-week gavage study with **n-butyraldehyde** in rats and mice at doses of 75, 150, 300, 600, and 1200 mg/kg bw/day resulted in nasal lesions at all doses and lesions of the stomach at 600 and 1200 mg/kg bw/day in rats. A dose-related increase in mortality was also observed in rats. In mice, treatment-related nasal lesions were noted at 300 mg/kg and above and mortality, stomach lesions, and decreased body weight gain were observed at 1200 mg/kg bw/day, resulting in a NOAEL of 150 mg/kg bw/day.

In a 103-week inhalation study with **isobutyraldehyde** vapor, rats and mice were exposed to 0, 500, 1000, or 2000 ppm (0, 1450, 2900, 5800 mg/m³). There was no treatment-related dose-dependent increase in the incidence of tumors in rats or mice. Non-neoplastic nasal lesions were significantly increased at all doses (females only at 500 ppm), resulting in a LOAEC of 500 ppm for rats. Survival of mice was reduced at 2000 ppm and mean body weights of females were reduced at 1000 and 2000 ppm. Degeneration of the olfactory epithelium was observed at the two highest doses in mice, for a NOAEC of 500 ppm in mice. A shorter (13-week) inhalation study in rats and mice using **isobutyraldehyde** vapor concentrations of 0, 500, 1000, 2000, 4000, and 8000 ppm (0, 1450, 2900, 5800, 11600, and 23200 mg/m³) resulted in mortality at 4000 and 8000 ppm in both species. Non-neoplastic lesions of the nasal

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cavity occurred at concentrations of 2000 ppm and greater in rats and 1000 ppm and greater in mice resulting in NOAECs of 1000 ppm and 500 ppm, respectively. Nasal lesions observed included necrosis, hyperplasia, squamous metaplasia, and olfactory epithelial degeneration.

In a combined repeated-dose toxicity study with reproduction and developmental toxicity screening test, rats were exposed to **propionaldehyde** vapor concentrations of 150, 750, and 1500 ppm (345, 1725, and 3450 mg/m³) via inhalation. Effects on the nasal epithelium were seen at all doses, including vacuolization in the low and intermediate dose groups and squamous metaplasia (in a few animals) and atrophy in the intermediate and high dose groups. Some effects on hematology (increased erythrocytes, hemoglobin and hematocrit values) and increased monocytes were observed at 1500 ppm. Increased kidney weights were also observed at the highest dose. The LOAEC is 150 ppm.

In vitro data on genetic toxicity are available for valeraldehyde and *in vivo* data are available for valeric acid. Valeraldehyde tested negative both in the presence and absence of a metabolic activation systems in several bacterial reverse mutation assays with several strains of *Salmonella typhimurium*. When tested in assays conducted in the absence of metabolic activation, valeraldehyde was positive in a mouse lymphoma assay and gene mutation assays in Chinese hamster V79 cells; it was negative in sister chromatid exchange assay in human lymphocytes. When tested in the presence of inherent or added metabolic activation, valeraldehyde was negative in a UDS (DNA repair) assay in human and rat hepatocytes and a mouse lymphoma gene mutation assay. Valeric acid, the “downstream” metabolite of valeraldehyde, did not result in increased micronuclei in an *in vivo* mouse micronucleus assay. These results show that valeraldehyde is genotoxic in some *in vitro* test systems in the absence of metabolic activation. However, negative results were obtained in those assays with inherent or added metabolic activation systems. Similar genotoxicity results were obtained for the structural analog, isobutyraldehyde. Isobutyraldehyde was negative in a two-year chronic inhalation bioassay in mice and rats; the only effects related to treatment were non-neoplastic degenerative lesions of the nasal olfactory epithelium. There is insufficient evidence to suggest that the chemical is mutagenic in humans.

Several studies with structurally similar aldehydes evaluated reproductive organs and one evaluated fertility. In a combined repeated-dose study with a reproduction/developmental toxicity screening test, no reproductive effects were observed in male and female rats exposed to 150, 750, or 1500 ppm (345, 1725, or 3450 mg/m³) **propionaldehyde** vapor resulting in a reproductive NOAEC of 1500 ppm. Male and female rats exposed to **isobutyraldehyde** concentrations up to 2000 ppm (5800 mg/m³) for 103 weeks had normal reproductive organs and tissues. Male and female rats exposed 0, 500, 1000, 2000, or 4000 ppm (1450, 2900, 5800, or 11600 mg/m³) **isobutyraldehyde** for 13 weeks had normal reproductive organs and tissues; no effect on sperm motility, density or morphology was observed in male rats exposed to 4000 and 2000 ppm, however motility was decreased at 500 and 1000 ppm. Significant mortality was observed in female rats at 4000 ppm, at which some differences in the relative time in different stages of estrous were observed in the surviving females. No effects were observed on vaginal cytology or average estrous cycle length. In the same study, male and female mice showed no reproductive effects.

Developmental toxicity data are available for propionaldehyde, isobutyraldehyde, and valeric acid. No external physical abnormalities were observed in neonates in the combined repeated-dose toxicity study with reproduction/developmental toxicity screening test using **propionaldehyde** vapor described above. However, pup body weight gain between lactation day 0 and 4 in the high dose group was slightly decreased resulting in a NOAEC of 750 ppm. The parental LOAEC was 150 ppm. Groups of pregnant female rats were exposed by inhalation to 0, 1000, 2500, or 4000 ppm (2900, 7250, or 11600 mg/m³) **isobutyraldehyde** vapor for 6 hr/day for ten consecutive days during gestational days (GD) 6 through 15. Maternal toxicity, as evidenced by a significant decrease in body weight gain, was observed in dams exposed to 2500 and 4000 ppm resulting in a maternal NOAEC of 1000 ppm. There was no effect on gestational or litter parameters; no embryofetal toxicity or fetal malformations were observed at any exposure level, resulting in a developmental NOAEC of 4000 ppm. A developmental toxicity study using **valeric acid** on groups of timed pregnant female rats by oral gavage during GD 6 through GD 15 at doses of 0, 50, 100, and 200 mg/kg bw/day resulted in severe maternal toxicity. Vocalization, rales, and dyspnea were noted in dams immediately after dosing of the material, and mortality occurred in all treatment groups (4% at 50 mg/kg, 13% at 100 mg/kg, and 42% at 200 mg/kg). Fetal body weights were reduced at all dose levels. Although maternal toxicity makes it difficult to interpret the significance of the results, the percent incidence of fetuses with small sternbrae or reduced ossification was statistically increased at all dose levels. No fetal malformations or other variations were observed.

Due to severe maternal toxicity a NOAEL couldn't be established for developmental toxicity.

The odor threshold for valeraldehyde (0.028 to 0.060 ppm) is well below the 8-hour TWA occupational exposure limit of 50 ppm established by ACGIH to prevent irritation. There are no human studies that evaluated the relationship between odor threshold and irritation.

Environment

The melting point of n-valeraldehyde is -91.5°C, the boiling point is 103°C, and the vapor pressure is 35 hPa at 20°C. The water solubility is 11,700 mg/L at 25°C. The photochemical removal of valeraldehyde, as mediated by hydroxyl radicals, occurs with a calculated half-life of 9.0 hours. Valeraldehyde is not anticipated to hydrolyze in water. Based on Level III fugacity modelling, and assuming all releases are to air and none to water or soil, it is estimated that the majority of valeraldehyde released into the environment will partition into air (93.4%), with a smaller amount into water (5.65%), soil (0.961%) and sediment (<0.1%). Valeraldehyde will volatilise readily from moving rivers, but only moderately from quiescent lakes and other surface water bodies (calculated volatilisation half-lives of 8.3 hours from a river and 5.4 days from a lake). Valeraldehyde is readily biodegradable under aerobic conditions. The octanol:water partitioning coefficient (log K_{ow}) for valeraldehyde ranges from 1.31 to 1.39 at 25°C (preferred value 1.38), and the estimated bioconcentration factors (BCF) range from 2.3 to 5.8 (preferred value 2.3). These data indicate that valeraldehyde has a low potential to bioaccumulate.

Data are available from valeraldehyde to address the acute aquatic toxicity endpoints. A GLP analytical study conducted according to OECD Guideline 203 with rainbow trout (*Oncorhynchus mykiss*) in a flow-through system demonstrated a 96-hr LC50 of 27.9 mg/L. Two additional flow-through studies with fathead minnows (*Pimephales promelas*) resulted in 96-hr LC50s of 12.4 mg/L and 13.4 mg/L. Two static studies that examined the toxicity of valeraldehyde to *Daphnia magna* resulted in 48-hr EC50s of 70.7 and > 100 mg/L for immobilization. A single 96-hr GLP study in algae conducted according to OECD Guideline 201 with *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capricornutum*) resulted in 72-hr and 96-hr EC50 values for growth inhibition of 32.4 mg/L and 42.2 mg/L, respectively; the 72- and 96-hr EC50 values for biomass (area under the curve) were 31.4 mg/L and 37.1 mg/L, respectively.

Exposure

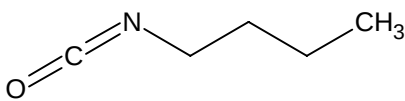
Valeraldehyde is used primarily as an industrial intermediate in the production of valeric acid and amyl alcohol. Reported minor uses include use in resin chemistry and to make rubber accelerators. Manufactured valeraldehyde does not appear intentionally in commercial or consumer products, although naturally-occurring valeraldehyde may be used as a flavoring agent in foods. Valeraldehyde has been identified as a naturally-occurring plant volatile and it has been detected in foods and beverages at low ppm concentrations. Consumption in 2006 is projected at 38,000 tonnes in the US, 32,000 tonnes in Western Europe, and approximately 100 tonnes in Japan in 2006. Valeraldehyde is a flammable liquid with a flammable range of 2.1 – 7.8 volume % in air (21,000 – 78,000 ppm) and a flash point of 5°C (41°F). In the US, due to its physical/chemical properties, valeraldehyde is manufactured in an enclosed, continuous process and stored in vapor-tight equipment under an atmosphere of oxygen-free nitrogen. Engineering controls and vapor collection systems are utilized during production, transfer, and loading operations to minimize flammability hazards as well as worker exposure. Workplace exposure during manufacture and use as industrial intermediate is also limited in the US by an occupational exposure limit of 50 ppm; the odor threshold for n-valeraldehyde (28-60 ppb) is well below the exposure limit and is expected to decrease the potential for significant worker exposure. Valeraldehyde may be released to the environment as a fugitive emission during production and use, or as naturally occurring emissions from vegetation, food products, and wood fires.

RECOMMENDATION 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 (skin, eye, respiratory irritation and potential reproductive/developmental effects based on data for analogous compounds). Based on data presented by the Sponsor country (relating to production in one country which accounts for 50-60% of the consumption in OECD countries and relating to the use pattern in several OECD countries), adequate risk management measures are being applied (engineering controls, occupational standards, Material Safety Data Sheets (MSDSs), and regulation as a food additive). Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment: The chemical has properties indicating a hazard for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However, the chemical is currently of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-36-4
Chemical Name	n-Butyl isocyanate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

n-Butyl isocyanate is a liquid with a high vapor pressure under ambient conditions, therefore the primary route of potential human exposure is inhalation (vapor saturation concentration (20 °C) = 81,546 mg/m³). Thus, the most relevant route of exposure for toxicity testing is via inhalation. In general, the toxicological effects observed resulting from inhalation exposure reveal a pattern characteristic of acute irritation and its sequelae. This mode of action for this class of compounds is wholly consistent with the chemical reactivity of the isocyanate functional group. Isocyanates will seek nucleophiles at the point of deposition, and the lung contains a relatively high level of non-protein sulfhydryls such as glutathione as well as proteins with accessible –SH, –OH, –NH and –COOH groups for interaction with isocyanate functional group. With this understanding of toxicological mode of action it is feasible that if the exposure concentration of n-butyl isocyanate is held below the threshold for respiratory tract irritation it is not expected that any systemic toxic effects would occur.

There are no reproductive, developmental, or *in vivo* genetic toxicity studies available for n-butyl isocyanate. However, since inhaled n-butyl isocyanate vapor would react primarily with lung tissue conducting studies to evaluate toxicity to systemic organ systems is not expected to yield useful information in assessing the human health hazard of n-butyl isocyanate. Any observed systemic effects may be secondary to direct effects on the respiratory tract.

No studies were found that presented data on toxicokinetics, metabolism and distribution.

After inhalation of isocyanate vapor, amine formation in the respiratory tract, if it occurs, is not expected to play a significant role rather the reactivity of the isocyanate group with nucleophilic groups located on the surfaces of the respiratory tract dominates. On the other hand, amine may occur to a significant extent after oral administration, i.e. in the acidic conditions prevalent in the stomach. The oral LD₅₀ was determined to be 360 mg/kg bw for rats. Toxic symptoms included apathy, stiff gait, and labored breathings. Acute inhalation toxicity studies revealed that n-butyl isocyanate is highly toxic when inhaled. The LC₅₀ (rat, 4h) value reported in a study according to OECD TG 403 with vapor inhalation is 59 mg/m³. Assessment of the acute inhalation toxicity data indicates that the primary toxic effects in response to exposure to evaporated n-butyl isocyanate are focused on the portal of entry, the respiratory tract. Thus death is due to severe respiratory tract lesions. Special investigations with male rats revealed overt inflammatory responses in the lung, which also could be confirmed histopathologically. The prominent microscopic changes were increased number of macrophages, perivascular round-cell infiltration, focal fibroproliferative reactions, emphysema, thickening septa, and abscessive pneumonia. Inflammation of the airways became prominent after exposure of a lethal concentration (50 mg/m³, 1x4h) and was marginally pronounced at a sublethal concentration (25 mg/m³, 1x4h)). No significant changes other than transient clinical signs were observed at 8 mg/m³. Ca. 3 mg/m³ were tolerated without any symptoms.

n-Butyl isocyanate is corrosive to skin and eyes of rabbits. The toxicity studies and one case report indicate that n-

butyl isocyanate vapor causes irritation of the respiratory tract. RD_{50} values for rat and mice of 40.4 mg/m^3 and 38.9 mg/m^3 , respectively, were determined and gave evidence for a moderate sensory irritation potential of n-butyl isocyanate. 1 mg/m^3 ($RD_{50} \times 0.03$) was regarded as the threshold for sensory irritation in humans. One study with guinea pigs provides evidence of a skin sensitizing potential of n-butyl isocyanate. No validated data regarding respiratory sensitization is available. Due to the well known reactivity of isocyanates respiratory sensitization is likely to occur.

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure. No subacute inhalation study according to OECD TG 412 is available. An exploratory subacute vapor inhalation study (1, 5, 15, 25 mg/m^3 , 5 x 6 hours/day) with male rats demonstrated obstructive and progressive lung disease (emphysema) at 25 mg/m^3 , which is considered to be the cause of delayed mortality. Repeated exposure of sublethal concentrations ($\leq 15 \text{ mg/m}^3$) did not lead to microscopic detectable adverse effects on the lung. Based on cageside observations and hypothermia a concentration of 5 mg/m^3 was tolerated without toxicologically significant effects. But changes in biochemical and cellular components in bronchoalveolar lavage fluid (BALF) gave evidence for inflammations of the airways at n-butyl isocyanate concentrations $\geq 5 \text{ mg/m}^3$. Thus the reported NOAEL is 1 mg/m^3 ; the LOAEL being 5 mg/m^3 which may be in excess of what is likely to be determined after inhalation during 28 days.

n-Butyl isocyanate did not induce gene mutations in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, and TA 100 with and without metabolic activation up to $5000 \text{ } \mu\text{g/plate}$ (OECD TG 471, 1983). The substance was genotoxic in the mouse lymphoma assay only in absence of a metabolic activation system. No differentiation between small and large colony mutants was performed in this test and therefore it cannot be concluded whether the positive result is attributable to gene mutations or chromosomal aberrations. However, the structural analogue methyl isocyanate is not mutagenic in bacteria, but gives consistently positive results in tests indicative for chromosomal aberrations *in vitro*. Therefore it is expected that the positive result in the mouse lymphoma assay with n-butyl isocyanate is based on chromosomal aberration. There are no genotoxicity studies *in vivo* available. Overall n-butyl isocyanate showed genotoxic potential *in vitro* and it is anticipated that it has the potential to be genotoxic *in vivo*.

There are no reproductive or developmental toxicity studies of n-butyl isocyanate available. No information with regard to reproductive organs is given in the 5-days inhalation study. Since inhaled n-butyl isocyanate vapor will react primarily with lung tissue so that other systemic organ systems or tissues would be affected only at exposure concentrations that produce sufficient lung toxicity. But the propensity of n-butyl isocyanate to cause lung effects consequently led to secondary effects such as hypoxia that could influence developmental endpoints. Therefore it is not expected to yield useful information from a reproductive or developmental toxicity study of n-butyl isocyanate vapor inhalation. Thus reproductive toxicity cannot be excluded, but it seems to be unlikely at non irritant n-butyl isocyanate exposure concentrations.

Environment

n-Butyl isocyanate is a colorless to yellowish, moisture/water sensitive liquid with a melting point of $-75 \text{ }^\circ\text{C}$ and a boiling point of $116 \text{ }^\circ\text{C}$ at 1013 hPa . n-Butyl isocyanate has a relative density of 0.88 g/cm^3 at $20 \text{ }^\circ\text{C}$ and a vapor pressure of ca. 25 hPa at $21 \text{ }^\circ\text{C}$. Measurements or calculations of water solubility for a substance rapidly hydrolyzing in water are not suitable. The flash point is $19 \text{ }^\circ\text{C}$ (closed cup), the ignition temperature is $425 \text{ }^\circ\text{C}$, and the viscosity is 0.04973 Pa at $20 \text{ }^\circ\text{C}$. n-Butyl isocyanate is highly flammable. n-Butyl isocyanate hydrolyzes completely in water within a few minutes at $20 \text{ }^\circ\text{C}$, forming n-butylamine.

The most important values of the degradation product n-butylamine (neutral form) concerning environmental behavior and ecotoxicology are a melting point of $-50 \text{ }^\circ\text{C}$, a vapor pressure of 127 hPa at $25 \text{ }^\circ\text{C}$, a $\log K_{OW}$ of 0.97 , and a water solubility of 202900 mg/l at $25 \text{ }^\circ\text{C}$.

In the atmosphere n-butyl isocyanate is degraded by photochemically produced OH radicals. The half-life is calculated to be about 4 days. For n-butylamine a half-life of 0.5 days is estimated.

A $DT_{90} < 1 \text{ d}$ was determined for n-butyl isocyanate in four different kinds of soil under different moisture and texture characteristics as well as different organic carbon content and pH conditions. After 4 days n-butyl isocyanate was completely removed. n-Butyl isocyanate and its degradation product n-butylamine are readily biodegradable. In an aquatic test on aerobic ready biodegradability conducted comparable to OECD TG 301D, 62 % biodegradation related

to ThOD was reported after 20 days for n-butyl isocyanate. For its degradation product, n-butylamine, 85 % biodegradation was observed after 14 days in a test system comparable to OECD TG 301C.

Due to the rapid hydrolysis of n-butyl isocyanate in water, the distribution of the hydrolysis product n-butylamine is calculated. With a pK_a of 10.77 at 20 °C, n-butylamine will exist predominantly in its protonated form in the environment. According to the Mackay fugacity model level I, the favorite target compartment of the protonated form of n-butylamine is water with 99.99 %.

The calculated Henry's Law constant for n-butyl isocyanate is 220 Pa m³/mol at 25 °C proving a high potential for volatilization from surface waters. Since n-butyl isocyanate hydrolyses rapidly in water, volatilization will not be an important fate process. Regarding the Henry's Law constant of 1.66×10^{-7} Pa m³/mole for the protonated form of n-butylamine, the substance is not expected to volatilize from water.

The bioconcentration factors (BCF) of 11 for n-butyl isocyanate and 3.2 for n-butylamine, calculated from the octanol-water partition coefficients as well as the measured BCF of 4.1 for n-butylamine in eggs of *Danio rerio* indicate that there is a low potential for bioaccumulation of n-butyl isocyanate and n-butylamine in aquatic organisms.

K_{OC} values were calculated with PCKOCWIN v. 1.66 (K_{OC} = 275 for n-butyl isocyanate, K_{OC} = 61 for n-butylamine, K_{OC} = 112 for n-butylammonium chloride). In addition, experimentally obtained adsorption coefficients (K_{OC}) revealed a low sorption potential of n-butylamine. The experimentally achieved K_{OC} values were in the range of 15 to 107 depending on soil properties. These results indicate a low sorption potential of n-butyl isocyanate and n-butylamine onto the organic phase of soils or sediments.

Concerning the toxicity of n-butyl isocyanate and its hydrolysis product n-butylamine towards aquatic species and bacteria, there are tests available with n-butylamine and these can be used to interpret the expected effects of n-butyl isocyanate. The lowest reliable effect values for aquatic species (based on nominal concentrations) with n-butylamine towards fish, *Daphnia*, and algae are:

Menidia beryllina: 96 h-LC₅₀ = 24 mg/l

Daphnia magna: 24 h-EC₅₀ = 43 mg/l

Microcystis aeruginosa: 8 d-EC₅₀ > 0.14 mg/l (biomass at test end)

(This test measured an EC₃ with a non standard organism.)

Based on a QSAR estimation with ECOSAR (aliphatic amines) for n-butylamine an EC₅₀ = 9.0 mg/l (96 h) is calculated for green algae.

For bacteria the lowest available toxicity value determined was a 16 h-EC₃ of 65 mg/l (*Pseudomonas putida*). For protozoa a 72 h-EC₅ of 8.8 mg/l (*Entosiphon sulcatum*) was determined. These effect values for microorganisms refer to nominal concentrations of n-butylamine, although toxicity data referring to n-butyl isocyanate are available, but in higher values.

Since there are acute test results available for the hydrolysis product n-butylamine, an assessment factor of 1000 was applied using the lowest available effect concentration (8 d-EC₅₀ of > 0.14 mg/l) which was obtained for *Microcystis aeruginosa*. Calculation yielded a PNEC_{aqua} > 0.14 µg/l. The expression of this value indicates the lowest toxicity threshold only. In this case, it will be appropriate to give the PNEC_{aqua} as a range. Regarding the lowest effect concentration of the other trophic levels, the lowest value for fish (*Menidia beryllina*) of 24 mg/l by applying an assessment factor of 1000, is taken into account. Thus, the PNEC_{aqua} is predicted to be PNEC_{aqua} > 0.14 µg/l < 24 µg/l. (Using the ECOSAR result the PNEC is 9.0 µg/l.)

Exposure

n-Butyl isocyanate is predominantly produced by reaction of phosgene with n-butylamine. The only EU production site is located in Germany, with an annual manufacturing volume of 1000 - 5000 metric tonnes, which is sold to customers world wide. Small quantities of n-butyl isocyanate are assumed to be manufactured in China. The global production volume of n-butyl isocyanate is estimated to be about 1000 - 5000 metric tonnes in 2004.

n-Butyl isocyanate is exclusively used as an intermediate in chemical processes, mainly in the synthesis of carbamate and urea insecticides and of fungicides, and to a small extent, for sulfonyl urea antidiabetic drugs and as a catalyst in the chemical industry. A direct use of n-butyl isocyanate is not known. Virtually all of the n-butyl isocyanate is converted into two fungicides: IPBC (3-Iodo-2-propynyl-butyl-carbamate, CAS 55406-53-6) and benomyl (1-

(butylcarbamoyl)-2-benzimidazol-methylcarbamate, CAS 17804-35-2), which is not permitted for use in the USA and in the EU (with the exception of Slovakia).

n-Butyl isocyanate is confidentially listed in the Danish Product Register as a product for industrial use in 2000, 2001, and 2002 (last years of record). It is not listed in the Finnish, Norwegian, Swedish and Swiss Product Registers. The main use category is "use in closed system".

From the manufacturing site of the Sponsor country virtually no n-butyl isocyanate (< 25 kg) was emitted into the environment in 2003. With a detection limit of 7 µg/l the hydrolysis product n-butylamine was not detectable in the effluent of the manufacturer's wastewater treatment plant. Due to the high vapor pressure of the substance, the most likely route of occupational exposure to n-butyl isocyanate is through inhalation. Dermal or oral exposure is unlikely to occur. At the manufacturer in the Sponsor country, exposure is controlled in occupational settings.

Pyrolytic n-butyl isocyanate was detected in smoke of building fires. Traces of pyrolytic n-butyl isocyanate were reported from smoked food and detected in the volatile flavor of fried bacon.

Overall, the exposure of consumers to n-butyl isocyanate is negligible.

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

Human Health: The chemical possesses properties indicating a hazard for human health (highly toxic to lung when inhaled, corrosive to skin and eye, moderately irritating to respiratory system, sensitization of skin and predicted to be a respiratory tract sensitizer because it is an isocyanate, potential for genotoxicity). Based on the data presented by the Sponsor country, exposure of workers in manufacturing in the only producer in the Sponsor country and of consumers is anticipated to be negligible. As no worker exposure data except from the producer in the Sponsor country is available, it is recommended to conduct an exposure and if indicated a risk assessment at the workplace apart from the production site. The chemical is a candidate for further work.

There are no reproductive, developmental, or *in vivo* genetic toxicity studies available for n-butyl isocyanate and the repeated dose study is limited to a 5 day exposure period with a major in lung toxicity. Because of the propensity for n-butyl isocyanate to produce portal-of-entry effects inhaled n-butyl isocyanate vapor would react primarily with lung tissue. Any observed systemic effects at irritant exposure concentrations may be secondary to direct effects on the respiratory tract. Furthermore, there is no evidence from acute and repeated exposure studies for "cumulative-dose" toxicity associated with n-butyl isocyanate. Thus conducting studies to evaluate toxicity to systemic organ systems is not expected to yield useful information in assessing the human health hazard of n-butyl isocyanate. Therefore for the purposes of satisfying SIDS testing requirements for hazard assessment it is concluded that no additional toxicity testing is necessary.

Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for 100 % of OECD production and relating to the use pattern in several OECD countries), emissions to the environment are anticipated to be low. 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	12070-12-1
Chemical Name	Tungsten Carbide
Structural Formula	WC

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

There is only limited information on the absorption, distribution and elimination of tungsten carbide available. Biomonitoring data of hard metal workers (exposed to various tungsten compounds, including tungsten carbide) as well as *in vitro* studies with human blood plasma and lung tissue cytosol, respectively, indicate that the bioavailability of inhaled tungsten carbide is comparatively low. Very low amounts of tungsten were found in the urine of 2 rats after single oral exposure to 2000 mg/kg bw of tungsten carbide.

The acute toxicity of tungsten carbide is very low. The LC₅₀ in rats is > 5300 mg/m³/4 hrs and the LD₅₀ after oral and the LD₅₀ after dermal application is > 2000 mg/kg bw, respectively. No clinical signs were observed in any of these studies. Intratracheal instillation produces only moderate acute inflammation and minimal prolonged reactions. Under *in vitro* conditions tungsten carbide showed a low toxicity towards alveolar type II cells from rats, and no cytotoxicity towards human alveolar type II cells.

Tungsten carbide was not irritating to the skin and eyes of rabbits (OECD TG 404 and 405) and not sensitizing in a guinea pig maximization test according to OECD TG 406.

Repeated inhalation of 15 mg/m³ tungsten carbide dust by rats caused chronic rhinitis and mild histopathological alterations in the lung consisting of focal reactions around the end airways. The changes were characterized by minimal to moderate alveolar wall thickening, type II cell hyperplasia and accumulations of pigmented macrophages. Mice exposed similarly to tungsten carbide tolerated the treatment without toxic symptoms except for rhinitis in females (LOEL, mice and rats, 13-weeks: 15 mg/m³ = lowest tested dose). Repeated intratracheal instillation of small doses of tungsten carbide to rats (10 mg/kg bw) yielded no alteration of bronchoalveolar lavage fluid composition and no histopathological changes in the lung except for the presence of fine black particles in alveolar macrophages.

Tungsten carbide was not mutagenic in the Ames test with and without metabolic activation. It has shown no evidence of clastogenic activity in cultured human lymphocytes in the absence of metabolic activation. There was, however, equivocal evidence of clastogenic activity with metabolic activation. *In vivo* data were not available.

There was no data available concerning the carcinogenicity of tungsten carbide.

There were no studies available which examined the effects of tungsten carbide on fertility and development. Based on histopathological examinations of reproductive organs and testis weights in subchronic inhalation studies of tungsten carbide dust in rats and mice there is no indication of a possible impairment of fertility by inhalative exposure to tungsten carbide dust. There are no studies available to assess the developmental toxicity of tungsten carbide. However, tungsten carbide has a very low bioavailability and has only minimal systemic effects, even if repeatedly administered to laboratory animals. There is, therefore, no indication that reproductive organs or the developing organism may be adversely affected by tungsten carbide.

This document may only be reproduced integrally. The conclusions and recommendations (and their rationale) in this document are intended to be mutually supportive, and should be understood and interpreted together.

Environment

Tungsten carbide is a grey metallic powder with a melting point of 2776 °C, and a boiling point of 6000 °C at 1013 hPa. The density is 15.63 g/cm³ at 18 °C. Based on the boiling point, the vapor pressure is expected to be extremely low. The solubility in water is < 0.0001 g/l at 20 °C. The substance is insoluble in water and dilute acids, but forms soluble salts in hot mixtures of HNO₃ and HF.

Photodegradation, the octanol-water coefficient, a possible bio- and geoaccumulation potential can not be calculated with the EPIWIN estimation program. Furthermore, also the distribution of tungsten carbide according to Mackay Level I cannot be estimated.

Due to the negligible vapor pressure of the substance, any processes of volatilization are unlikely to occur. In the ambient atmosphere, the substance will exist solely in the particulate phase and may be removed from the air by wet and dry deposition.

Due to the physical-chemical properties of tungsten carbide biodegradation and bioaccumulation of the substance are unlikely to occur.

Tungsten carbide exists in a hexagonal crystalline form as an uncharged solid substance and therefore no adsorption to suspended solids and sediment can be expected. Concerning the toxicity of tungsten carbide to aquatic species reliable acute experimental results of tests with fish, *Daphnia*, and algae are available. The tests were performed according to standard procedures and conducted with nominal concentrations high above the water solubility of tungsten carbide. The effect values from short-term tests are (n= nominal concentration):

<i>Danio rerio</i> :	96 h-LC ₅₀	> 1000 mg/l (n)
<i>Daphnia magna</i> :	48 h-EC ₅₀	> 1000 mg/l (n)
<i>Desmodesmus subspicatus</i> :	72 h-EC ₅₀ growth rate	> 1 mg/l (n)

Based on these data, tungsten carbide is not toxic to aquatic organisms at its water solubility.

Exposure

Tungsten carbide is manufactured by direct carburization of tungsten with carbon or by several other methods. In the Sponsor country, the only manufacturer has an annual manufacturing volume of 1000 - 5000 tonnes/a. The following production volume (tonnes/a) are estimated in 2004: Western Europe 13 000, Eastern Europe 1600, USA 5800, Japan 4500, China 13 000, others 1170; global about 39 000.

Tungsten carbide is used exclusively in industrial applications. About 90 % of the global manufacturing volume of tungsten carbide is used for sinter alloys ("hard metals") which are used in the manufacture of tools.

According to the Nordic Product Registers, tungsten carbide was used in 169 preparations in Denmark and Sweden with a tonnage of ca. 3000 tonnes/a in 2002. No consumer preparation is listed. For Finland and Norway there are confidential listings. Tungsten carbide is used as a raw material for the manufacture of metals, resulting in inclusion into or onto matrix. In the Swedish Product Register (2005), 25 products containing 20 - 80 % WC with a tonnage of 853 tonnes/a and 88 products containing 80 - 100 % WC with a tonnage of 3543 tonnes/a are registered currently. The most frequent use is "raw material for production of metals". The Swiss Product Register (2005) contains 12 commercial products with 10 - 80 % for galvanic purposes, but no consumer products.

From the manufacturing site of the Sponsor country virtually no tungsten carbide (< 25 kg) was emitted into the environment in 2004. Occupational exposure to tungsten carbide is most likely to occur through inhalation. At the manufacturer site in the Sponsor country, exposure is controlled.

In the air of several workplaces in the hard metal industry (including tungsten carbide manufacturing) tungsten and several other metals were detected. Tungsten was detected in urine, blood, lungs, hair, and nails of workers employed at these workplaces, but it was not clear in which form tungsten was taken up by these occupationally exposed individuals.

In the vicinity of a hard metal (cemented tungsten carbide) tool grinding factory elevated levels of tungsten (part of it in the form of hard metal) were detected due to poor waste management in this factory. No other data on environmental occurrence were identified. Consumer exposure to tungsten carbide is not likely to occur since all

tungsten carbide is used only in industrial applications which result in the inclusion into or onto a matrix.

**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 (indications for a clastogenic activity *in vitro*). While exposure of consumers is anticipated to be negligible, exposure to tungsten carbide occurs in occupational settings. The equivocal results in clastogenicity tests *in vitro* should be further investigated for clarification of possible human relevance.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	16090-02-1 56776-30-8
Chemical Name	Disodium 4,4'-bis[(4-anilino-6-morpholino-1,3,5-triazin-2-yl)amino]stilbene-2,2'-disulfonate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Rationale**

Fluorescent Brightener FWA-1 is a technical product which belongs to a group of stilbene type brighteners. As the active ingredient of C.I. Fluorescent Brightener 339 this compound is the most important member of this group of chemicals whose properties have been evaluated. The commercial forms of Fluorescent Brightener FWA-1 (CAS No. 16090-02-1) are granules/powders that may contain added salts or are aqueous slurries that contain small amounts of dispersants. Few tests are based on a commercial form that contains 82.5 % FWA-1, water, sodium chloride and sulfate.

Environmental fate or monitoring studies refer to the anionic form of FWA-1 due to the fact that the salt dissociates completely. Some toxicity tests have been performed with a surrogate (C.I. Fluorescent Brightener 220), that has identical structural characteristics but different substituents.

The compound is registered under the CAS Numbers 56776-30-8, with double bond geometry defined as (E). In dilute aqueous solutions, when irradiated with daylight, FWA-1 photo-isomerizes to a compound with double bond geometry defined as (Z). A further CAS Number is 60650-94-4 (no structure diagram available, referring to the names "C.I. Fluorescent Brightener 339" and "Tinopal AMS-GX"). The free acid is registered with the CAS Number 32466-46-9. There are two additional C.I. names for the compound with CAS-No. 16090-02-1: C.I. Fluorescent Brightener 71 is defined by this CAS-No., the CA Index Name. C.I. Fluorescent Brightener 71 replaces the generic name C.I. Fluorescent Brightener 260 which is discontinued.

All types of FWA-1 are based on the identical organic diamino stilbenedisulfonate (DAS) which determines the ecological and toxicological properties.

Human Health

After oral exposure, rats excreted FWA-1 almost completely in the feces within 48 hours. There was no measurable

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skin penetration of FWA-1 when topically applied in a detergent solution to rats. When applied at 0.43 mg/ml in ethanol, approximately 0.01 $\mu\text{g}/\text{cm}^2$ penetrated rat skin within 2 days.

The acute oral LD_{50} in rats was greater than 5000 mg/kg bw. Clinical signs were unspecific and included sedation, dyspnea, ruffled fur, and curved body position. The acute dermal LD_{50} in rats was greater than 2000 mg/kg bw. No systemic toxicity was observed after dermal exposure. No reliable studies were available on the acute inhalation toxicity of FWA-1.

FWA-1 was slightly irritating to the skin and eyes of rabbits. The chemical was not a skin sensitizer in animal studies or in human repeat insult patch tests.

No substance-related effects were found in a comprehensive oral 28-day study on rats up to and including the highest tested dose of 825 mg/kg bw/day (= No-Observed-Adverse-Effect-Level, NOAEL). The No-Observed-Effect-Level (NOEL) in a combined 2 year chronic toxicity / carcinogenicity feeding study was 1000 ppm (corresponding to 51 mg/kg bw/day for male animals and to 78 mg/kg bw/day for female animals) based on increased kidney weights. In the absence of histopathological kidney changes and in the absence of accompanying hematological or biochemical changes, the effects on kidney weights are considered treatment related but not toxicologically relevant. Therefore, 10 000 ppm (corresponding to 524 and 791 mg/kg bw/day for males and females, respectively) can be established as a NOAEL for the 2-year study.

FWA-1 was not mutagenic in several bacterial tests (Ames tests) with and without metabolic activation. The chemical did not induce structural chromosome aberrations in V79 Chinese hamster cells. No increase in micronuclei was induced by FWA-1 in a mouse bone marrow micronucleus assay.

No indication of a carcinogenic effect of FWA-1 was found, neither after dermal administration (3 times/week for one year, up to 30 μl , 0.01 %) to mice on irradiated skin, nor after chronic oral administration (24 months, up to 10 000 ppm = 524 mg/kg bw/day for males, 791 mg/kg bw/day for females) to rats, respectively.

In the absence of any valid reproductive or developmental toxicity studies with FWA-1, results from modern guideline studies with a structurally very similar compound (Fluorescent Brightener C.I. 220), as well as results from a pilot developmental study with the free acid form of FWA-1 were used to evaluate the reproductive and developmental toxicity.

With Fluorescent Brightener C.I. 220, the NOAEL for parental toxicity in a 2-generation study was at 300 mg/kg bw/day. At 1000 mg/kg bw/day (highest dose tested) an increase in kidney weight was observed; in the same study, the NOAEL for parental reproductive performance was established at 1000 mg/kg bw/day; for offspring growth and development, the NOAEL was also at 1000 mg/kg bw/day.

The developmental toxicity study with Fluorescent Brightener C.I. 220 on rabbits revealed NOAELs for maternal and developmental toxicity at 100 mg/kg bw/day each (LOAEL, maternal and developmental toxicity: 400 mg/kg bw/day, based on clinical signs and bloody intestinal contents in the dams, and reduced fetal weight). In a similar study, performed on rats, the NOELs for both maternal and developmental toxicity were 1000 mg/kg bw/day (highest dose tested). Pilot oral prenatal developmental toxicity studies on rabbits and on rats were performed with the free acid form of FWA-1 and resulted in maternal and developmental NOAELs of 1000 mg/kg bw/day (highest dose tested) for both species. Based on the available data, it can be concluded that the potential of FWA-1 to induce reproductive or developmental toxicity is probably very low.

Environment

FWA-1 is a yellowish solid compound with a melting point of 337°C and a relative density of 1.54 g/cm^3 at 22 °C. It has a water solubility of 1.9 g/l (at 20 °C and at pH = 10.5) and an extrapolated vapor pressure of $4 \cdot 10^{-18}$ hPa at 25 °C. The measured log K_{OW} is -1.58 (at 25 °C and at pH = 6.6).

In the atmosphere FWA-1 is degraded by photochemically produced OH radicals. The half-life is calculated to be about 1 hour. Due to the negligible vapor pressure this degradation process is not relevant. In natural water (Lake Greifensee, Switzerland) photodegradation half-life was measured as 4.1 – 5.1 hours. Under natural winter time

conditions, 70 % photolysis was calculated within 28 days for the same lake. FWA-1 is hydrolytically stable in water in the dark; the hydrolytic half-lives are more than one year.

Like many other FWAs also FWA-1 is not readily biodegradable. However, elimination by adsorption is significant as it was conducted in a Modified Zahn-Wellens Test (OECD TG 302 B) to a level of 98.8 % on day 28 and earlier.

In sewage treatment plants, adsorption onto sludge was observed up to a rate of 85 %, but no evidence was found for biodegradation during aerobic biological treatment and anaerobic-mesophilic digestion of sewage sludge.

The calculation of the distribution of FWA-1 between the environmental compartments according to the Mackay Fugacity Level I model and of the Henry's law constant does not seem appropriate as the substance is ionized under environmental conditions. From the physico-chemical properties (in specific a high water solubility and a low $\log K_{OW}$) it might be concluded that the sole target compartment for FWA-1 is water. However, as a high adsorption to soil was calculated, it might be assumed that the substance will strongly adsorb also to the sediment and soil compartment. K_{OC} values were calculated as $9.545 \cdot 10^9$ but might be overestimated. In an adsorption/desorption study according OECD TG 106 without distinguishing between isomers, K_{OC} values have been measured for three soil types: $K_{OC} = 1040$ l/kg sand, $K_{OC} = 860$ l/kg loamy sand and $K_{OC} = 2240$ l/kg sandy loam. All these values will lead to a high adsorption potential to soil, sediment and suspended solids.

The measured BCF values of 1.4 to 28 give no indication for a significant bioaccumulation potential.

Results on acute aquatic toxicity are available for fish (*Oryzias latipes* 48-hour LC_{50} : 50 mg/l; *Danio rerio*: 96-hour LC_{50} : 337 mg/l for the E-isomer; 14-day LC_{50} : 165 mg/l (geometric mean of the LC_0 and the LC_{100})), invertebrates (*Ceriodaphnia cf. dubia*; EC_{50} (48 hours): 6.9 mg/l; *Daphnia magna*; EC_{50} (24 hours): > 1000 mg/l), and algae (*Desmodesmus subspicatus*; EC_{50} (96 hours): 41.1 mg/l). In a chronic toxicity test on reproduction of the water flea *Daphnia magna*, the NOEC (21 days) was 0.8 mg/l, indicating potential to cause long-term adverse effects in the aquatic environment.

The toxicity of FWA-1 to micro-organisms and earthworms was determined to be low: the $L(E)C_{50}$ values were > 100 mg/l and > 1000 mg/kg dw, respectively.

According to the EU risk assessment procedure, a $PNEC_{aquatic}$ of 0.008 mg/l was obtained by applying an assessment factor of 100 on the lowest endpoint, the result of the chronic *Daphnia* test.

Exposure

There are several producers of FWA-1 in Europe and world-wide. The total production volume for FWA-1 is estimated by the European Commission to 10 000 – 50 000 tonnes/a in 1999. In the Sponsor country the annual production volume is in the range of 500 to 600 tonnes/a by only one producer.

The chemical is produced in a closed system. From the manufacturing site of the Sponsor Country releases into the atmosphere do not exceed legally limiting values (< 25 kg/a). Releases into the hydrosphere may occur during manufacture, formulation and processing as well as during widespread usage due to the relatively low removal efficiency in sewage treatment.

The total European usage was estimated to be approximately 2100 tonnes of active ingredient in 2001. More than 90 % of this brightener is used in household detergents in concentrations ranging from 0.05 to 0.35 %. It is also used to a far lesser extent (< 10 % in total) in textiles and paper. It is used also in combination with distyrylbiphenylsulfonate (DSBP)-type FWAs. FWA-1 behaves like colorless direct cotton dyes, i.e., during the washing process, FWA-1 penetrates the textile fibers by diffusing on the surface of the pore walls. Measurements have shown that up to 72 % of FWA-1 of the end-use concentration may be adsorbed on to the fiber.

FWA-1 can be found in water, sludge, sediment and soil.

The range of concentrations was 20 - 337 ng/l for 3 West-German rivers and 123 - 2097 ng/l for two East-German rivers.

In a monitoring program in Switzerland, the range of concentrations in rivers was 6 - 986.2 ng/l.

The maximum concentration in sediment cores of Lake Greifensee (Switzerland) were 1.2 mg FWA-1/kg sediment in the 1970's and leveled out at 0.7 mg/kg sediment from 1983 onward (no indication of wet or dry weight basis). The 90th percentile value is 1.597 mg/kg sediment.

A point of high concentrations is the river Rhine below the production site of FWA-1 with a 90th percentile of 740 ng/l and an average of 549 ng/l.

The seawater and freshwater monitoring of 16 sites in Tokyo Bay and adjacent rivers demonstrated that FWA-1 is

widely distributed in the riverine environments of Tokyo. Dissolved FWA-1 concentrations in the rivers were around 1 µg/l. The concentration ranges of FWA-1 detected in Tokyo Bay were 21.3 - 127.4 ng/l. At most stations the concentrations were several tens of ng/l.

Exposure of workers to FWA-1 may occur during manufacture, use, transport and disposal of FWA-1, mainly through the respiratory and dermal routes of exposure. Exposure of workers is controlled by personal protective equipment, local exhaust ventilation techniques and regular workplace surveys. FWA-1 is widely used in household detergents, with a maximum FWA-1 concentration in these products of ca. 0.35 %. The maximum total systemic exposure of consumers via direct or indirect skin contact, inhalation of detergent dust or via the oral route has been estimated to be about 0.23 mg/kg bw/day.

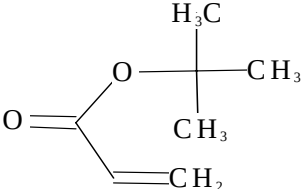
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work due to its low hazard profile.

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (chronic toxicity to daphnia). Therefore, an exposure assessment and, if then indicated, an environmental risk assessment is recommended.

Note: There is a HERA (Human and Environmental Risk Assessment) Report for FWA-1 available, produced by A.I.S.E. and Cefic in 2004 (<http://www.heraproject.com>).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1663-39-4
Chemical Name	Tert.-Butyl Acrylate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Tert. butyl acrylate was tested for relative rates of hydrolysis by a representative mammalian esterase (porcine hepatic esterase) *in vitro*. No hydrolysis to acrylic acid and the alcohol could be detected.

Animal studies with tert. butyl acrylate show an inhalation LC₅₀ (rat) of 7 mg/l/4 h; dermal LD₅₀ > 4000 mg/kg bw (rat) and ca. 2000 mg/kg (rabbit); and an oral LD₅₀ (rat) of ca. 1047 mg/kg bw. Some of the major clinical signs include rapid and irregular breathing, unsteady/spastic gait, tremors, decreased motility, convulsions (oral), and prone/abdominal or lateral position. Tert. butyl acrylate is slightly irritating to skin and eyes of rabbits. Guinea pig maximization and Freund's complete adjuvant tests showed a sensitizing effect. Based on the structural similarities to other acrylates a tert. butyl acrylate is suggested to be a sensitizer.

In a combined sub-chronic inhalation toxicity study with a reproduction /developmental toxicity screening test, rats were exposed to 20, 60 and 180 ppm (0.106, 0.319 and 0.956 mg/l) 6 hours/day and 5 days/week. The males were treated for approx. 13 weeks (10 weeks pre-mating, 3 weeks mating and post mating). In females treatment lasted from 10 weeks pre-mating, during mating and gestation through day 4 after delivery (approx. 15 weeks). Inhalation of 180 ppm (0.956 mg/l) tert.-butyl acrylate caused slight irritation of the eyes and upper respiratory tract, retarded body weight development, and mild impairment of renal function in the males. The test compound evoked significant systemic toxicity including mortality in pregnant and lactating female rats at this high dose level. Whereas the capability to cohabitate and to generate offspring were not affected in both genders at this concentration, the pre- and postnatal development of offspring was significantly impaired. The impaired postnatal development (lower weight gain and viability) of the offspring from the high dose group is probably secondary to the marked maternal systemic toxicity. The lower weight gain and the pup losses were the consequence of an insufficient maternal care in the dams with liveborn pups.

Local effects, systemic toxicity, impairment of fertility and pre- and postnatal toxicity were not observed at the lower concentrations. The NOAEC and LOAEC from this study is 60 ppm (0.319 mg/l) and 180 ppm (0.956 mg/l), respectively. The NOAEC for reproductive toxicity is 180 ppm (0.956 mg/L).

Tert. butyl acrylate was not mutagenic in the Ames test and not clastogenic *in vivo* in the mouse micronucleus test.

Environment

Tert Butyl acrylate has a melting point - 69°C, a boiling point 121 °C and the vapor pressure 22.66 hPa at 25.7 °C. The water solubility of tert. butyl acrylate is 2 g/L (25 °C) and specific gravity is 0.883g/cm³ at 20 °C. The measured log P_{ow} is 2.32. Tert butyl acrylate is photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 13.22 hours (calculated). The hydrolysis rate of tert. butyl acrylate is low at pH 7, the half-life is ca. 23.6 years and at pH 8 it is 2.4 years (calculated). Tert. butyl acrylate is not readily biodegradable.

Distribution modeling using Mackay Level I indicates that the main target compartment will be air (97.98 %) with smaller amounts partitioning into water (1.95 %) soil (0.0322 %), and sediment (0.0326 %). Also with Fugacity Model Level III, the air is the main target compartment, the results are: 75.3 % (air), 22.2 % (water), 2.4 % (soil) and 0.094 % (sediment). A BCF of 12.2 was determined, based on a log P_{ow} of 2.32, indicating a low bioaccumulation potential.

In acute aquatic toxicity studies, the key study is from a recalculated measured value, the LC₅₀ for fish (*Leuciscus idus*) is 1.6 mg/l. In aquatic invertebrates, the reported 48-h EC₅₀ (*Daphnia magna*) is 8.74 mg/l. In algae, (*Desmodesmus subspicatus*) the 72-hr EC₅₀ for growth rate and biomass are 14.6 and 7.21 mg/l, respectively. (SAR prediction for tert-butyl acrylate are as follows: 96 hr LC₅₀ for fish = 1.9 mg/L; 48 hr EC₅₀ for daphnia = 11.2 mg/L; and 96 hr EC₅₀ for green algae = 1.1 mg/L)

Exposure

Tert. butyl acrylate is a chemical intermediate, manufactured and processed to polymer within closed systems, therefore exposure to environment is expected to be low. In the U.S., production volume is approximately 226 tonnes according to the 2002 IUR (US EPA Inventory Update Rule). About 1000 –10000 tonnes are produced in Europe. Other production sites are in Asia with an expected production volume between 100 and 1000 tonnes. Workers exposure is adequately controlled (strict industrial hygiene controls, use of personal protective equipment) at production plants in the country of the lead company. Tert. butyl acrylate is mainly used to form homopolymers and copolymers. Since end-use consumer products contain only trace levels of acrylic acid and esters (≤ 10 ppm as a result of polymerization and manufacturing), the consumer exposure to acrylate monomers is estimated to be negligible.

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 (skin, eye, and upper respiratory tract irritation, sensitization, and developmental effects at high doses in rats). Based on data presented by the country of the lead manufacturer, 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 has properties indicating a hazard for environment (aquatic toxicity). However the chemical is of low priority for further work for the environment because of its low exposure potential as it is manufactured and processed to polymers in closed systems.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	17689-77-9
Chemical Name	Ethyltriacetoxysilane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

Ethyltriacetoxysilane undergoes rapid hydrolysis in moist/aqueous environments ($t_{1/2}$ is less than 13 seconds) to acetic acid and the corresponding trisilanol, thus observed toxicity is likely due primarily to acetic acid. Abiotic hydrolysis products of the test substance undergo continuous condensation reactions to produce higher molecular weight cyclic and linear siloxanes (the number-average and weight-average molecular weights were 633 and 809 with 22 area % of the chromatogram higher than 1000 molecular weight at the 1-hr reaction time; at the 4-hr reaction time, the number-average and weight-average molecular weights increased to 750 and 1085 with 38 area % of the chromatogram higher than 1000 molecular weight, respectively). The alkyl silanols condense to siloxane oligomers; this condensation of silanols is affected by both concentration and pH, and since both change over time it is not feasible to isolate specific silanols for analysis. While the hydrolysis of ethyltriacetoxysilane is rapid, the polymerization products, while not volatile, are in a molecular weight range small enough to be considered, at least in part, biologically available. The structural analogue methyltriacetoxysilane (CAS number 4253-34-3) has been used for in vitro bacterial gene mutation and chromosomal aberrations endpoints. The hydrolysis product, acetic acid (CAS number 64-19-7) and its salts [calcium acetate (CAS number 62-54-4), potassium acetate (CAS number 127-08-2) and sodium acetate (CAS number 127-09-3)], have been used to assess the acute aquatic toxicity (fish, aquatic invertebrate and algae), repeated dose toxicity, fertility and developmental toxicity endpoints. Acetic acid and its salts are grouped together because of their close structural relationships and the salts are the neutralized form of the acid that can be more easily administered, their natural occurrence in plants and animals, and their fundamental role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the citric acid or Krebs's cycle), which is where humans get their energy. In addition the structural analogue vinyltriacetoxysilane (CAS number 4130-08-9) has been used to support the acute aquatic toxicity endpoints. Data from both ethyltriacetoxysilane and vinyltriacetoxysilane are representative of acetic acid, based on the rapid hydrolysis of these materials.

Human Health

The acute toxicity of ethyltriacetoxysilane is described by an LD₅₀ rat (oral) = 1462 mg/kg. Clinical signs included decreased activity; lethargy; lacrimation; salivation; irregular gait; hunched posture; decreased body weight, food consumption and fecal volume; red urine; red staining of the snout, eyes and extremities; and labored respiration. Although acute toxicity data for the inhalation or dermal routes of exposure are not available for ethyltriacetoxysilane,

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these exposures will likely result in local site of contact effects from acetic acid. Ethyltriacetoxysilane is severely irritating and corrosive to the skin, is expected to be severely irritating to the eyes of animals, and is likely to be a respiratory irritant based on production of acetic acid following hydrolysis.

In a 7-day oral range-finding study (gavage) rats were treated with undiluted ethyltriacetoxysilane (dose levels of 0, 17 (males), 23 (females), 100, 500 and 1000 mg/kg/d). Ethyltriacetoxysilane rapidly hydrolyzes (in seconds) to acetic acid and a trisilanol (3:1). The silanol generated is insignificant in both quantity and toxicity relative to the production of acetic acid and its associated toxicity. Animals from the 17 (males), 23 (females) and 100 mg/kg/day dose groups survived to day 7. Animals from the 500 and 1000 mg/kg/day dose groups were sacrificed after the third dose as a consequence of two deaths (one from each group), marked body weight loss, and severity of lesions (ulceration and erosion of stomach and esophagus) observed in necropsied animals. The stomach lesions observed resembled irritation from acetic acid production. This 7-day range-finder study indicated that a maximum dose level of less than 20 mg/kg/day would be required for a longer duration repeated dose study in order to avoid death or obvious suffering due to the corrosivity of the hydrolysis product, acetic acid. Based on the findings of the 7-day range-finder, a longer duration study will present technical difficulty questioning dosing accuracy and a very low nominal systemic dose. Additional testing (repeated dose, reproductive effects or developmental toxicity) with ethyltriacetoxysilane has not been conducted. Toxicity is represented by an irritative mechanism following single or repeated dosing, likely due to production of acetic acid during hydrolysis. NOAELs following repeated exposure to acetic acid and its salts range from 210 mg/kg bw/day (2-4 month acetic acid drinking water study; systemic toxicity) to 3600 mg/kg bw/day (acetic acid, sodium salt, 4 week dietary study; no effects reported). Signs of irritation/corrosion at the site of contact as well as systemic toxicity have been reported. Prolonged inhalation exposure to acetic acid results in muscle imbalance, increase in blood cholinesterase activity, decreases in albumins and decreased growth at concentrations greater than 0.01 mg/m³/day.

Groups of 20 mice/sex were given 0.025% sodium acetate in the drinking water (about 60 mg/kg bw/day) for 1 week before breeding, during a 9-day breeding period and (females only) throughout pregnancy, lactation and until the offspring were weaned at 3 weeks of age. The male offspring were given the same solution until they were 5-7 weeks old and were then examined in a 24-hour activity test. No effects on fertility were observed. Examination of the litters revealed no overt deformities, and pup weights were normal at day 1 and day 21. The activity of offspring of the treated group was lower than that of controls during the first 12 hours but was similar during the second 12 hours. It is unknown if the decreased activity observed in the sodium acetate treated group was a result of exposure in utero and/or post-weaning, since the pups were exposed during both time periods. Acetic acid had no effects on implantation or on maternal or fetal survival in rats, mice or rabbits dosed via gavage on days 6-19 to doses up to 1600 mg/kg/day. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring in the controls. Sodium acetate had no effect on parents or offspring when mice were administered 1000 mg/kg bw, by gavage on days 8-12 of gestation.

In vitro, ethyltriacetoxysilane and methyltriacetoxysilane were negative in bacterial mutagenicity assays. Methyltriacetoxysilane did not induce chromosomal aberrations in CHO cells.

Environment

The melting point of ethyltriacetoxysilane is 8.4°C and the boiling point is 227 °C at 1013 hPa. The vapor pressure is 0.05 hPa at 20 deg C. The estimated water solubility of ethyltriacetoxysilane is 42 g/L; the estimated log Kow is 0.74. The water solubility and log Kow values may not be reliable because the chemical is hydrolytically unstable. The overall reaction half-life in air is estimated to be less than 3 minutes because of rapid hydrolysis of the material with moisture in the atmosphere. Photodegradation as a mode of removal is therefore unlikely because ethyltriacetoxysilane is hydrolytically unstable in this medium. In addition, photodegradation of the parent silane is not expected to be a significant degradation process in the aquatic environment due to the rapid rate of hydrolysis. Although, the vapor pressure indicates that ethyltriacetoxysilane resides in the atmosphere and may undergo photodegradation due to ozone and/or hydroxyl radicals, due to extremely rapid hydrolysis, the substance is not expected to reside in the air compartment and the vapor pressure of the substance may not be relevant.

Ethyltriacetoxysilane is hydrolytically unstable ($t_{1/2} < 13$ seconds) over a range of environmentally relevant pH and

temperature conditions. At pH 7, the half-life is = <13 seconds. Rapid hydrolysis of this material produces acetic acid and trisilanols.

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 = 47.3%; Soil = 47.4%; Water = 5.3%; Sediment = 0.0. However, ethyltriacetoxysilane is unlikely to be found in the environment, as this material is hydrolytically unstable. Ethyltriacetoxysilane is readily biodegradable; however this material rapidly hydrolyzes and generates 3 moles of acetic acid for every mole of parent material. Thus, the biodegradation observed is likely reflective of the hydrolysis product, acetic acid. The biodegradation rate for acetic acid after 14 days under aerobic conditions is 74%. Bioaccumulation is not anticipated since this material is hydrolytically unstable.

Ethyltriacetoxysilane undergoes rapid hydrolysis in aquatic media, and thus the exposures to ethyltriacetoxysilane are likely to be transient. Limited data are available for ethyltriacetoxysilane, therefore, data from a structural analog, vinyltriacetoxysilane, as well as the primary hydrolysis product, acetic acid are used to address the acute aquatic toxicity endpoints. The 96-hour LC50 of ethyltriacetoxysilane for *Brachydanio rerio* is 251 mg/L (the test media was not neutralized). Studies have been conducted on a structural analog, vinyltriacetoxysilane, as well as the primary hydrolysis product, acetic acid. The 96-hour LC50 of vinyltriacetoxysilane for *Oncorhynchus mykiss* is 51 mg/L and for *Lepomis macrochirus* is 68 mg/L (in both cases the test media was not neutralized).. The 72 hour LC50s for acetic acid are 75, 79-88 (pH $\leq$ 5.9) and 251 mg/L (several species of fish). The 48 hour EC50 for ethyltriacetoxysilane is 62 mg/L for *Daphnia magna*. The 48 hour EC50 of vinyltriacetoxysilane is 100 mg/L for *Daphnia magna* (the test media was not neutralized. Under static conditions, the 48 hour EC50 for acetic acid is 65 mg/L for aquatic invertebrates (the test media was not neutralized). When the test solutions are neutralized, the static EC50 for acetic acid is 6000 mg/L. In renewal systems with aquatic invertebrates, 48 hour EC50s for acetic acid are 100 mg/L and 180 mg/L. Ethyltriacetoxysilane toxicity to *Scenedesmus subspicatus* provided a 72 hour EC50 of 73 and 76 mg/L for biomass and growth rate, respectively (the test media was not neutralized). When results are expressed on the basis of the amount of acetic acid generated from the hydrolysis reaction, the toxicity of the parent material is comparable to the reported toxicity of acetic acid (EC₅₀ = 50-450 mg/L, depending on test species). Studies have been performed with a silanol monomer, trimethylsilanol (CAS No. 1066-40-6). Although this silanol is not expected to be produced following hydrolysis of methyltriacetoxysilane. A semistatic 96h study with trimethylsilanol and rainbow trout (*Oncorhynchus mykiss*) resulted in a No Observed Effect Concentration (NOEC) of 128 mg/L and an LC₅₀ of 271 mg/L.

Exposure

The commercial use of this material is almost exclusively as a cross linker for silicone sealants and adhesives. The final formulated sealant and adhesive is sold in consumer, industrial and construction markets. In production, this material is mostly handled in closed systems. Necessary engineering controls during production 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 pipe, drums, or tanks rather than in open systems to minimize loss of this material (through hydrolysis). Ethyltriacetoxysilane is transported from the production site as the parent silane to sealant formulators. The parent silane partially reacts during sealant formulation and then completely reacts during curing of the sealant into the polymer matrix and is no longer available for consumer or worker exposure. Ethyltriacetoxysilane does not volatilize during cure of sealants. Instead this material hydrolyzes and condenses, releasing acetic acid. Therefore, there is no human exposure to ethyltriacetoxysilane from use in silicones sealants. Generally, ethyltriacetoxysilane is used as a cross linker at 3% to 5%. As ethyltriacetoxysilane is compounded into a consumer or industrial sealant or adhesive, it reacts with the silicone. After curing the parent silane becomes crosslinked into the silicone rubber matrix and no longer exists, this greatly reduces the potential for consumer or worker exposure. Any toxicological effects of the silane are greatly reduced as a result of this crosslinking process. The production volume of ethyltriacetoxysilane in the sponsor country was 891 tonnes in 2001.

The reactive nature of this material destroys the parent material in any moisture-containing environment, thus limiting environmental exposure to the parent silane. In a spill situation, the parent material is hydrolyzed; the rapid hydrolysis means that the parent silane is unlikely to be found in the environment. If ethyltriacetoxysilane monomer is slowly released into the environment such that resulting concentrations of the parent compound are low, it is less

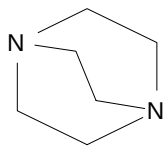
likely that polymerization will occur and more likely that free triol or short-chain oligomers will result. The spectrum of by-products will depend upon the initial concentration of the parent compound.

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

Human Health: The chemical possesses properties indicating a hazard for human health (severe irritation and corrosivity caused by acetic acid). Due to the extremely rapid hydrolysis to acetic acid and the corresponding trisilanol and based on exposure data presented by the Sponsor country, the parent material will not be available for exposure, and therefore this chemical is currently of low priority for further work. The identified hazards should nevertheless be noted by chemical safety professionals and users.

Environment: The chemical has properties indicating a hazard for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However the chemical is currently of low priority for further work for the environment because of its rapid hydrolysis and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	280-57-9
Chemical Name	1,4-Diazabicyclo[2.2.2]octane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Specific information on the metabolism of 1,4-diazabicyclo[2.2.2]octane is not available. Since tertiary amines are poor substrates for monoamine oxidase, 1,4-diazabicyclo[2.2.2]octane might presumably be metabolized via N-oxidation by a P450 monooxygenase, or via N-oxygenation by a flavin-containing monooxygenase.

1,4-Diazabicyclo[2.2.2]octane has an acute oral LD₅₀ range of 700 - 2260 mg/kg bw in rats, while the dermal LD₅₀ in rabbits is >2000 mg/kg bw. The acute inhalation LC₅₀ in rats is >20.2 mg/L nominal concentration (20% solution) (1 hour) or greater than the saturated vapor concentration (8 hour). In oral studies, at non-lethal doses transient depression and poor grooming were observed. At lethal doses, severe depression and ataxia rapidly progressed to coma and death within a few hours. In the dermal studies, severe erythema which disappeared within a few days was the only finding of note. In the inhalation studies, mild transient irritation of the eyes and mucous membranes and slight depression were the only notable findings. Pharmacologic effects particularly on blood pressure have been observed in cats and dogs when 1,4-diazabicyclo[2.2.2]octane is administered intravenously.

Skin and eye irritation studies in rabbits indicate that 1,4-diazabicyclo[2.2.2]octane is moderately irritating to the skin and is severely irritating to the eye. 1,4-diazabicyclo[2.2.2]octane is not a guinea pig skin sensitizer. In humans, glaucopsia (blue haze or halovision) has been reported at some foam manufacturing facilities and has been attributed to the presence of high concentrations of tertiary amines in the air. When sampling has been performed at properly ventilated foam manufacturing facilities, 1,4-diazabicyclo[2.2.2]octane concentrations are typically 1 ppm or less and no glaucopsia has been reported.

Rats were exposed via inhalation to aerosolized 1,4-diazabicyclo[2.2.2]octane 6 hours/day, 5 days/week for four weeks (20 exposures) at nominal concentrations of 0, 0.0058, 0.063 and 0.62 mg/L (analytical concentrations were 0, <0.011, 0.06 and 0.41 mg/L/6h/day). The low dose was below the analytical limit of detection (0.011 mg/L). The control animals were exposed to the vehicle (distilled water) only. One female in the high dose group died on day 5. The high-dose animals exhibited necrotic dermatitis of the ears, nose and eyes. Food consumption and body weight gain were decreased in the high-dose group. Histopathology revealed moderate chronic laryngitis in the mid- and high-dose groups. The female that died had severe acute necrotizing laryngitis. No compound-related effects were seen at the lowest dose level. Absolute and relative testes weights and relative adrenal weights (males) were statistically significantly increased at study termination; however, microscopic examination of these organs did not reveal any treatment-related effects. Since the lowest dose level could not be measured analytically, a NOAEC cannot

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be ascertained. However, the LOAEC for this study was 0.06 mg/L/6h/day and is based on local toxicity at the site of contact, namely, the upper respiratory tract.

1,4-Diazabicyclo[2.2.2]octane is not mutagenic in bacteria and was not clastogenic in an *in vivo* mouse micronucleus study.

In a combined repeated-dose/reproductive/developmental toxicity screening test, rats were exposed orally to 1,4-diazabicyclo[2.2.2]octane at dose levels of 0, 100, 300 and 1000 mg/kg bw/day for 28 days. Dosing solutions were administered by gavage at a dose volume of 5 ml/kg. The control group received the vehicle (deionized water) only. Oral administration of 1,4-diazabicyclo[2.2.2]octane resulted in parental (F₀) systemic toxicity in both males and females at a dose level of 1000 mg/kg bw/day. This was evidenced by changes in clinical condition of the animals, reduced body weight and food consumption, reduced motor activity (females only), increased serum alkaline phosphatase concentrations (females only), increased liver weights (females only) and microscopic changes (inflammatory and/or proliferative lesions) in the kidneys and/or urinary bladder. With the exception of lesions in the kidneys and urinary bladder of a single 1000 mg/kg bw/day group female, none of the above findings persisted to the end of the 14-day recovery period. F₀ systemic toxicity in the 300-mg/kg bw/day group was limited to chronic inflammation of the kidneys in the males. There were no indications of F₀ systemic toxicity in the 100 mg/kg bw/day group males and females.

Mating and fertility indices were not affected by 1,4-diazabicyclo[2.2.2]octane administration. Reproductive and F₁ neonatal toxicity were exhibited at 1000 mg/kg bw/day by increased resorptions, decreased live litter size, decreased postnatal pup survival and decreased pup body weights. No indications of neonatal toxicity were observed at 100 and 300 mg/kg bw/day. Based on the data obtained, the NOAELs (no-observed-adverse-effect-level) for F₀ reproductive toxicity and F₁ neonatal toxicity were 300 mg/kg bw/day. The NOAEL for F₀ male and female systemic toxicity were 100 and 300 mg/kg bw/day, respectively.

Environment

1,4-Diazabicyclo[2.2.2]octane is a hygroscopic white crystalline solid with a melting point of 158°C, boiling point of 174°C, and vapor pressure 0.6 to 0.68 hPa at 20°C. 1,4-Diazabicyclo[2.2.2]octane has a water solubility of 610 g/L, a calculated soil K_{oc} of 95, and its log K_{ow} ranges from -1.13 to -0.49.

Using a hydroxyl rate constant of 76×10^{-12} cm³/molecule.sec, the calculated half-life for indirect photolysis (reaction with hydroxyl radicals) of 1,4-diazabicyclo-[2.2.2]octane in air is 1.7 hours. Following equal releases to air, water and soil, the EPIWIN EQC Level III model predicts 1,4-diazabicyclo[2.2.2]octane to distribute in the environment to the aqueous (55.6%) and soil (43.6%) compartments. In water, hydrolysis and photodegradation are not expected to occur. 1,4-Diazabicyclo[2.2.2]octane is not readily biodegradable. Based on a log K_{ow} of -0.49, 1,4-diazabicyclo[2.2.2]octane has a calculated BCF of 3.2. A bioconcentration study conducted in carp determined the BCF of 1,4-diazabicyclo[2.2.2]octane to be < 13. Therefore, this chemical is not likely to bioaccumulate.

1,4-Diazabicyclo[2.2.2]octane produced EC/LC₅₀ values of >100 mg/L in short-term tests with fish, daphnids, and algae. The following aquatic effect /no effect concentrations are available:

Fish [Cyprinus carpio] LC₀ (96 hr) = 100 mg/L (96-h LC₅₀ >100 mg/L)

Invertebrates [Daphnia magna] EC₀ (48 hr) = 92 mg/L (48-h EC₅₀ >92 mg/L)

Algae [Selenastrum capricornutum (new name: *Pseudokirchneriella subcapitata*)] EC₅₀ (72 hr) = 110 mg/L (biomass); EC₅₀ (0-72 hr) = 180 mg/L (growth rate)

Exposure

1,4-Diazabicyclo[2.2.2]octane is used primarily as a catalyst in the production of polyurethane foam. Approximately 90% of the 1,4-diazabicyclo[2.2.2]octane produced is used for this purpose. 1,4-Diazabicyclo[2.2.2]octane is also used as a chemical intermediate and as an anti-fade reagent. The global market for 1,4-diazabicyclo[2.2.2]octane in 2004 was in the range of 1000 to 5000 tonnes.

Under normal conditions and following standard manufacturing practices, there are no air emissions or aqueous waste streams associated with the manufacture of 1,4-diazabicyclo[2.2.2]octane. Low levels of air emissions may occur as a result of spills and cleaning operations. Small amounts of 1,4-diazabicyclo[2.2.2]octane from spills and cleaning operations may be present in the discharge to the wastewater treatment plant.

Occupational exposure may occur via inhalation and skin contact during polyurethane foam production. 1,4-Diazabicyclo[2.2.2]octane is not consumed in this reaction. Much of the catalyst is trapped inside the cells of the foam. 1,4-Diazabicyclo[2.2.2]octane vapors are then released during certain foam production operations, such as, the foam crushing operation; foam removal from the mold; and during the finishing, trim and repair operations. Vapors are removed from the work area through process ventilation or through general exhaust ventilation. In humans, glauropsia (blue haze or halovision) has been reported at some foam manufacturing facilities and has been attributed to the presence of high concentrations of tertiary amines in the air. When sampling has been performed at properly ventilated foam manufacturing facilities, 1,4-diazabicyclo[2.2.2]octane concentrations are typically 1 ppm or less and no glauropsia has been reported. Currently no occupational exposure limit exists for 1,4-diazabicyclo[2.2.2]octane.

Even though polyurethane foam is used in a wide variety of consumer products, the 1,4-Diazabicyclo[2.2.2]octane that is remaining in the foam after the crushing process appears to be strongly bound into the foam. Attempts to remove 1,4-Diazabicyclo[2.2.2]octane from foam by heating or solvent extraction have not been successful. Only very polar solvents, such as methanol, are effective. Data are not available for exposure to consumers. However, based on the noted difficulty in removing it from foam, consumer exposure to 1,4-Diazabicyclo[2.2.2]octane is expected to be minimal.

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 (skin, eye, and upper respiratory tract irritation, and developmental effects in rats at high doses). Based on data presented by the Sponsor country (relating to production by two producers in two countries which account for an unknown fraction of the global production and relating to the use pattern in two OECD countries), 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: This chemical is currently of low priority for further work because of its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	4253-34-3
Chemical Name	Methyltriacetoxysilane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

Methyltriacetoxysilane undergoes rapid hydrolysis in moist/aqueous environments ($t_{1/2}$ is less than 12 seconds) to acetic acid and the corresponding trisilanols, thus observed toxicity is likely due primarily to acetic acid. Abiotic hydrolysis products of the test substance undergo continuous, condensation reactions to produce higher molecular weight cyclic and linear siloxanes (the number-average and weight-average molecular weights (MW) were determined to be 1247 and 6208, respectively, with 69% of the chromatogram represented by a MW range higher than 1000 at the 1-hr reaction time; at the 4-hr reaction time, the number-average and weight-average molecular weights increased to 1629 and 152600 with 77% of the chromatogram higher than 1000 molecular weight, respectively). The polymerization products are not volatile and are in a molecular weight range large enough to be considered biologically unavailable. The structural analogue, ethyltriacetoxysilane (CAS number 17689-77-9) and hydrolysis product, acetic acid (CAS number 64-19-7) [and its salts: calcium acetate (CAS number 62-54-4), potassium acetate (CAS number 127-08-2) and sodium acetate (CAS number 127-09-3)] have been used for assessing the biodegradation, acute aquatic toxicity (fish, aquatic invertebrate, and algae) and repeat dose toxicity endpoints. Acetic acid and its salts are grouped together because of their close structural relationships and the salts are the neutralized form of the acid that can be more easily administered, their natural occurrence in plants and animals, and their fundamental role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the citric acid or Krebs's cycle), which is where humans get their energy. Acetic acid and its salts have also been used to address the reproductive and developmental toxicity endpoints. In addition the structural analogue, vinyltriacetoxysilane (CAS number 4130-08-9) has been used for the acute aquatic toxicity endpoints. Data from both ethyltriacetoxysilane and vinyltriacetoxysilane are representative of acetic acid, based on the rapid hydrolysis of these materials

Human Health

The acute toxicity of methyltriacetoxysilane is described by LD50s in the rat (oral) of 1602 (neat) and 2850 (in corn oil vehicle) mg/kg bw. The clinical signs included decreased body weight and food consumption, labored breathing,

rales, red stains around the snout and extremities, salivation, lacrimation, lethargy, irregular gait, hunched posture, red urination, black/brown anogenital staining, paleness, chromodacryorrhea and hypothermia. Necropsy findings, mainly involving the stomach were stomach adhesions, thickened walls and abnormal stomach contents. Although acute toxicity data for the inhalation or dermal routes of exposure are not available for methyltriacetoxysilane, these exposures will likely result in local site of contact effects from acetic acid. Methyltriacetoxysilane is severely irritating and corrosive to the skin, and corrosive to the eyes of animals and is likely to be a respiratory irritant based on production of acetic acid following hydrolysis.

In a 7-day oral range-finding study (gavage) rats were treated with undiluted ethyltriacetoxysilane (dose levels of 0, 17 (males), 23 (females), 100, 500 and 1000 mg/kg/d). Ethyltriacetoxysilane rapidly hydrolyzes (in seconds) to acetic acid and a trisilanol (3:1). The silanol generated is insignificant in both quantity and toxicity relative to the production of acetic acid and its associated toxicity. Animals from the 17 (males), 23 (females) and 100 mg/kg/day dose groups survived to day 7. Animals from the 500 and 1000 mg/kg/day dose groups were sacrificed after the third dose as a consequence of two deaths (one from each group), marked body weight loss, and severity of lesions (ulceration and erosion of stomach and esophagus) observed in necropsied animals. The stomach lesions observed resembled irritation from acetic acid production. This 7-day range-finder study indicated that a maximum dose level of less than 17 (males) and 23 (females) mg/kg/day would be required for a longer duration repeated dose study in order to avoid death or obvious suffering due to the corrosivity of the hydrolysis product, acetic acid. NOAELs following repeated exposure to acetic acid and its salts range from 210 mg/kg bw/day (2-4 month acetic acid drinking water study; systemic toxicity) to 3600 mg/kg bw/day (acetic acid, sodium salt, 4 week dietary study; no effects reported). Signs of irritation/corrosion at the site of contact as well as systemic toxicity have been reported. Prolonged inhalation exposure to acetic acid results in muscle imbalance, increase in blood cholinesterase activity, decreases in albumins and decreased growth at concentrations greater than 0.01 mg/m³/day.

In vitro, methyltriacetoxysilane was negative in bacterial gene mutations assay and did not induce structural and numerical chromosome aberrations in CHO cells.

Groups of 20 mice/sex were given 0.025% sodium acetate in drinking water (about 60 mg/kg bw/day) for 1 week before breeding, during a 9-day breeding period and (females only) throughout pregnancy, lactation and until the offspring were weaned at 3 weeks of age. No effects on fertility were observed. The male offspring were given the same solution until they were 5-7 weeks old and were then examined in a 24-hour activity test. Examination of the litters revealed no overt deformities and normal pup weights at day 1 and day 21. The activity of offspring of the treated group was lower than that of controls during the first 12 hours but was similar during the second 12 hours. It is unknown if the decreased activity observed in the sodium acetate treated group to was a result of exposure in utero and/or post-weaning, since the pups were exposed during both time periods.). Acetic acid had no effects on implantation or on maternal or fetal survival in rats, mice or rabbits dosed via gavage during gestation days 6-19 at doses up to 1600 mg/kg/day. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring in the controls. Sodium acetate had no effect on pregnant mice or offspring when mice were administered 1000 mg/kg bw, by gavage on days 8-12 of gestation.

Environment

The melting point of methyltriacetoxysilane is 41°C and the boiling point is 220°C at 1013 hPa. The vapor pressure is 0.26 hPa at 20 deg C. The estimated water solubility of methyltriacetoxysilane is 91 g/L; the estimated log Kow is 0.25. The water solubility and log Kow values may not be reliable because the chemical is hydrolytically unstable. The atmospheric half-life based only on photodegradation (i.e., reaction with hydroxyl radical) is 58 days. The atmospheric half-life based on photodegradation and hydrolysis is <2 min. However, photodegradation as a mode of removal is unlikely because methyltriacetoxysilane is highly reactive and hydrolytically unstable, such that acetic acid and methylsilanetriol are rapidly generated upon contact with water or water vapor. Consequently, reaction with water vapor is likely the predominant degradation process for methyltriacetoxysilane in air. The vapor pressure indicates that methyltriacetoxysilane resides in the atmosphere and may undergo photodegradation due to ozone and/or hydroxyl radicals. Due to the very fast hydrolysis, the substance is not expected to reside in air and vapor pressure of the substance may not be relevant.

Methyltriacetoxysilane is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions. At pH 7, the half-life is $\approx$ <12 seconds. Rapid hydrolysis of this material produces acetic acid and trisilanols.

Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 1000 kg/h for each media, shows the following percent distribution: Air = 47.8%; Soil = 47.8%; Water = 4.3%; Sediment = 0.00%. However, methyltriacetoxysilane is unlikely to be found in the environment, as this material is hydrolytically unstable. Methyltriacetoxysilane is likely to be readily biodegradable based on results with a close structural analog, ethyltriacetoxysilane; however these materials rapidly hydrolyze and generate 3 moles of acetic acid for every mole of parent material. Thus, the biodegradation observed is likely reflective of the hydrolysis product, acetic acid. The biodegradation rate for acetic acid after 14 days under aerobic conditions is 74%. Bioaccumulation is not anticipated since this material is hydrolytically unstable.

Acute aquatic toxicity studies are available from two structural analogs, ethyltriacetoxysilane, and vinyltriacetoxysilane, as well as the primary hydrolysis product, acetic acid. The 96-hour LC₅₀ of ethyltriacetoxysilane for *Brachydanio rerio* is 251 mg/L (the test media was not neutralized). The 96-hour LC₅₀ of vinyltriacetoxysilane for *Oncorhynchus mykiss* is 51 mg/L and for *Lepomis macrochirus* is 68 mg/L (in both cases the test media was not neutralized). The 72 hour LC₅₀s for acetic acid are 75, 79-88 (pH $\leq$ 5.9) and 251 mg/L (several species of fish). The 48 hour EC₅₀ of ethyltriacetoxysilane is 62 mg/L for *Daphnia magna*. The 48 hour EC₅₀ of vinyltriacetoxysilane is 100 mg/L for *Daphnia magna* (the test media was not neutralized). Under static conditions, the 48 hour EC₅₀ value for acetic acid is 65 mg/L for aquatic invertebrates (the test media was not neutralized). When the test solutions are neutralized, the static 48 hour EC₅₀ for acetic acid is 6000 mg/L. In renewal systems with aquatic invertebrates, 48 hour EC₅₀s for acetic acid are 100 mg/L and 180 mg/L. Ethyltriacetoxysilane toxicity to *Scenedesmus subspicatus* provided a 72 hour EC₅₀ of 73 and 76 mg/L for biomass and growth rate, respectively (the test media was not neutralized). When results are expressed on the basis of the amount of acetic acid generated from the hydrolysis reaction, the toxicity of the parent material is comparable to the reported toxicity of acetic acid (EC₅₀ = 50-450 mg/L, depending on test species). Studies have been performed with a silanol monomer, trimethylsilanol (CAS No. 1066-40-6). Although this silanol is not expected to be produced following hydrolysis of methyltriacetoxysilane. A semistatic 96h study with trimethylsilanol and rainbow trout (*Oncorhynchus mykiss*) resulted in a No Observed Effect Concentration (NOEC) of 128 mg/L and an LC₅₀ of 271 mg/L.

Exposure

The commercial use of this material is almost exclusively as a cross linker for silicone sealants and adhesives. The final formulated sealant and adhesive is sold in consumer markets. In production, this material is mostly handled in closed systems. Necessary engineering controls during production 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 pipe, drums, or tanks rather than in open systems to minimize loss of this material (through hydrolysis). Methyltriacetoxysilane is transported from the production site as the parent silane to sealant formulators. The parent silane partially reacts during sealant formulation and then completely reacts during curing of the sealant into the polymer matrix and is no longer available for consumer or worker exposure. Methyltriacetoxysilane does not volatilize during cure of sealants. Instead this material hydrolyzes and condenses, releasing acetic acid. Therefore, there is no human exposure to methyltriacetoxysilane from use in silicones sealants. Generally, methyltriacetoxysilane is used as a cross linker at 3% to 5%. As methyltriacetoxysilane is compounded into a consumer or industrial sealant or adhesive, it reacts with the silicone. After curing the parent silane becomes cross linked into the silicone rubber matrix and no longer exists, this greatly reduces the potential for consumer or worker exposure. Any toxicological effects of the silane are greatly reduced as a result of this coupling process. The production volume of methyltriacetoxysilane in the sponsor country was 1389 tonnes in 2001.

The reactive nature of this material destroys the parent material in any moisture-containing environment, thus limiting environmental exposure to the parent silane. In a spill situation, the parent material is hydrolyzed; the rapid hydrolysis means that the parent silane is unlikely to be found in the environment. If methyltriacetoxysilane monomer is slowly released into the environment such that resulting concentrations of the parent compound are low, it is less likely that polymerization will occur and more likely that free triol or short-chain oligomers will result. The

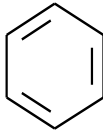
spectrum of by-products will depend upon the initial concentration of the parent compound.

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

Human Health: The chemical possesses properties indicating a hazard for human health (severe irritation and corrosivity caused by acetic acid). Due to the extremely rapid hydrolysis to acetic acid and the corresponding trisilanol and based on exposure data presented by the Sponsor country, the parent material will not be available for exposure, and therefore this chemical is currently of low priority for further work. The identified hazards should nevertheless be noted by chemical safety professionals and users

Environment: The chemical has properties indicating a hazard for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However the chemical is currently of low priority for further work for the environment because of its rapid hydrolysis and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	71-43-2
Chemical Name	Benzene
Structural formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

The toxicokinetics of benzene have been studied in both animals and humans. The key findings suggest that benzene is absorbed by all routes (inhalation, dermal and oral) with inhalation as the most important route of exposure. Benzene is rapidly distributed in the body and higher concentrations are found in fat and in lipid rich tissues compared to blood. After absorption via inhalation, the dermal or the oral route, most of benzene is metabolized and the metabolites are excreted after phase-II-conjugation mainly in the urine. Oxidative metabolism of benzene is a prerequisite to toxicity and follows similar pathways in humans and animals. The liver is the major site of benzene metabolism, but metabolism in the bone marrow may be associated with the haematotoxic and leukaemogenic effects of benzene.

There is considerable support for the idea that benzene works via a multiple metabolite type of mechanism, that not just one metabolite is responsible for benzene toxicity but multiple metabolites are involved. These multiple metabolites of benzene are capable of interacting to induce cytotoxic and cytogenetic responses particularly in bone marrow myeloid and stromal cells. There are apparent species differences in the rate of benzene metabolism, in V_{max} at higher exposure to benzene, and in the proportion of toxification (oxidative) versus detoxification (conjugation) metabolic pathways.

Acute oral toxicity for rats ranges from 810 mg/kg bw to 10000 mg/kg bw. Experiments using high numbers of rats suggest that the oral LD₅₀ is above 2000 mg/kg bw. Depending on the dose the main clinical signs are sedation and narcosis. Pathological findings include among others hyperaemic and haemorrhagic lungs, adrenals and spine. Acute inhalation toxicity is low with a LC₅₀ value of 44500 mg/m³ after a 4-hour exposure to female rats (OECD TG 403). Depression of the central nervous system appeared to be related to death. The main pathological findings were congestion of the lungs and liver. A dermal LD₅₀ value of >8260 mg/kg bw for rabbits and guinea pigs has been reported.

An oral uptake of about 15 ml benzene by humans (176 mg/kg bw) can cause collapse, bronchitis and pneumonia. The direct aspiration of liquid benzene into the lungs causes immediate pulmonary oedema and haemorrhage at the site of contact with the pulmonary tissue. Very high concentrations of benzene vapours produce narcotic effects and can lead to death by respiratory arrest. Fatal effects can occur after inhaling a benzene concentration of 65000 mg/m³ for 5-10 minutes. Exposure of 30 minutes to benzene concentrations of 25000 mg/m³ can be dangerous to life threatening. After inhalation exposure to 160-480 mg/m³ for 6 hours headache and lassitude occur while after inhalation of 80 mg/m³ for 6 hours no acute toxic effects were documented. The odor threshold is reported to be 4.8 mg/m³. In a report on three fatalities of acute benzene poisoning by acute dermal and inhalation exposure second degree chemical burns to face, trunk and limbs, haemorrhagic lungs and pulmonary oedema were documented. A relationship between chemical burns and death was not mentioned.

In a Draize test with rabbits according to OECD TG 404 benzene is irritant to the skin. Undiluted benzene caused serious damage to eyes. Inflammation and slight swelling of the eyelids, and questionable or just perceptible transient superficial necrosis of the cornea involving an area of less than 50% were documented. Airborne concentrations up to 972 mg/m³, as used in different inhalation studies, did not reveal local effects in the respiratory tract of mice. In humans, high concentrations of benzene vapour are irritant to mucous membranes of the eyes, nose and respiratory tract. Second

degree chemical burns of the face, trunk and limbs after acute benzene vapour poisoning are reported.

Data on animal tests on sensitization is not available. Furthermore no reports are available on skin sensitization or respiratory hypersensitivity for workers. That is expected taking into account the chemical structure of benzene..

Repeated inhalation exposure in mice using different exposure regimes was effective at concentrations from 32 mg/m³ benzene (LOAEC). No NOAEC could be derived.

The interaction of inhaled benzene with hematopoietic stem cells (multipotential hematopoietic stem cell CFU-S, granulocyte/macrophage progenitor cell CFU-GM), marrow and spleen cells was studied in three experiments using different exposure regimens and concentrations. Exposure of male CD-1 mice for 6 hr/d for 5 days to 3.5, 32, 320, 979, 1930, 4083, 7731, or 15558 mg/m³ showed that spleen weight, femoral and splenic cellularities (total number of nucleated cells, granulocytes, lymphocytes and nucleated red cells), total number of CFU-S in femur and spleen, and the number and concentration of splenic CFU-GM were significantly reduced at concentrations ≥ 320 mg/m³. In femur, absolute numbers of CFU-GM were marginally reduced at ≥ 320 mg/m³ and significantly at all higher doses, whereas the fraction of CFU-GM was increased to variable amount in most doses of ≥ 320 mg/m³ and higher. Exposure to 979 mg/m³ resulted in reduced concentration of splenic and marrow CFU-S. In peripheral blood, WBC, neutrophils and lymphocytes were depressed ≥ 320 mg/m³. RBC counts were depressed only at the two highest exposure levels.

A further experiment with exposure of CD-1 mice to 32 mg/m³ over 50 days (6 hr/d, 5 d/w) resulted in higher spleen weight, elevated splenic cellularity and increased number and concentration of CFU-S, but no changes in the CFU-S content of bone marrow were detected. CFU-GM were not evaluated in this experiment. No differences in the peripheral blood, bone marrow, or body weight were detected in exposed mice.

Exposure of CD-1 mice to 966 mg/m³ (6 hr/d, 5 d/w) for 26 weeks showed lower spleen weight, marked depression in marrow and spleen cellularity with depressed marrow and spleen CFU-S (total number and concentration) and marrow CFU-GM (total number and concentration) and spleen CFU-GM (total number). Marked changes in the peripheral blood included depressed WBC counts, RBC counts and percentages of lymphocytes, while the number of neutrophils appeared to be elevated.

In vivo and in vitro evaluations of hematopoiesis, specifically erythropoiesis, were performed with C57B1/6J male mice by exposure of 32 mg/m³ benzene (6 hr/d, 5 d/w) for up to 178 days. The numbers of circulating RBC and lymphocytes were significantly depressed in benzene-exposed mice. At 178 days, the exposed mice exhibited depressions in splenic nucleated cellularity and in splenic nucleated RBC numbers. Bone marrow cellularity and marrow-nucleated RBC counts were unaffected by the exposures. Benzene exposed mice showed a progressive decline in bone marrow and splenic colony-forming unit-erythroid (CFU-E) colonies during the exposure period, reaching 5% and 10%, respectively, of control values after 178 days.

Short-term inhalation exposure to 32, 99, 320, and 960 mg/m³ benzene vapour to male C57B1/6J mice on 6 days (6 hr/d) produced a depression of lymphocyte counts at all dose levels and at ≥ 320 mg/m³. Reduced numbers of B-lymphocytes in the femoral bone marrow and reduced T-lymphocytes in the spleen were also observed at ≥ 320 mg/m³.

In Sprague-Dawley rats exposure to benzene concentrations of 3.2, 32, 96 or 960 mg/m³ (6 hr/d, 5 d/w, whole body exposure) for up to 13 weeks (method similar to OECD TG 413) showed a decrease in WBC counts and percentage of lymphocytes at 960 mg/m³. The NOAEC for hematological effects on peripheral blood circulation is 96 mg/m³.

In NTP studies, B6C3F1 mice were evaluated for cumulative toxicity of benzene in 17 week and two-year studies. In the 17-week studies, mice of each sex were administered 0, 25, 50, 100, 200, 400 or 600 mg/kg bw/d benzene in corn oil by gavage. Mice receiving 100 mg/kg bw or higher showed lower final body weights. Dose-related leucopenia and lymphocytopenia were registered in male mice at ≥ 50 mg/kg bw and in female mice at ≥ 400 mg/kg bw. In the NTP cancer study, mice of each sex were administered to 0, 25, 50, or 100 mg/kg bw benzene by gavage (5 d/w) for 103 weeks. Weight gain reductions occurred in high dose males and females. Hematologic effects were limited to lymphocytopenia and associated leukocytopenia at all doses. Thus, the LOAEL in chronic oral studies

on mice was 25 mg/kg bw/d.

In a NTP study Fischer 344 rats were evaluated for cumulative toxicity of benzene in 17-week studies and two-year studies. In the 17-week study, rats were administered 0, 25, 50, 100, 200, 400 or 600 mg/kg benzene in corn oil by gavage. Final body weight was depressed in both sexes at doses of ≥ 200 mg/kg bw. Dose-related leucopenia and lymphocytopenia were observed in male rats at ≥ 200 mg/kg bw and in female rats at ≥ 25 mg/kg bw. In the spleen, lymphoid depletion of B-cells was evident in both sexes at ≥ 200 mg/kg, and increased extramedullary hematopoiesis was seen in male and female rats at 600 mg/kg bw/d. In the NTP cancer study male rats were administered to 0, 50, 100, or 200 mg/kg bw and female rats to 0, 25, 50, or 100 mg/kg bw benzene by gavage, 5 d/w for 103 weeks. Weight gain reductions occurred in mid and high dose males rats, and high dose female rats. Hematologic effects were limited to lymphocytopenia and associated leukocytopenia in all male rat groups; a similar but less pronounced response was observed in females during the same time period. Histopathology revealed increased incidences at all dose groups of lymphoid depletion in the spleen (male and female rats) and the thymus (male rats). The LOAEL in chronic oral studies on rats was 25 mg/kg bw/d for females and 50 mg/kg bw/d for males.

Besides of leukocytopenia and other effects on the lymphocyte cellularity several studies on the immune response revealed that benzene is suppressive on the cellular and humoral immunity of C57B1/6J mice at concentrations of 32 mg/m³ and higher (6 hr/d, 6 d, inhalation) or of CD-1 mice at doses of 40 and 180 mg/kg bw/d, given orally via drinking water for 4 weeks.

Related to the benzene effects on the bone marrow and peripheral blood the mouse seemed to be more sensitive than the rat. Several studies showed that benzene exposure resulted in disparate toxic responses among various strains of mice.

Chronic benzene exposure in humans leads to depression of white and red blood cells. This effect is reversible after long time exposures (years) with low concentrations (reported concentration range: > 32-64 mg/m³). Exposure to 192 mg/m³ of benzene for about one week may be associated with an increased proportion of large granular lymphocytes, and not severe narrow effects nor specific cytopenias. At higher concentrations, benzene may lead to aplastic anaemia which can be fatal. A review suggests a fatal outcome in 13% of the cases (as opposed to 85% for idiopathic aplastic anaemia).

The prevalence of leucopenia correlates with the exposure concentration of benzene. Drawn from these data, the LOAEC for leucopenia is in the range between 40 mg/m³ and 64 mg/m³. A higher prevalence for leucopenia is given at concentrations above 320 mg/m³. The LOAEC for red blood depression may be somewhat lower at 32 mg/m³. Thus, for blood cell depression an overall LOAEC is suggested to be 32 mg/m³.

Recent case control studies showed that the most sensitive reaction in humans to chronic benzene exposure is lymphopenia. A collective of workers exposed to benzene concentrations in a range between 3.2 mg/m³ and 100 mg/m³ had significantly reduced lymphocyte counts as compared to a cohort of non-exposed workers. A NOAEC for that effect of 3.2 mg/m³ is derived from these studies.

Benzene did not induce in vitro gene mutations in bacteria using standard Ames test conditions (OECD TG 471). Weakly positive effects were obtained when, in presence of S-9 mix, *S. typhimurium* strain TA 1535 was incubated with benzene in a desiccator to enhance exposure. Mammalian cell gene mutation tests carried out in various human, mouse and Chinese hamster cells according to OECD TG 476 resulted in mixed results. Treatment of human lymphocytes and various animal cells in vitro with benzene can lead to chromosomal aberrations and SCEs (OECD TG 473, OECD TG 479). However, mixed results have been obtained. Negative findings may be due to insufficient activities of benzene-activating enzymes.

Benzene is an in vivo mutagen in mammals, especially chromosomal aberrations and micronuclei are induced. After oral application the lowest dose with observed mutagenic effect was about 25 mg/kg bw for acute as well as for long-term exposure (micronucleus tests in mice according to OECD TG 474). According to one report a single low dose of 3.2 mg/m³ induced micronuclei in bone marrow cells of rats after inhalation exposure (OECD TG 474). However, in investigations on chromosomal aberrations in rats according OECD TG 475 positive effects were obtained only at concentrations of 320 mg/m³ and higher (single exposure) or 32 mg/m³ and higher (repeated exposure). In mice, the lowest effective concentration is reported to be 32 mg/m³ (micronuclei after single exposure).

Studies with intraperitoneal administration on mice showed that benzene has the potential for induction of transplacental genetic effects. Only few valid data on germ cell mutagenicity in mammals are available. In mice chromosomal aberrations are induced in spermatogonia by oral doses ranging from 220 to 880 mg/kg bw (OECD TG 483).

Concerning human data it is reported that benzene exposure induces genotoxic effects in human lymphocytes *in vivo*. A fully reliable conclusion, however, cannot be drawn due to poor exposure data and methodological insufficiencies. Therefore, it is not possible to deduce a dose-effect relationship. It is unlikely that exposure levels up to 64 mg/m³ induce observable genotoxic effects in humans.

Benzene induced neoplasms in both sexes of different strains of mice and rats on multiple sites by inhalation and oral administration. Target organs of benzene induced carcinogenic effects in animals included the haematopoietic system and a spectrum of tissues of epithelial origin indicating that benzene is a multipotential animal carcinogen. Lymphomas were induced in several mouse studies, however not all studies demonstrated clearly increased lymphatic tumour rates. Additionally, the tumour responses were not homogeneous in different mouse strains.

Inhalation exposure of male C57Bl/6J mice for about 70 weeks to 960 mg/m³ benzene (6 hr/d, 5 d/w) resulted in the development of malignant lymphomas. However, benzene exposure of male AKR/J mice to 320 mg/m³ for lifetime did not induce significantly lymphomas. In mice of each strain, exposure to benzene produced anemia and lymphocytopenia, but only in the 40 male C57Bl/6J mice neutrophilia, granulopoietic or myeloid bone marrow hyperplasia and in six males lymphocytic lymphoma with thymic involvement, one plasmacytoma, and one hemocytoblastic leukaemia was reported.

In the oral NTP study increased incidences of malignant lymphomas were reported in B6C3F1 mice given doses of 25, 50, or 100 mg/kg bw/d benzene in corn oil (5 d/w) for 103 weeks. Bone marrow hematopoietic hyperplasia was observed at increased incidences in dosed mice of each sex. The incidences of Zymbal gland carcinomas in mid and high dose male mice and in high dose female mice were greater than in controls. In the same dose groups, the incidences of epithelial hyperplasia of the Zymbal gland were also increased. Incidences of squamous cell papillomas or carcinomas (combined), hyperkeratosis, and epithelial hyperplasia of the forestomach were increased in some dosed groups of male and female mice.

Only few data existed which described the induction of myelogenous leukaemias. An increased rate of leukaemias without specification of the predominant cell type was found in RF/J mice treated with 500 mg/kg bw/d for 52 weeks.

No clear effect on the extent of lymphoma formation was observed in long term inhalation studies on pregnant Sprague-Dawley rats (13 week-old adults) with exposure from the twelfth day of pregnancy on to 650 mg/m³ for 7 weeks (4 hr/d, 5 d/w), then on 12 weeks to 640 mg/m³ for 7 hr/d, followed by 980 mg/m³ (7 hr/d, 5 d/w) for 85 weeks. The 12-day old offsprings were exposed to a similar treatment schedule; treatment was stopped after 104 weeks. Leucopenia mainly due to lymphocytopenia was evident in male and female offsprings following 104 weeks of exposure. At 150 weeks after study begin, benzene caused in animals treated for 104 weeks increased incidences of carcinomas of Zymbal gland, oral cavity, nasal cavity, skin, and forestomach and hepatomas.

Oral treatment of Fischer 344 rats for 2 years (NTP studies) with 50, 100, or 200 mg/kg bw/d (males) and 25, 50, or 100 mg/kg bw/d (females) increased the incidences of Zymbal gland carcinomas in mid and high dose male rats and in all females. Benzene was associated with increased incidences of neoplasms of the skin and oral cavity of rats. The incidences of squamous cell papillomas and squamous cell carcinomas of the skin in the high dose male rats were greater than in controls. Increased incidences of uncommon squamous cell papillomas or squamous cell carcinomas (combined) of the oral cavity were observed in dosed male and female rats. However, no increased incidence of tumours of the lymphatic system were observed in Fischer 344 rats, and no incidences in lymphomas were observed in Sprague-Dawley and Wistar rats (poorly documented, Maltoni, 1989).

Increased frequencies of leukaemia in comparison to controls were found in benzene exposed Sprague-Dawley rats and Wistar rats given orally 50 or 250 mg/kg bw/d for 52 weeks and 500 mg/kg bw/d for 104 weeks.

There is sufficient scientific evidence from the numerous human epidemiological studies to assume a causal relationship between benzene exposure and acute non-lymphatic leukaemia. It is unclear,

however, if there exists a threshold level of benzene exposure above which the risk of leukaemia significantly increases. Previous studies concluded that the leukaemic risk is increased at relatively low levels of benzene exposure. Using modeling techniques, which were based on revised estimates of the benzene exposures in the Pliofilm cohort with an update of the follow-up (until 1987) analyses assume a negligibly increased mortality attributable to benzene if the average exposure is $< 3.2 \text{ mg/m}^3$ over 40 years. From the recently published cohort study from exposed Chinese workers an elevated risk was shown for acute non-lymphocytic leukaemia and myelodysplastic syndrome at average benzene exposure levels of less than 32 mg/m^3 .

The data of the meta-analysis by Wong and Rabe (1995) have been used to define a NOAEC in misinterpreting the results as an indication that a benzene exposure related carcinogenic effect can be excluded at the mean exposure level ($700 \text{ } \mu\text{g/m}^3$) of the 19 different studies. However, the data do not allow to establish such a threshold level with the appropriate certainty.

The issue of linearity in the dose-response relation of benzene induced haematotoxicity and leukaemia was addressed by various publications. Especially for extrapolation to low doses, arguments have been presented for a non-linear, a sub-linear, and a supra-linear dose relationship. In addition, arguments have been presented for epigenetic factors responsible for leukaemia induction which lead to the suggestion of a threshold approach. Nevertheless, present knowledge is insufficient to support any quantitative deviation from the linear dose-response curve, at least from a regulatory point of view. Recent data support the view that the risk of developing acute myeloid leukaemia and chronic lymphocytic leukaemia (but not non-Hodgkins lymphoma or multiple myeloma) is increased at very low benzene exposure without clear cut-off concentration.

Inhalation studies with Sprague-Dawley rats ($32, 160, \text{ and } 1600 \text{ mg/m}^3$, day 6 to day 15 of gestation, 7 hr/d) showed that benzene may lead to fetal growth retardation as evidenced by decreased fetal body weight and body length, and/or skeletal variation including delayed ossification at 160 mg/m^3 and higher. A NOAEC developmental toxicity (no fetal growth retardation) of 32 mg/m^3 has been derived from this study on rats. The NOAEC maternal toxicity was 32 mg/m^3 . No specific embryotoxic and teratogenic potential could be revealed in further teratogenicity and developmental toxicity studies with rats, mice and rabbits. An available non-guideline fertility study in Sprague-Dawley rats is recognised from which it appears that female fertility is not affected at inhalation exposures (6 hr/d, 5 d/w) of up to and including 960 mg/m^3 , however, this study is not considered sufficient and adequate for overall assessment of an impairment of male/female fertility. Data from 90 day inhalation repeated dose toxicity studies ($3.2, 32, 96 \text{ and } 960 \text{ mg/m}^3$, 6 hr/d, 5 d/w) revealed some effects of benzene to the organs of the reproductive system in CD-1 mice (histomorphologic changes and decrease in mean testes weights) at 960 mg/m^3 (NOAEC 96 mg/m^3), but not in Sprague-Dawley rats. The significance of this finding in relation to possible impairment of fertility remains unclear, since adequate functional studies are not available. Since benzene is a germ cell mutagen and genotoxic carcinogen the substance has the potential to be toxic to reproduction. Therefore, further testing is not warranted.

Evidence from human data for an effect of benzene exposure on female reproduction is not sufficient to demonstrate a causal association due to poorly designed studies and inadequately quantified exposure to benzene as well as to other chemicals. Epidemiological studies in males on effects on fertility are not available. Likewise epidemiological studies implicating benzene as a developmental toxicant have many limitations thus not providing sufficient information to assess the effects on the human fetus.

Environment

Benzene is a clear colourless liquid with a melting point of 5.5°C and a boiling point of 80.1°C (at 1013 hPa). Benzene has a log Kow of 2.13, a water solubility of 1.8 g/l (at 25°C) and a vapour pressure of 99.7 hPa (at 20°C). With a Henry's law constant of $432 \text{ Pa m}^3 \text{ mol}^{-1}$ benzene is rapidly volatilized from aqueous solution and surfaces.

Benzene does not undergo hydrolysis or direct photolysis. It is classified as readily biodegradable in sewage treatment plants, the hydrosphere, sediments and soils. In the atmosphere benzene will be degraded by reaction with OH radicals with a half-life of 13.4 days.

Level III calculations show that benzene has the tendency to stay airborne, when released to air and to volatilise with a half-life of 11.5 d from water to air, when released into surface waters. According to this model the favourite target compartment of benzene is air with 99.0%, followed by water with 0.9%.

Bioaccumulation studies with fish show that benzene has a low bioaccumulation potential. BCFs

related to whole fish of 11 and < 10 were found.

For benzene short- and long-term studies with fish, daphnids and algae are available. Fish were the most sensitive species in both short- and long-term tests. The following results were found in long-term tests: *Pimephales promelas* (FELS): 32d-NOEC = 0.8 mg/l; *Ceriodaphnia dubia*: 7d-NOEC = 3 mg/l; *Selenastrum capricornutum*: 72h-EbC50 = 28 mg/l, 72h-EbC10 = 8.3 mg/l. All effect values are related to measured concentrations. With an assessment factor of 10 a PNEC of 0.08 mg/l was derived from the fish early-life-stage study.

The following results were found in short-term tests: *Oncorhynchus mykiss*: 96h-LC₅₀=5,3 mg/l; *Daphnia magna*: 48h-EC₅₀=10 mg/l;

Benzene seems not to be of concern for plants with regard to exposure via the atmosphere except at very high concentrations. No formal PNEC was established because of lack of appropriate long-term studies.

Exposure

In the European Union, 7,084 kt/a of pure benzene are produced and isolated as chemical intermediate. The worldwide production volume in 1995 was 22,300 kt. The most important secondary products manufactured from benzene in Western Europe in 1994 were ethylbenzene (52 %), cumene (20 %), cyclohexane (13 %), nitrobenzene (9 %), alkylbenzene (3 %), maleic anhydride (2 %) and chlorobenzene (1 %). Small quantities are also used as a laboratory reagent and solvent. Petroleum refinery streams containing benzene are blended with other petroleum streams to formulate petrol. This benzene used in petrol is in addition to the benzene of chemical intermediate production.

Benzene is released from a number of man-made sources. The primary sources of environmental benzene are automobile exhaust emissions, evaporative losses and refuelling emissions. Benzene in automotive exhaust is a mixture of incompletely burned benzene and benzene produced in the motor during combustion through dealkylation of toluene and xylenes. From industrial sources, it primarily enters the environment as fugitive emissions from industrial intermediate production and processing operations and through air emissions from waste water treatment plants.

Natural sources of benzene emissions such as volcanos and forest fires exist.

Benzene is used and emitted in large quantities. Because benzene is a volatile organic compound, it is mainly emitted to the air and emissions to soil and water partly lead to emission to the air. As a result most of the benzene is found in the air compartment.

Exposure of consumers to benzene may result from filling gasoline at filling stations and from use of contaminated paints and due to release from car interior accessories when driving a car. Inhalation is the dominant pathway for benzene exposure in humans, whereas oral and dermal exposure can be neglected. The following exposure estimates of benzene concentrations for consumers are available: filling gasoline (1.3 mg/m³), painting (0.017 mg/m³), and from car interior accessories 0.012 (1.3 mg/m³).

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 (repeated dose toxicity, mutagenicity, carcinogenicity, suspicion in reproductive toxicity) indicating a hazard to human health. Due to the widespread use of the substance leading to continuous exposure member countries are invited to perform an exposure assessment, and if necessary, a risk assessment for human health.

Note: A risk assessment to be performed in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union reveals concern for consumers due to mutagenic and carcinogenic properties of the substance.

Benzene exposure arising from handling gasoline is not formally a part of the EU risk assessment.

Regarding the very low benzene exposure from materials in new cars (interior accessories) further measurements are needed.

Occupational risk assessment revealed concern for all exposure scenarios at the workplace (risk reduction measures concerning benzene in gasoline should await a special risk assessment of gasoline).

Benzene will be easily absorbed after inhalation and skin contact. Mainly inhalation is the cause for relevant exposure levels. Internal body burdens after dermal exposure generally are low because of rapid evaporation of benzene. If, however, skin contact is prolonged either by inappropriate use of gloves or by repeated initial contacts, dermal exposure might become relevant concerning health risks at the workplace

From the toxicological point of view areas of concern are mutagenicity, carcinogenicity, repeated dose toxicity and reproductive toxicity. Several working scenarios give rise to concern under different aspects. In case of inhalative exposure levels below 1 ppm (3.2 mg/m³) or prolonged skin contact concern concentrates on the aspects of mutagenicity and carcinogenicity. In the light of these two endpoints it should be reflected whether the occupational exposure limit of 1 ppm, recently adapted in the EU, is considered to be sufficient to reduce the occupational risks. Furthermore measures to prevent prolonged skin contact appear indicated.

Environment:

The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (aquatic toxicity). Although the chemical is readily biodegradable and has a low potential for bioaccumulation, concern was identified in a risk assessment performed in the context of the EU Existing Substances Regulation (793/93/ECC) for industrial waste-water treatment plants and surface water receiving effluents from production sites. Other member countries are invited to perform an exposure assessment, and if necessary a risk assessment for the environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7758-89-6
Chemical Name	Copper monochloride
Structural Formula	$\text{Cu}^+ \text{Cl}^-$

SUMMARY CONCLUSIONS OF THE SIAR

Note: The current assessment focuses exclusively on copper monochloride and the results of tests performed with copper monochloride. This assessment should be considered as a contribution to an overall assessment of copper and copper compounds. The conclusions reached in this assessment only apply to copper monochloride, acknowledging that other test results with other copper compounds could lead to revisions of these conclusions.

Human Health

There are no reliable acute oral toxicity results available. In an acute dermal toxicity study (OECD TG 402), one group of 5 male rats and 5 groups of 5 female rats received doses of 1000, 1500 and 2000 mg/kg bw via dermal application for 24 hours. The LD₅₀ values of copper monochloride were 2,000 mg/kg bw or greater for male (no deaths observed) and 1,224 mg/kg bw for female. Four females died at both 1500 and 2000 mg/kg bw, and one at 1,000 mg/kg bw. Symptom of the hardness of skin, an exudation of hardness site, the formation of scar and reddish changes were observed on application sites in all treated animals. Skin inflammation and injury were also noted. In addition, a reddish or black urine was observed in females at 2,000, 1,500 and 1,000 mg/kg bw. Female rats appeared to be more sensitive than male based on mortality and clinical signs.

No reliable skin/eye irritation studies were available. The acute dermal study with copper monochloride suggests that it has a potential to cause skin irritation.

In repeated dose toxicity study performed according to OECD TG 422, copper monochloride was given orally (gavage) to Sprague-Dawley rats for 30 days to males and for 39 – 51 days to females at concentrations of 0, 1.3, 5.0, 20, and 80 mg/kg bw/day. The NOAEL value was 5 and 1.3 mg/kg bw/day for male and female rats, respectively. No deaths were observed in male rats. One treatment-related death was observed in female rats in the high dose group. Erythropoietic toxicity (anemia) was seen in both sexes at the 80 mg/kg bw/day. The frequency of squamous cell hyperplasia of the forestomach was increased in a dose-dependent manner in male and female rats at all treatment groups, and was statistically significant in males at doses of ≥ 20 mg/kg bw/day and in females at doses of ≥ 5 mg/kg bw/day doses. The observed effects are considered to be local, non-systemic effect on the forestomach which result from oral (gavage) administration of copper monochloride.

An *in vitro* genotoxicity study with copper monochloride showed negative results in a bacterial reverse mutation test with *Salmonella typhimurium* strains (TA 98, TA 100, TA 1535, and TA 1537) with and without S9 mix at concentrations of up to 1,000 µg/plate. An *in vitro* test for chromosome aberration in Chinese hamster lung (CHL) cells showed that copper monochloride induced structural and numerical aberrations at the concentration of 50, 70 and 100 µg/mL without S9 mix. In the presence of the metabolic activation system, significant increases of structural aberrations were observed at 50 and 70 µg/mL and significant increases of numerical aberrations were observed at 70 µg/mL. In an *in vivo* mammalian erythrocyte micronucleus assay, all animals dosed (15 - 60 mg/kg bw) with copper monochloride exhibited similar PCE/(PCE+NCE) ratios and MNPCE frequencies compared to those of the negative control animals. Therefore copper monochloride is not an *in vivo* mutagen.

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Concerning the carcinogenicity, there was insufficient information to evaluate the carcinogenic activity of copper monochloride.

In the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), copper monochloride was given orally (gavage) to Sprague-Dawley rats for 30 days to males and for 39 – 51 days to females at concentrations of 0, 1.3, 5.0, 20, and 80 mg/kg bw/day. The NOAEL of copper monochloride for fertility toxicity was 80 mg/kg bw/day for the parental animals. No treatment-related effects were observed on the reproductive organs and the fertility parameters assessed. For developmental toxicity the NOAEL was 20 mg/kg bw/day. Three of 120 pups appeared to have icterus at birth; 4 of 120 pups appeared runted at the highest dose tested (80 mg/kg bw/day).

Environment

Copper monochloride exists as a white crystalline powder or as cubic crystals. It is slightly soluble in water (47 mg/L at 20 °C). It has a density of 4.14 g/cm³ at 25 °C, a melting point of 430 °C and a boiling point of 1,400 °C. A vapour pressure is not assignable due to the high melting point. When considering inorganic copper species the partition coefficient in n-octanol/water is not applicable.

In the atmosphere, copper monochloride turns green and the substance turns blue to brown on exposure to light in the presence of moisture. The copper (I) ion is unstable in aqueous solution, tending to disproportionate to copper (II) and copper metal unless a stabilizing ligand is present. The copper (I) compounds stable in water are insoluble ones such as the sulfide, cyanide and fluoride. The fugacity based environment fate model is of limited use to inorganic substances.

The results from studies with aquatic organisms are as follows:

Fish (*Oryzias latipes*): LC₅₀ (96 h) = 0.039 mg/L

Invertebrates (*Daphnia magna*): EC₅₀ (48 h) = 0.25 mg/L

Green algae (*Pseudokirchneriella subcapitata*): E_rC₅₀ (72 h) = 0.058 mg/L

These toxicity values are based on total dissolved concentrations (copper chloride) which do not normalize for bioavailability influenced parameters. In natural environment, toxicity threshold of copper monochloride can be modified with variation of pH, water hardness and dissolved organic matter.

Exposure

In Korea the estimated production volume of copper monochloride was 8000, 6000, and 4000 tonnes/year in 2002, 2003, and 2004. In Denmark the estimated production volume of copper monochloride was 2.7 tonnes/year in 2003. Copper monochloride is produced by reaction of copper with chloride gas at 700 °C in a closed system. Copper monochloride occurs in nature as the mineral nantokite.

Copper monochloride has a wide variety of uses such as in the denitration of cellulose, in gas analysis to absorb carbon monoxide, as a catalyst for organic reactions, as a decolorizer and a desulfuring agent in petroleum industry, as a condensing agent for soaps, fats and oils, as a catalyst for manufacturing CO and H₂, and as a raw material for manufacturing coloring agents.

Korea has periodically collected the monitoring data of the treated sewage and the exhaust gas for copper concentration in the manufacturing process. The measured concentrations of copper in the treated sewage and the exhaust gas were not detected and 4 mg/m³ respectively, which were below the effluent and emission standard of 3 mg/L and 10 mg/m³ in Korea.

In the production and processing facilities of Korea, workers might be exposed to copper monochloride dust by inhalation during putting or packaging the raw material. Occupational exposure is controlled with personal protective equipments such as dust masks, gloves and protective clothing and with ventilation. The 8hr-TWA concentrations of dust at the workplace in copper monochloride and dye manufacturing factories ranged from 0.5 to 0.9 mg/m³, in case

of copper ranging from N.D. to 0.0007 mg/m³.

Copper monochloride is used as a raw material for coloring agents such as copper phthalocyanine blue crude, the C.I. No. Acid Blue 62, 40 and the C.I. Reactive Blue 19 and a catalyst for manufacturing CO and H₂ in Korea and consumer exposure is not expected in the Sponsor country.

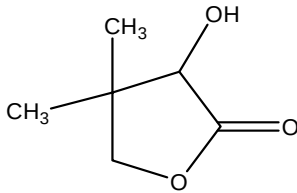
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: This chemical is currently a low priority for further work. The chemical possesses properties indicating hazards for human health (acute toxicity, repeated dose toxicity, uncertainty regarding developmental toxicity). Based on the data presented by the Sponsor country (relating to production in one country which accounts for an unknown fraction of the global production and relating to the use pattern in one country), the exposure is low at the workplace. There is no consumer exposure to copper monochloride in the Sponsor country. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: This chemical is a candidate for further work. The chemical possesses properties indicating hazards for environment (acute aquatic toxicity). Based on the use pattern of this chemical, member countries are invited to perform an exposure assessment and if necessary a risk assessment for this compound.

Consideration should be given to the assessment of other copper compounds in the OECD HPV Chemicals Programme.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-50-5
Chemical Name	2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl (DL-lactone)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

There is no information on the toxicokinetics of DL-lactone available.

The acute oral LD₅₀ of DL-lactone in rats and mice is above 2000 mg/kg bw.

In a test with rabbits (OECD 404) DL-Lactone was not irritating to the skin. However, based on occupational exposure experience in humans, DL-lactone is expected to be irritating to the eyes and upon prolonged and intensive exposure also to the skin. No sensitisation potential is found in the guinea-pig maximisation test (OECD 406).

In a combined repeated dose reproduction/developmental toxicity screening study (OECD 422) female rats treated at an oral dose of 1000 mg/kg bw/day showed aggression and restlessness during part of the study period. Findings on body weight, food consumption, haematology, clinical chemistry, organ weights, macroscopy and histopathology were within normal ranges. The NOAEL for repeated dose toxicity was set at 200 mg/kg bw/day.

DL-lactone was negative in an Ames test (OECD 471) and an *in vivo* micronucleus test (OECD 474). There are no indications that DL-lactone possesses mutagenic properties.

In an OECD 422 repeated dose reproduction/developmental toxicity screening study with rats exposed to DL-lactone, no effects on reproductive performance, stage of spermatogenesis, pup mortality, weight, sex and viability were reported up to oral doses of 1000 mg/kg bw/day. Animals were dosed prior to and during mating, gestation and following gestation until lactation day 4. Based on the available data, DL-lactone does not show evidence of reproductive or developmental toxicity. The NOAEL for reproductive toxicity is ≥ 1000 mg/kg bw/day.

Environment

DL-lactone is a white crystalline powder with a melting point of 78°C, boiling point of 247°C and a vapour pressure of about 0.1 hPa at 25°C (calculated from experimental vapour pressure at 60°C). The substance is very soluble in water (> 500 g/l) and has a log Kow of -0.69 (OECD 107). Based on its pKa (>13) DL-lactone is most likely present in the unionised form under environmental conditions. The substance is readily biodegradable. Hydrolysis half-life for DL-lactone is expected to be one year at pH 4, 30 days at pH 7 and approximately 12 days at pH 9 (25°C).

Various model calculations (based on log Kow) indicate that DL-Lactone does not bioaccumulate in fish and/or

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worms.

DL-lactone has an LC_{50} of >140 mg/L in fish, an EC_{50} of >130 mg/L in daphnia and an EC_{50} for biomass and growth rate of >78 mg/L (nominal 100 mg/L) in algae. Data on the toxicity towards micro-organisms of the d-isomer are indicative of an EC_{50} for micro-organisms above 100 mg/L.

Exposure

For the year 2004 the global market for DL-lactone was estimated to be 1000-5000 tonnes. DL-lactone is used in the synthesis of cosmetics and pharmaceuticals. At the production site of the main producer in UK DL-lactone is further processed on-site in closed systems in the synthesis of Calcium D-Pantothenate. Only a small amount (<0.5%) is isolated and sold to a third party. According to the product registers in Nordic Countries (Norway, Sweden and Denmark) and in Switzerland DL-lactone is not used in industrial and consumer products.

Occupational exposure may occur during synthesis, mainly through completion of process sampling and potentially during drumming-off operations.

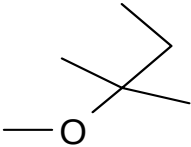
Based on a production mass balance at the manufacturing plant of the main producer in UK for the year 2004, a maximum of 0.4 % of the total produced DL-lactone is lost to the waste water and a maximum of 0.75 % to the distillation residues which are incinerated. Waste water is treated in an on-site wastewater treatment plant. Since DL-lactone is readily biodegradable releases to surface water with effluents will be low.

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 (skin and eye irritation). These hazards do not warrant further work as they are related to reversible effects. They should nevertheless be noted by chemical safety professionals and users.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	994-05-8
Chemical Name	2-Methoxy-2-methylbutane (TAME)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

TAME is absorbed efficiently from the rat intestine. TAME is rapidly absorbed from lungs; the respiration net uptake is 40 %. Studies with *tert*-methyl butyl ether (MTBE) suggest one third or less of a dermal TAME dose is absorbed. In rats, TAME is distributed evenly in the body. Urine is the main route of elimination. Based on human volunteer studies, the half-lives in blood varied between 1.2 and 6.3 hours. The main urine metabolites are 2-methyl-2,3-butanediol, 2-hydroxy-2-methylbutyric acid and 3-hydroxy-3-methylbutyric acid. Free and conjugated TAA (*tert*-amyl alcohol) and TAME were only minor metabolites in urine.

The acute toxicity of TAME is not high. The LC50 value via inhalation is over 5.3 mg/l. The predicted oral LD50 was for females 1602 mg/kg, males 2417 mg/kg and combined 2152 mg/kg. Although no dermal studies were available, toxicity via skin is not likely to be higher than via oral route. TAME is not irritating to skin or eyes or sensitizing.

The toxicity caused by TAME in repeated exposures is not severe. A NOAEC of 250 ppm (1060 mg/m³) is selected for respiratory exposure based on the organ weight increases of liver, adrenals and kidneys seen in a 90 day study in F-344 rat with both sexes. Via oral route, a LOAEL of 125 mg/kg was established based on the adrenal weight increase in the male rats.

TAME did not cause point mutations in bacterial assays or in Chinese hamster ovary cell. In Chinese hamster ovary cells *in vitro*, TAME caused a clear dose-related increase of chromosome aberrations, which increased when metabolic activation was present. However, a micronucleus study conducted in mice was negative at all sampling times. In the light of present data, TAME cannot be considered mutagenic. No reliable carcinogenicity studies were available

In a 2-generation reproductive study, TAME was not toxic to reproduction in rat (NOAEC of 3000 ppm (12720 mg/m³)). In the same study, NOAEC of 250 ppm was found for offspring toxicity and for adult systemic toxicity. In a developmental toxicity study with rats, the only noted effect was foetal weight reduction at 3500 ppm. From a developmental toxicity study with mice, a NOAEC of 250 ppm (1063 mg/m³) was selected for developmental effects based on malformations (cleft palate) seen at 1500 ppm and 3500 ppm. It is plausible that cleft palates are a secondary effect related to anesthesia and/or maternal stress. Taking into consideration that the cleft palates were seen only at very high TAME concentrations, and because there were no adverse developmental effects seen in rats, the effect noted in mice is not likely to be of consequence to humans.

Environment

TAME is a volatile (vp. 90 hPa at 20 °C) liquid which is hydrolytically stable and moderately soluble in water (11 g/l at 20 °C). Static equilibrium partitioning between environmental compartments at 20 °C is as follows: air 95.6, water 4.25, sediment 0.001 and soil 0.038 (EQC ver1.1). TAME is very mobile in soil and may easily leach to groundwater (transported with water). TAME is easily volatilized into the atmosphere from top soil and surface water.

Photodegradation in the atmosphere is the primary route of removal in the environment and degradation half-life $t_{1/2}$ is ca. 3 – 5 days. Biodegradation in soil, sediment, surface- and groundwater is very slow and TAME may be regarded persistent in these compartments. However, in industrial waste water sewage treatment plants having continuous TAME exposure, adapted microbial population capable of effectively degrading TAME may exist.

It is unlikely that TAME would bioconcentrate in high extent or would accumulate in biota for long time periods. The measured log Kow is 1.55 and the calculated BCF in fish is 4.

The lowest valid aquatic acute and (one) chronic toxicity test results for fish (1), daphnids (2), algae (3) and bacteria (4) are below. Terrestrial toxicity results are not available.

(1): *Oncorhynchus mykiss*: 96h-LC50 = 580 mg/l

(2): *Daphnia magna*: 48h-EC50 = 100 mg/l and *Americamysis bahia*: 96h-LC50 = 14 mg/l, 28-day NOEC = 3.4 mg/l

(3): *Pseudokirchneriella subcapitata*: 72h-EbC50 = 230 mg/l; 72h-ErC50 = 780 mg/l; 72h-NOEC = 77 mg/l

(4): *Pseudomonas putida*, cell multiplication inhibition test: 16h-EC10 = 25 mg/l; 16h-EC50 580 mg/l

The aquatic PNEC is 0.068 mg/l based on the *Americamysis bahia* chronic test result (AF=50) and the PNEC for intermittent release is 1.4 mg/l (AF=10). The PNEC for micro-organism is 25 mg/l (AF=1). The terrestrial PNEC is 0.035 mg/kg ww calculated from the aquatic PNEC using the equilibrium partitioning method.

Exposure

TAME is a high exposure potential chemical used as a gasoline component/additive worldwide in blending rates from < 1% to > 10% vol. Annual consumption volume in EU region is ca. 300 000 t/a (in 2003). TAME has minor use as an intermediate in chemicals industry. The primary source of environmental exposure of TAME is emissions to air from evaporative and exhaust gases of gasoline fuelled vehicles and engines. Gasoline distribution chain causes also evaporative emission to air and may cause local soil contamination and groundwater pollution.

Highest consumer exposures occur at service station during and after refuelling of car combined to living near to (50 m) a service station. An indirect human exposure via contaminated drinking water is possible in contaminated areas such as near service stations.

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

Human Health: The chemical is of low priority for further work due to its low hazard profile.

Environment: The chemical is a candidate for further work. Although TAME does not possess properties indicating a hazard for the environment or the human health, a risk assessment performed in the context of the EU Existing Substances Regulation identified a concern:

- To general quality of ground water and aesthetic quality of drinking water. This conclusion is not directly based on toxicological or ecotoxicological endpoints, but to very low taste and odour thresholds of TAME in water and exposure arising from leaking underground storage tanks and tank piping.
- To aquatic environment because of exposure arising from intermittent release to surface water from terminal site gasoline storage tank bottom waters.

In the EU, a risk reduction strategy is currently under discussion. Other countries are therefore recommended, as post-SIDS activity, to review the exposure situation in their countries to determine the need for similar measures

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	111-90-0, 112-15-2, 6881-94-3, 124-17-4, 112-59-4
Category Name	Diethylene glycol ethers category (Di EGEs)
Structural Formulas	$\text{HO}(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_3$ Diethylene glycol ethyl ether (DGEE, CAS No. 111-90-0), $\text{CH}_3\text{C}(=\text{O})\text{O}(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_3$ Diethylene glycol ethyl ether acetate (DGEEA, CAS No. 112-15-2), $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_2\text{CH}_3$ Diethylene glycol propyl ether (DGPE, CAS No. 6881-94-3), $\text{CH}_3\text{C}(=\text{O})\text{O}(\text{CH}_2\text{CH}_2\text{O})_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ Diethylene glycol butyl ether acetate (DGBEA, CAS No. 124-17-4), $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ Diethylene glycol hexyl ether (DGHE, CAS No. 112-59-4)

SUMMARY CONCLUSIONS OF THE SIAR**Category and Use of Supporting Chemicals Justification**

The category includes five diethylene glycol ethers or acetates (DGEE, DGEEA, DGPE, DGBEA and DGHE). The members of this category all have similar molecular structures, functionality and metabolic pathways and demonstrate similar physicochemical and environmental fate properties and mammalian toxicity. However, for aquatic toxicity, diethylene glycol ethers (DGEE, DGPE and DGHE) and diethylene glycol ether acetates (DGEEA and DGBEA) are considered separately because diethylene glycol ether acetates do not hydrolyze readily in water at environmental conditions.

Three additional structural analogs are included to support this category. Each of them has previously been endorsed at a SIAM. The chemicals are: diethylene glycol butyl ether (DGBE, CAS No. 112-34-5; SIAM4), ethylene glycol hexyl ether (EGHE, CAS No. 112-25-4; SIAM19), and ethylene glycol butyl ether acetate (EGBEA, CAS No. 112-07-2; SIAM19). EGHE and EGBEA are members from the monoethylene glycol ethers category. DGBE is included to fill data gaps for mammalian and aquatic toxicity and provide supplemental data for the other category members. The molecular weight of DGBE is in between DGPE and DGHE, and DGBEA is rapidly hydrolyzed to DGBE in mammalian systems. The reader should refer to the existing SIDS dossier (SIAM 4) and EU Risk Assessment for additional information. Additionally, EGHE and EGBEA are included for the aquatic toxicity endpoints. These materials provide missing information for the corresponding diethylene glycol ethers/acetates DGHE and DGBEA. The reader should refer to the existing SIDS dossier (SIAM19) for any additional information.

Toxicokinetics

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The rate of dermal absorption of DGBE and DGBEA is similar. Once absorbed, DGBEA is rapidly hydrolyzed to DGBE by enzymes present in rat blood. Available metabolism studies in animals for members of the diethylene glycol ethers category indicate the principal route of elimination is via the urine. Only small or trace amounts of metabolites are found in expired air or feces. Limited human data indicate similar conclusions. The primary urinary metabolites of diethylene glycol ethers and acetates are alkoxyethoxy acetic acids. The metabolic fate of DGEE, DGPE and DGHE is expected to be similar to that of DGBE due to similarities in structure. Since DGBEA is rapidly hydrolyzed to DGBE by rat blood, DGEEA is expected to undergo rapid hydrolysis to DGEE in vivo. Therefore, the toxicological profiles of the acetates are expected to be similar to those of their corresponding glycol ethers.

Human Health

There are adequate oral, inhalation and/or dermal toxicity studies on the category members. Oral LD₅₀ values in rats for all category members are all > 3000 mg/kg bw, with values generally decreasing with increasing molecular weight. Four to eight hour acute inhalation toxicity studies were conducted for all category members except DGPE in rats at the highest vapour concentrations achievable. No lethality was observed for any of these materials under these conditions. Dermal LD₅₀ values in rabbits range from 2000 mg/kg bw (DGHE) to 15000 mg/kg bw (DGEEA). Signs of acute toxicity in rodents are consistent with non-specific CNS depression typical of organic solvents in general. All category members are slightly irritating to skin and slightly to moderately irritating to eyes (with the exception of DGHE, which is highly irritating to eyes). Sensitization tests with DGEE, DGEEA, DGPE, DGBE and DGBEA in animals and/or humans were negative.

Valid repeated-dose studies have been performed using most category members. One inhalation study with DGEE in rats (nose only, for 28 days) showed mild respiratory effects at 270 or 1100 mg/m³ but no systemic toxicity. Repeated inhalation exposure of up to 94 mg/m³ DGBE for 90 days had no effect on Wistar rats. Dermal studies were conducted in rabbits with DGEE, DGBEA, and DGHE as well as the supporting chemical DGBE. Effects from two dermal DGEE studies (30 days and 12 weeks) included unspecified percent mortality (unspecified doses in the 30 day study), and some kidney and liver effects, although results could not be verified. A 90-day dermal study with 489 to 3912 mg/kg/day DGBEA in rabbits resulted in hemoglobinuria and hemolysis at unspecified doses; a subchronic LD₅₀ of 1956 mg/kg bw/day was determined. DGBE via the dermal route (13 weeks) had slight effects in rats (e.g., skin irritation at ≥ 200 mg/kg/day, slight blood in urine at ≥ 600 mg/kg/day). In a 9-day dermal study in rabbits, 100 to 1000 mg/kg DGHE resulted in skin irritation and/or dermatitis. Valid oral studies conducted using DGEE, DGPE, DGBEA, DGHE and the supporting chemical DGBE ranged in duration from 30 days to 2 years. Effects predominantly included kidney and liver toxicity, absolute and/or relative changes in organ weights, and some changes in hematological parameters. All effects were seen at doses greater than 800-1000 mg/kg bw/day from oral or dermal studies; no systemic effects were observed in inhalation studies with less than continuous exposure regimens.

DGEE, DGEEA, DGBE, DGBEA and DGHE generally tested negative for mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and DGBEA tested negative in *E. coli* WP2uvrA, with and without metabolic activation. *In vitro* cytogenicity and sister chromatid exchange assays with DGBE and DGHE in Chinese Hamster Ovary Cells with and without metabolic activation and *in vivo* micronucleus or cytogenicity tests with DGEE, DGBE and DGHE in rats and mice were negative, indicating that these diethylene glycol ethers are not likely to be genotoxic.

Reliable reproductive toxicity studies on DGEE, DGBE and DGHE show no effect on fertility at the highest oral doses tested (4,400 mg/kg/day for DGEE in the mouse and 1,000 mg/kg/day for DGBE and DGHE in the rat). The dermal NOAEL for reproductive toxicity in rats administered DGBE also was the highest dose tested (2,000 mg/kg/day). Although decreased sperm motility was noted in F₁ mice treated with 4,400 mg/kg/day DGEE in drinking water for 14 weeks, sperm concentrations and morphology, histopathology of the testes and fertility were not affected. Results of the majority of adequate repeated dose toxicity studies in which reproductive organs were examined indicate that DGPE and DGBEA do not cause toxicity to reproductive organs (including the testes). Test material-related testicular toxicity was not noted in the majority of the studies with DGEE or DGEEA. However < in one study, DGEE of unknown purity reported testicular edema at a very high dose (approximately 4000 mg/kg bw/day). It is possible that the testicular effect was due to an impurity although a direct effect of DGEE cannot be

ruled out.

Results of the developmental toxicity studies conducted with DGEE, DGBE and DGHE are almost exclusively negative. In these studies, effects on the fetus are generally not observed (even at concentrations that produced maternal toxicity). Exposure to 102 ppm (560 mg/m³) DGEE by inhalation (maximal achievable vapor concentration) or 1385 mg/kg/day DGEE by the dermal route during gestation did not cause maternal or developmental toxicity in the rat. Maternal toxicity and teratogenesis were not observed in rabbits receiving up to 1000 mg/kg/day DGBE by the dermal route during gestation; however a transient decrease in body weight was observed, which reversed by Day 21. In the mouse, the only concentration of DGEE tested (3500 mg/kg/day by gavage) caused maternal, but no fetal toxicity. Also, whereas oral administration of 2050 mg/kg/day DGBE (gavage) to the mouse and 1000 mg/kg/day DGHE (dietary) caused maternal toxicity, these doses had no effect on the developing fetus.

Environment

Members of the category are high boiling liquids (boiling points in the 196-259°C range), with low melting points (-90 to -25°C). Vapor pressures are in the range of <0.01-0.168 hPa at room temperature. The diethylene glycol ethers are soluble in water. Octanol-water partition coefficients (log Kow values) range from -0.69 to +1.3. Henry's Law Constants range from 8.63 E-10 to 9.91 E-8 atm-m³/mole. Estimated hydroxyl radical-induced atmospheric photodegradation half-lives range from 3.18 to 4.41 hours.

DGEE, DGPE, and DGHE possess no functional groups in their molecular structures that are readily subject to hydrolysis in the presence of water. The acetate ester groups of DGEEA and DGBEA will hydrolyze, with the hydrolysis rate dependent on temperature, pH and possible presence of impurities that can act as catalysts for hydrolysis. Level III fugacity modeling indicates that category members, when released to air and water, will partition to water (48.7-66.6%), soil (30.4-50.7%), air (0.52-2.88%), and sediment (0.08-0.15%). Estimates of soil and sediment partition coefficient (Kocs ranging from 1 – 10) suggest that category members would exhibit high soil mobility. Estimated bioconcentration factors (log BCF) range from 0.299 to 0.609. Category members for which adequate data are available (DGEE, DGHE and DGBEA) are readily biodegradable. These physicochemical and environmental fate properties indicate that category members will not persist in the environment or bioaccumulate.

The aquatic toxicity data for the diethylene glycol ethers (DGEE, DGPE and DGHE) and diethylene glycol ether acetates (DGEEA and DGBEA) are considered separately because diethylene glycol ether acetates do not hydrolyze readily in water at environmental conditions. The EC/LC₅₀ values for the diethylene glycol ethers in fish range from 200 (for DGHE) to > 5000 mg/l (for DGPE and DGEE). In invertebrates, values range from 433 for DGHE to > 10,000 mg/l for DGEE and DGPE. No algae data are available for the category members; based on data from supporting chemicals, toxicity is expected to be > 100 mg/l for DGHE and > 500 mg/l for other category members.

The LC₅₀ values for fish are 110 mg/l for DGEEA and 77 mg/l for DGBEA. Measured or estimated values for invertebrates are higher (665 mg/l measured for DGBEA, with higher estimated values for both chemicals). No algae data are available for the acetates; based on experimental data for EGBEA, EC₅₀ values are expected to be > 500 mg/l.

Exposure

Annual U.S. production volumes for DGEEA, DGPE, and DGHE are each in the range of 450-2,270 metric tons. Annual U.S. production volumes of DGEE and DGBEA are each in the range of 4,500 – 22,700 metric tons. The use patterns for these materials are similar, with qualitative differences. All are used predominately as solvents or coalescing aids in formulations, such as for surface coatings, automotive coatings, metal cleaners, printing and silk screen inks, brake fluids. These are applications mostly in industrial settings. Some use is as chemical intermediates.

Numerous uses in consumer product formulations include in latex paints, lacquers, thinners, varnishes, window cleaners, kitchen, bathroom and other household cleaners, air fresheners, floor polishes and finishes, and paint and

varnish removers. DGEEA is used in cosmetic formulations and DGEE is used in hair colorants. Consumer products are reported to contain 1-25% of diethylene glycol ethers.

Human exposures to category members occur primarily via inhalation and dermal contact. Exposures occur to some extent during manufacture and formulation into products, but are more likely to be associated with the widespread uses given above. Exposure during manufacture is limited by the predominately closed, continuous nature of the process and equipment. Some releases to the atmosphere and water may occur during manufacture through venting and aqueous streams. Aqueous waste streams are routinely biologically treated. Although engineering controls and work practices may limit exposures during industrial processing and use, solvent application conditions may vary widely, and atmospheric releases are expected through solvent evaporation.

Consumers may be exposed through use of consumer products containing category members and also from environmental concentrations. Because category members photodegrade and biodegrade readily in the environment, environmental exposure will be decreased. Exposure monitoring information is not readily available.

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

Human Health: The chemicals are currently of low priority for further work. The substances in the category possess properties indicating a hazard for human health (skin and eye irritation and potential testicular toxicity of DGEE at high doses). Although these hazards do not warrant further work (as they are related to reversible effects or toxicity which may become evident only at high exposure levels), they should nevertheless be noted by chemical safety professionals and users. Although hemolysis is noted in rats, mice and rabbits repeatedly exposed to high oral or dermal concentrations of DGEE, DGPE, DGBE and DGBEA humans are many-fold less sensitive to red blood cell hemolysis by the major metabolites of similar chemicals (the monoethylene glycol ethers) than rats.

Environment: DGEE, DGPE, DGHE and DGEEA are of low priority for further work due to their low hazard profile. DGBEA has properties indicating a hazard for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However the chemical is currently of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos. and Chemical names	(1300-72-7 and 827-21-4) Xylenesulfonic acid, sodium salt (12068-03-0) Toluenesulfonic acid, sodium salt (26447-10-9) Xylenesulfonic acid, ammonium salt (28348-53-0 and 32073-22-6) Cumenesulfonic acid, sodium salt (37475-88-0) Cumenesulfonic acid, ammonium salt (28088-63-3) Xylenesulfonic acid, calcium salt (30346-73-7) Xylenesulfonic acid, potassium salt (16106-44-8) Toluenesulfonic acid, potassium salt The 6 compounds in bold are sponsored HPV chemicals; the remaining 4 compounds are supporting/supported chemicals in the category.
Category Name	Hydrotropes
Structural Formulas	 -SO₃Na toluene sulfonic acid, sodium salt  -SO₃Na xylene sulfonic acid, sodium salt  -SO₃Na cumene sulfonic acid, sodium salt The category also includes isomeric forms (ortho, meta, and/or para) of the respective sulfonic acid salts (sodium, ammonium, calcium and potassium).

SUMMARY CONCLUSIONS OF THE SIAR**Category Identification/ Justification**

Hydrotropes are supported as a category because of the close consistency of the compounds, their commercial uses, fate, and health and environmental effects. The hydrotropes are used as coupling agents to solubilize the water insoluble and often incompatible functional ingredients of household and institutional cleaning products and personal care products. These hydrotropes are not surfactants but are used to solubilize complex formulas in water. They function to stabilize solutions, modify viscosity and cloud-point, limit low temperature phase separation and reduce foam formation. Manufactured products are used as aqueous solutions (30-60% active substance) or as granular

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solids containing 90-95% active substance.

The hydrotropes category may be initially considered as three sub-groups: the methyl, dimethyl and methylethyl benzene sulfonates, (or the toluene, xylene and cumene sulfonates). Although the counter ion will also determine the physical and chemical behavior of the compounds, the chemical reactivity and classification for this purpose is not expected to be affected by the difference in counter ion (i.e., Na^+ , NH_4^+ , Ca^{++} , or K^+). Note that two of the compounds (xylene and cumene sulfonic acid, sodium salts) have more than one CAS number. This is a result of differences in industry nomenclature practice and/or use patterns across geographical regions at the time of notification. This practice has led to differences in how some substances are identified on national and regional chemical inventories. The structures as well as the physical/chemical and toxicological properties of these chemical entities are essentially the same.

In general, the presence of one or two methyl groups or a methylethyl group on the benzene ring is not expected to have a significant influence on chemical reactivity. Alkyl substituents are known to be weak ortho- and para-directing activators, and the difference between methyl and methylethyl will be negligible. On going from methylbenzene (toluene) to dimethylbenzene (xylene) and to methylethylbenzene (cumene), the number of carbon atoms – and thus the organic character – increases. This will improve solubility in apolar solvents and reduce solubility in polar solvents like water. Hence, reactivity in watery solutions may differ somewhat for the hydrotropes. However, the decisive factor in determining water solubility of these compounds will be ionic character, not the number and identity of the alkyl substituents on the benzene ring.

It was therefore concluded that the three sub-groups are expected to be generally comparable and predictable in their chemical behavior (as such or in solution) and that members from one sub-group may be useful for read across to other sub-groups and to the hydrotropes category as a whole.

Human Health

Toxicological studies have been conducted with numerous members of the hydrotropes category. Data on all SIDS-endpoints are available and indicate a relatively low toxicity for these compounds.

No studies on absorption, distribution, metabolism and elimination for the hydrotropes category were identified. However, based on the physico-chemical properties such as molecular weight, water solubility and octanol-water partition coefficient, and the available toxicological studies, it can be concluded that significant absorption occurs following oral administration while absorption following dermal application is limited.

Across the hydrotropes category, toxicity results are consistent across the toluene, xylene and cumene sulfonates and their various salts. The acute oral LD50 in rats ranges from 1044 mg a.i./kg bw (calcium xylene sulfonate) to 6500 mg a.i./kg bw (sodium xylene sulfonate), the dermal LD50 in rabbits is >624 mg a.i./kg bw (calcium xylene sulfonate), and the inhalation LC50 in rats is >557 mg/L (557 g/m³ sodium toluene sulfonate) and in rabbits >6.41 mg/L (6.41 g/m³ ammonium xylene sulfonate). The inhalation studies are from secondary sources. Clinical signs observed in acute oral toxicity studies included decreased activity, weakness, prostration, increased salivation, diarrhea, ptosis and anogenital staining. Necropsy findings reported in these same studies included slight pulmonary inflammation, gastrointestinal inflammation and hemorrhage, mild liver changes, congestion of liver, kidneys, adrenal glands and gastrointestinal tract, and redness of stomach mucosa in animals that died. Observations were within normal limits with a report of slight to moderate congestion of adrenal glands in animals that survived. Clinical signs observed in acute dermal exposure included erythema with additional desquamation. At necropsy findings reported were focal or multifocal red discoloration and desquamation of the treated skin.

A series of rabbit skin and eye irritation studies are reported for members of the hydrotropes category. Sodium xylene sulfonate is not a skin irritant. Calcium xylene sulfonate and sodium cumene sulfonate are not skin irritants and both caused slight but reversible eye irritation. There is no indication of skin sensitization for the hydrotropes category based on the available animal (GLP Buehler study). No reliable human data are available for sensitization.

Thirteen oral and dermal repeat dose toxicity studies (subchronic and chronic) conducted in rats or mice are available

for the hydrotropes category. Test durations ranged from 17 days up to 2 years and exposure doses ranged from 6 to 2000 mg a.i./kg bw/day sodium xylene sulphonate by the dermal route and from 1.1 up to 4092 mg a.i./kg bw/day sodium xylene sulphonate by the oral route. No significant systemic toxicity was observed in any of the dermal studies. Local effects were reported in one of six dermal studies. In that study the LOAEL was 1300 mg a.i./kg bw/day of sodium xylene sulphonate and the adverse effect was epidermal hyperplasia at the site of application in both male and female mice. The corresponding NOAEL was 440 mg a.i./kg bw/day. In the same study, the mean body weight gain of the high dose males was significantly greater (105%) than that of the control group. This change was not considered to be biologically significant by the authors (US National Institute of Health).

One of the eight oral repeat dose studies reported a 17% (statistically significant) decrease in relative spleen weight in female rats exposed 90 days to sodium xylene sulfonate. No adverse effects were reported in males. The LOAEL for this study was 4092 mg a.i./kg bw/day and the NOAEL was 763 mg a.i./kg bw/day. A 12% (statistically significant) reduction in body weight gain of female rats was reported in an older (1968) 91-day oral study with sodium cumene sulfonate at the dose level of 159 mg a.i./kg bw/day. No effects were observed in male rats. The study report stated that the decrease in body weight gain for females was within the established ranges for animals of this species and age and was therefore not considered an adverse effect by the authors. The decrease in body weight gain was not associated with any other effects. Two more recent (1980) and well reported 90 day studies with rats and mice exposed to sodium xylene sulfonate did not report a reduction in body weight gain at much higher doses, and consequently the effect in the sodium cumene sulfonate study is considered questionable. The most appropriate NOAEL for systemic toxicity from mammalian toxicity studies was therefore determined to be 763 mg a.i./kg bw/day based on a reduction in relative spleen weight in female rats.

The hydrotropes category has been assessed for mutagenic potential in a variety of *in vivo* and *in vitro* assays. Specifically mouse micronucleus cytogenetic assays with calcium xylene sulfonate and sodium cumene sulfonate, Ames assay with calcium xylene sulphonate, sodium cumene sulphonate and sodium xylene sulphonate and mouse lymphoma, sister chromatid exchange, and chromosome aberration assays with sodium xylene sulfonate. No positive results were seen *in vitro* or *in vivo* in any of the studies. Thus the available data indicate that the chemicals in the hydrotropes category do not have a genotoxic potential.

Chronic toxicity/carcinogenicity data exist for the hydrotropes category for both rats and mice dermally exposed for 2 years. There was no evidence of a carcinogenic potential for the hydrotropes category in these dermal exposure studies. It is noted that there is limited dermal absorption of hydrotropes.

No reproductive toxicity studies are reported for the hydrotropes category. However, the 91-day oral rat feeding study with sodium cumene sulfonate, the 90-day feeding study with sodium xylene sulfonate and the 90-day and 2-year dermal studies with sodium xylene sulfonate included examination of sex organs such as the prostate, testes and ovaries. There is no evidence from these repeat dose studies to suggest that these chemicals would have an adverse effect on reproductive organs.

Calcium xylene sulfonate has been evaluated for the potential to cause developmental toxicity in rats. Calcium xylene sulfonate (31% a.i.) was administered via gavage to female rats (30 per dose) at 0, 150, 1500 or 3000 mg/kg bw in water on days 6 to 15 of gestation. This study followed the US EPA TSCA Guideline 1985. Only one animal died during the study (mid-dose). No treatment related effects were observed. An increase in food intake observed at the highest dose was considered to be within ranges of biological variation for this species. There was no evidence of developmental toxicity in rats. The NOAEL for maternal and foetal toxicity was the highest dose tested at 3000 mg/kg bw/day (corresponding to 936 mg a.i./kg bw/day).

Environment

Hydrotropes are solid at ambient temperatures. Melting point experiments were carried out with calcium xylene sulfonate and sodium toluene sulfonate. Calcium xylene sulfonate decomposed in a melting point experiment at a temperature between 100°C and 375°C. No clear melting point was observed up to 300°C with sodium toluene sulfonate. Modelled estimates across the range of hydrotropes for melting points are in excess of 200°C and boiling points are in excess of 450°C. Hydrotropes are water soluble (>1000 mg/L) and have low volatility with a vapour

pressure of $<2.0 \times 10^{-5}$ Pa for sodium xylene sulfonate at 25°C (vapour pressure was measured at 240-250°C and extrapolated to 25°C). A measured octanol-water partition coefficient (logKow) value of -2.7 exists for calcium xylene sulfonate, which correlates with modeled logKow estimations ranging between -2.4 and -1.5 for the sodium xylene, toluene and cumene sulfonates. Fugacity modelling across the range of hydrotropes predicts a 99+% residence in the water compartment following environmental release.

Biodegradation constitutes the primary elimination mechanism from the environment. Studies across the hydrotropes category demonstrate rapid and complete biodegradation under aerobic conditions and the hydrotropes are considered to be readily biodegradable according to OECD criteria. No data are available on anaerobic degradation. There is photodegradation potential for hydrotropes based upon modelled atmospheric oxidation half-lives of 40 hours for the cumene sulfonates, 41 hours for the xylene sulfonates, and 105 hours for the toluene sulfonates. Hydrotropes are not subject to hydrolysis. Commercial products containing hydrotropes are often aqueous solutions and they are stable. Removal of hydrotropes from secondary activated sludge sewage treatment processes is greater than 94%, as observed in a modified SCAS study with calcium xylene sulfonate. Bacterial toxicity studies indicate that the hydrotropes category is not expected to negatively impact sewage treatment microorganisms. Fish bioconcentration studies conducted at two exposure concentrations with sodium xylene sulfonate and sodium toluene sulfonate reported BCF values of <2.3 . Model predictions using the measured and estimated log Kow values of -2.7 to -1.5 also indicate low bioaccumulation potential. The highest estimated Bioconcentration Factor [BCF] was approximately 3. Monitoring data are not available for the hydrotropes category.

Reliable ecotoxicity data are available on all SIDS-endpoints for selected members of the category. The data cover fish, invertebrates and algae for xylene sulfonate (sodium, ammonium and calcium salts) and cumene sulfonate (sodium salt). While the toluene benzene derivative is not represented in the available data set, results are consistent for the chemicals tested, providing confidence in the ability to read-across for other category members. Based on hazard data, aquatic toxicity is considered to be uniformly low across the hydrotropes category.

Fish acute LC₅₀ values are >400 mg/L in six studies. *Daphnia* acute EC₅₀ values are >318 mg/L in five studies. The acute LC₅₀ to the marine invertebrate *Artemia* is >400 mg/L in one study. Freshwater green algae are considered the most sensitive species with EC₅₀ values ranging between 230-236 mg a.i./L and No Observed Effect Concentrations (NOECs) ranging between 31-75 mg a.i./L. The 48-hr EC10 for the bacteria *Pseudomonas putida* exposed in a Bringmann-Kuehn-Test is reported as $>16,000$ mg/L sodium cumene sulfonate. A daphnid 21-day chronic toxicity NOEC value of approximately 30 mg/L has been reported for sodium cumene sulfonate, however the data is sourced from secondary literature with limited reliability.

The suggested aquatic Predicted No Effect Concentration (PNEC) is 2.3 mg/L calculated as the lowest EC₅₀ for three species (algae, fish, daphnia) divided by an assessment factor of 100. The lowest EC₅₀ is 230 mg/L (based on algal toxicity for sodium xylene sulfonate), this divided by 100 equals 2.3 mg/L. A PNEC of 2.3mg/L is consistent with what would be predicted using the chronic daphnia NOEC divided by 10, or using the 96-hour algal NOEC as a chronic endpoint divided by 10.

Exposure

Current hydrotrope volumes (production + importation) based on 100% active material are approximately 29,000 metric tonnes in the U.S., 1,100 metric tonnes (40% concentration) in Australia, and 19,000 metric tonnes in Europe. Hydrotropes are used at active concentrations between 0.1 and 15% in consumer cleaning and personal care products. They function as coupling agents in liquid and powder laundry detergents, hand dishwashing liquid detergents, machine dishwashing rinse aids, hard surface cleaners, body washes, shampoos, hair conditioners, liquid face and hand soaps, toilet treatments, solvent hand cleaners, carpet cleaners and optical brightener products. In Australia, a relatively small volume (about 55 tonnes per year) is used in liquid sulphur textile dyes present at 7.5 – 50%, acidic recirculation cleaning products present at 10-25%, wetting agent for tanning industry present at 10%, enzymatic recirculation cleaner for dairy and food processing applications at 4%, coolant system conditioner at 6.9%, car wash detergents at 1.3–6.3%, cleaners and degreasers at 0.1–6.3%, vinyl, plastic rubber restorer at 0.2% and floor stripper at 2.7–9 %. There are no industrial process intermediate uses of the hydrotropes.

There is potential for workers to be exposed during manufacturing, formulation and industrial end use of products. Exposure could occur as a result of inhalation and/or dermal contact with aqueous and particulate material. The potential for human exposure to hydrotropes by inhalation is minimized by its low volatility and because most of the production, formulation and industrial end use of products are in aqueous solutions. Inhalation exposure to the solid form is likely to be minimal as dust generation is low. Dermal exposure is possible. Engineering controls (e.g., closed system operations, exhaust ventilation, dust collection) and personal protective equipment (e.g., protective clothing, eyewear, and gloves) at manufacturing and formulation facilities further mitigate worker exposure. No special engineering controls or additional personal protective equipment are uniquely specified for the hydrotropes category. No workplace air monitoring data are available.

Hydrotropes are used in consumer/professional cleaning and personal care products, which may be used “as is”, or diluted prior to or during use. Dermal contact will occur with these products. There is some potential for incidental or accidental ingestion of, inhalation of, and/or eye contact with products during handling and use. Exposure to hydrotropes in formulated consumer products is mitigated by following use and precaution instructions on product labels. Human exposure will be mitigated by the fact that residues from many of these products are washed or rinsed off.

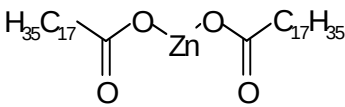
Environmental releases from production facilities and from down-the-drain discharges following product use may lead to potential environmental exposures in surface waters and indirect human exposures via drinking water and/or fish consumption. Environmental exposure will be mitigated by the fact that hydrotropes, which reside predominantly in the water compartment, are readily biodegraded and are removed to a large degree during wastewater treatment and have low potential for bioaccumulation.

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

Human Health: The chemicals in this category are of low priority for further work because of their low hazard profile.

Environment: The chemicals in this category are of low priority for further work because of their low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS Numbers with Chemical Names and Structural Formula	7440-66-6	Zinc metal	Zn
	1314-13-2	Zinc oxide	ZnO
	557-05-1/ 91051-01-3	Zinc distearate	
	7646-85-7	Zinc chloride	ZnCl ₂
	7733-02-0	Zinc sulphate	ZnSO ₄
	7779-90-0	Trizinc bis (orthophosphate)	Zn ₃ (PO ₄) ₂ • 2-4H ₂ O

SUMMARY CONCLUSIONS OF THE SIAR**Category Justification**

The Zincs Category includes six CAS numbers that are similar from a hazard point of view. It is assumed that all zincs either dissociate or form the zinc cation that is responsible for the hazardous effects. In the environment the zinc cation is formed via several speciation or transformation reactions, while furthermore it is assumed that, where appropriate, the counter ion does not significantly attribute to the major effects seen. In the human health assessment of the hazards it is assumed that for systemic toxicity the hazardous properties can be attributed again to the zinc cation and the counter ion be ignored.

Human Health

Being an essential element, zinc plays an important role in many processes in the body. Although zinc deficiency can lead to notable health effects, the risk assessment for an essential element like zinc does not concern deficiencies but excess in exposure over natural background levels.

A lot of information was available for evaluation of the data-rich zinc compounds. The database not only included toxicity data on the six zinc compounds. In case of systemic effects also data on other zinc compounds were used, based on the assumption that after intake the biological activities of the zinc compounds are determined by the zinc cation.

Within certain limits, the total body zinc as well as the physiologically required levels of zinc in the various tissues can be maintained, both at low and high dietary zinc intake. Regulation of gastrointestinal absorption and gastrointestinal secretion probably contributes the most to zinc homeostasis. In spite of this a regular exogenous supply of zinc is necessary to sustain the physiological requirements because of the limited exchange of zinc between tissues.

The Zn²⁺ absorption process in the intestines includes both passive diffusion and a carrier-mediated process. The absorption can be influenced by several factors such as ligands in the diet and the zinc status.

Persons with adequate nutritional levels absorb 20-30% and animals 40-50%. However, persons that are Zn-deficient absorb more, while persons with excessive Zn intake absorb less. For zinc oxide it has been shown that bioavailability is about 60% of that for soluble zinc salts, corresponding to 12-18%.

Although quantitative data on the absorption of zinc following inhalation exposure (especially relevant in

occupational settings) are not available it is concluded that inhalation absorption for the soluble zinc compounds is at maximum 40%, while for the less soluble/insoluble zinc compounds inhalation absorption is at maximum 20%. Some animal data suggest that pulmonary absorption is possible. For dermal exposure (relevant in both occupational and consumer settings) adequate quantitative data on the absorption of zinc are not available. However, it is concluded that the dermal absorption of solution or suspensions of zinc or zinc compounds is 2%, whereas for dust exposure to zinc or zinc compounds this value is 10-fold lower.

Zinc is distributed to all tissues and tissue fluids and it is a cofactor in over 200 enzyme systems. Zinc is primarily excreted via feces, but can also be excreted via urine, saliva, hair loss, sweat and mothermilk.

Zinc metal, zinc oxide, zinc distearate, and zinc phosphate have a low acute toxicity, are not corrosive and irritating to the skin, eyes, or respiratory tract, and are not sensitizing to the skin. In contrast, zinc chloride is corrosive, irritating to the respiratory tract, and acutely toxic after inhalation ($LC_{50} \leq 1975 \text{ mg/m}^3$, 10 min. exposure time) and ingestion ($LD_{50} 1100\text{-}1260 \text{ mg/kg bw}$). Zinc sulfate is also acutely toxic after ingestion ($LD_{50} < 2000 \text{ mg/kg bw}$), as well as severely irritating to the eyes.

When present as ultrafine ($\leq 0.1 \mu\text{m}$) particles in fumes, zinc oxide may cause metal fume fever upon inhalation. The generation of ultrafine zinc oxide particles occurs only at very specific operations, such as the welding of steel. In humans, the LOAEL for metal fume fever was 5 mg/m^3 . This was concluded from a study in which 4 persons were exposed for 2 hours to control furnace gases or ultrafine zinc oxide particles (5 mg ZnO/m^3). Inhalation of zinc chloride fumes also resulted in adverse effects in humans: local effects in the respiratory tract were observed at a LOAEL of $4.8 \text{ mg ultrafine zinc chloride/m}^3$ after an exposure of 30 minutes to zinc chloride fume).

In repeated dose toxicity studies with rats and mice, oral zinc exposure resulted in copper deficiency and pathological changes in the pancreas and the spleen as the most sensitive effects, with a NOAEL of $13.3 \text{ mg Zn}^{2+}/\text{kg bw/day}$. In studies with human volunteers, women appeared to be more sensitive than men to the effects of repeated zinc supplementation. In women, supplementation at a level of $150 \text{ mg Zn}^{2+}/\text{day}$ (2.5 mg/kg bw/day , based on a body weight of 60 kg; LOAEL) resulted in clinical signs such as headache, nausea and gastric discomfort, and in indications for disturbance of copper homeostasis. The NOAEL in women supplemented with zinc was $50 \text{ mg Zn}^{2+}/\text{day}$ ($0.83 \text{ mg/kg bw/day}$). The background intake of zinc via food is approximately 10 mg/day .

The results of *in vitro* genotoxicity studies indicate that zinc has genotoxic potential *in vitro*. However, there is no clear evidence from *in vivo* genotoxicity studies that zinc is genotoxic *in vivo*. There is also no clear experimental or epidemiological evidence for a direct carcinogenic action of zinc, albeit that zinc deficiency or supplementation may influence carcinogenesis given that promoting and inhibiting actions have been reported.

Available data in experimental animals on zinc excess indicate that adverse effects on fertility and fetal development may occur at dose levels ($200 \text{ mg Zn}^{2+}/\text{kg bw/day}$) at which other effects such as perturbation of parental and fetal copper homeostasis are evident. The only available data in humans indicate that additional zinc up to $0.3 \text{ mg Zn}^{2+}/\text{kg bw/day}$ during pregnancy did not result in adverse reproductive or developmental effects. In analogy with the findings in animals, where reproductive toxicity was observed at higher dose levels than those at which other effects were already present, it was considered unlikely that in humans reproductive effects will occur at exposure levels at which clinical signs are not manifest.

Environment

The zinc compounds from the Zinc Category are all solids. Melting points are higher than 130°C and boiling points higher than 732°C . Vapour pressure for the zinc metal is 31 Pa (at 450°C) and for zinc chloride 1.33 hPa (at 428°C). From the category members, zinc chloride has the highest water solubility ($4,320 \text{ g/L}$), followed by zinc sulphate (220 g/L), zinc oxide ($<1.6 \text{ mg/L}$) and zinc distearate (0.97 mg/L). Zinc phosphate and zinc metal are insoluble in water. An octanol-water partition coefficient is only available for zinc distearate ($\log K_{ow}$ of 1.2).

The chronic ecotoxicity data, if based on the total zinc concentrations (i.e. added plus background concentration), have been transformed into the added zinc concentrations, to allow the use of the “added risk approach”. The “added risk approach” allows one to cope with essentiality and natural background concentrations in the environment. In this approach both the PEC and the PNEC are determined on the basis of the added amount of zinc, resulting in an

“added Predicted Environmental Concentration” (PEC_{add}) and “added Predicted No Effect Concentration” ($PNEC_{add}$), respectively.

Chemical and biological processes will affect the speciation of zinc in the environment. Bioavailability of zinc in water, soil and sediment and its implications for the hazard and exposure assessment has been dealt with via bioavailability correction factors (water and soil) and the Acid Volatile Sulphide (AVS)-method (sediment).

For the aquatic environment, the following values for pH, hardness, DOC (dissolved organic carbon) and background zinc concentrations have been used for ecotoxicity data selection: pH between 6 and 9, total hardness between 24 and 250 mg/l as $CaCO_3$, $DOC < 2$ mg/l (only used for reconstituted waters) and minimal background zinc concentration for soluble zinc around 1 μ g/L. These abiotic conditions are known to affect bioavailability and, implicitly, the hazard assessment of zinc in surface water (see above). The selected abiotic ranges are based on current OECD test guidelines for aquatic toxicity testing and relevance for the EU region; other regions may select other ranges for their hazard assessment.

The lowest $L(E)C_{50}$ values expressed as soluble metal (mg Zn^{2+} /L) were found to be 0.136 mg/L for the algae *Selenastrum capricornutum*, 0.07 mg/L for the crustacea *Daphnia magna* and 0.14 mg/L for the fish *Oncorhynchus mykiss*.

The lowest “species mean” NOEC of 17 μ g/l, for *Pseudokirchneriella subcapitata*, formerly known as *Selenastrum capricornutum*, is based on the geometric mean value of 25 NOEC values from different tests (endpoint growth).

The lowest NOEC for sediment-dwelling organisms (benthic macro-invertebrates) is 488 mg/kg dwt, based on tests in sediment-water systems with Zn-spiked sediment.

For terrestrial microbial processes a lowest NOEC of 17 mg/kg d.w. was found in two respiration tests. For the group plants/invertebrates a lowest NOEC of 32 mg/kg d.w. was found in an invertebrate test species, *Folsomia candida*, and in plant tests with *Trifolium pratense*, *Vicia sativa* and *Hordeum vulgare*. The selected tests with terrestrial organisms typically refer to the EU region; other regions may select other criteria for their hazard assessment.

The bioaccumulation potential of zinc in herbivorous and carnivorous mammals, but also in several invertebrates, will be low (homeostasis). Secondary poisoning and the related issues bioaccumulation and biomagnification are therefore considered less relevant for zinc.

Exposure

Zinc is an essential and naturally occurring element in the environment. Zinc in fresh water or seawater can occur in both suspended and dissolved forms and is partitioned over a number of chemical species. The natural zinc concentrations in soils are highly variable and dependent on the native soil material and the soil characteristics, especially the clay and organic matter content. Zinc in soil is distributed between a number of fractions.

Emissions to the environmental compartments are possible from the production, the use and waste phase of the substances. Zinc and zinc compounds are used in a great number of applications, ranging from steel coating (galvanizing) to cosmetics. It is emphasized that zinc may enter the environment via a variety of point and diffuse sources: a.o. industry, mining, agriculture, historical pollution, etc.

The total production volume of primary zinc metal in the EU in 1995 was about 2,193,000 tonnes. In the Western World the mine production of zinc was 4,730,000 tonnes in 1990, while 1,940,000 tonnes of zinc were produced from secondary sources.

Zinc is a compound that is incorporated in a great number of regional or national monitoring programs. Zinc monitoring data for surface water, soil and sediment could therefore be collected for a number of EU countries.

Exposure in the workplace is limited to the inhalation and dermal route, assuming that oral exposure is prevented by personal hygienic measures. Zinc compounds are used in several consumer products, e.g., in applications of metallic zinc (watering-cans, buckets, nails, gutters, etc.), in paints, cosmetics (eye shadow, sunscreen, deodorant, dandruff shampoo), and drugstore products (baby care ointment, gargle, eye drops). Zinc compounds are also used in dietary supplements, which consumers can buy over the counter. Zinc and zinc compounds are released to the environment through waste water and air effluents at the sites where they are produced and processed. Humans may thus be

exposed to these compounds indirectly via the oral and inhalation route. The background intake of zinc via food, due to the natural occurrence of zinc in the environment, is approximately 10 mg/day. This appeared to be the most important exposure to zinc, compared to which the intake via drinking water and ambient air is negligible.

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

Human Health: The chemicals in this category possess properties indicating hazards for human health (acute inhalation toxicity, corrosive to skin and eyes, respiratory irritation (zinc chloride), eye irritation (zinc sulfate) and metal fume fever (zinc oxide).

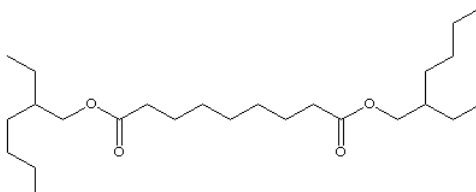
A risk assessment was performed in the context of the EU Existing Substances Regulation. For human health risks were identified regarding occupational exposure to two members of the Zinc category:

- zinc oxide: metal fume fever due to acute inhalation exposure could not be excluded in a certain occupational exposure scenario, and systemic effects after repeated dermal exposure at the workplace could not be excluded in other scenarios.
- Zinc chloride: where acute local effects to the respiratory tract could not be excluded in a certain occupational exposure scenario.

In the EU an risk reduction strategy is currently under discussion. Other member countries are invited to perform an exposure assessment and if necessary a risk assessment for human health.

Environment: The chemicals in this category possess properties indicating hazard for the environment (aquatic toxicity). Based on the wide spread use of these chemicals, member countries are invited to perform an exposure assessment and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	103-24-2
Chemical Name	Bis(2-ethylhexyl) azelate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

There was no available information on toxicokinetics, metabolism and distribution.

In an acute toxicity study [OECD TG 401] of bis(2-ethylhexyl) azelate in rats, the oral LD₅₀ was considered to be more than 2000 mg/kg bw in both sexes.

Available studies indicate that this chemical possessed low potential for skin and eye irritation. There was no available information on sensitisation.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], rats (13 animals/sex/dose) were given bis(2-ethylhexyl) azelate by gavage at 0, 100, 300 or 1000 mg/kg bw/day. Males were dosed for a total of 42 days beginning 14 days before mating and females were dosed for a total of 42-53 days beginning 14 days before mating to day 4 of lactation throughout the mating and pregnancy period. There were no deaths in any group. Body weight gain was suppressed in males at 1000 mg/kg bw/day. No changes in general conditions, food consumption, detailed clinical observations or neurobehavioral tests were found in males and females in any group treated with this chemical. Decreases in the number of white blood cells and levels of calcium were observed in females at 1000 mg/kg bw/day. The albumin/globulin (A/G) ratio was increased at 1000 mg/kg bw/day in both sexes and at 300 mg/kg bw/day in females. The increase in A/G ratio noted in females at 300 mg/kg bw/day was not considered as an adverse effect because no changes were observed in total protein or albumin at this dose. Lowered total protein was found in females at 1000 mg/kg bw/kg. Increases in relative weight of the liver in males and females, in absolute and relative weights of the kidney in males, and in relative weight of the kidney in females were noted at 1000 mg/kg bw/day. In histopathological examinations, a tendency of increased incidence of hypertrophy of the centrilobular hepatocytes was observed in males at 1000 mg/kg bw/day. Based on these findings, the NOAEL for repeated dose toxicity was considered to be 300 mg/kg bw/day in male and female rats.

This chemical was not genotoxic with or without an exogenous metabolic activation system in a bacterial test and in a chromosomal aberration test *in vitro*.

There was no available information on carcinogenicity.

In the above mentioned combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], histopathological examinations of the testes, epididymides and ovaries revealed no toxicological changes. There were no adverse effects on copulation index, fertility index, precoital interval,

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gestation length, gestation index or number of corpora lutea. No significant changes were observed in numbers of implantations and pups and live pups, and in indexes for implantation, delivery, birth and live birth. There were no treatment-related changes in body weight, external appearance or necropsy findings in offspring of rats. The NOAEL for reproductive and developmental toxicity was considered to be 1000 mg/kg bw/day.

Environment

Bis(2-ethylhexyl) azelate is a clear colourless liquid (melting point = -78 °C) without a specific odour. The substance has a very low vapour pressure (5.04×10^{-6} hPa at 25 °C) and water solubility (< 0.0004 mg/L at 20 °C). An experimentally obtained log Kow is 11.9 (by extrapolation) and a calculated log Koc (soil-adsorption co-efficient) is 5.48, and these parameters indicate that the water is not a target compartment. The substance is readily biodegradable under aerobic conditions (OECD TG301C, >94%, 28-d and 10-d window met). A calculated log BCF value of 0.5 indicates that bioaccumulation in aquatic organisms is not likely. Environmental distribution using Mackey level III suggests that when the substance is released into the environment, it distributes mainly into soil and sediment. In the atmosphere bis(2-ethylhexyl) azelate is indirectly photodegraded by reaction with OH radicals with a half-life of 0.4 days.

Eco-toxicity data of this chemical were available in aquatic species from three trophic levels. The GLP tests using a freshwater fish (OECD TG 203, *Oryzias latipes*), a daphnid (OECD TG 202, *Daphnia magna*) and a green alga (OECD TG 201, *Pseudokirchneriella subcapitata*) were conducted as limit tests. No adverse effects were observed in the studies. The reliable acute aquatic toxicity results are:

Oryzias latipes; 96 h LC₅₀ > 0.072 mg/L (> water solubility)

Daphnia magna; 48 h LC₅₀ > 0.093 mg/L (> water solubility)

Pseudokirchneriella subcapitata; 72 h EC₅₀ > 0.08 mg/L (for both growth rate and biomass method, > water solubility)

Chronic toxicity results with daphnids (OECD TG 211, *Daphnia magna*) and algae (OECD TG 201, *Pseudokirchneriella subcapitata*) are available from GLP limit tests. These tests indicated that bis(2-ethylhexyl) azelate showed no adverse effects up to its water solubility. The reliable toxicity results are:

Daphnia magna; 21 d NOEC > 0.064 mg/L (> water solubility)

Pseudokirchneriella subcapitata; 72 h NOEC > 0.08 mg/L (for both growth rate and biomass method, > water solubility).

Exposure

In Japan bis(2-ethylhexyl) azelate was commercially produced by at least four manufactures with an annual production volume of approximately ca. 150 tonnes in 2004. Worldwide production volume outside Japan was not available

Main use patterns (up to 95%) of bis(2-ethylhexyl) azelate produced and/or imported is used as a plasticizer for celluloses, polystyrene and vinyl plastics in order to improve low temperature resistance. A limited use of the substance as a lubricant at industrial sites was reported (less than 5%).

Bis(2-ethylhexyl) azelate is produced in a closed system and therefore significant exposure from the production and processing sites are not foreseen in the sponsor country. At production and processing sites, mainly during the maintenance and cleaning, bis(2-ethylhexyl) azelate can be released into wastewater streams and is treated by biological and chemical processes. During the use and due to deterioration of rubber products, it is expected that a small portion of the substance may be released into the environment. However, the substance is readily biodegradable and therefore exposure of the environment should not be significant.

Since the chemical has a very low vapour pressure and a low water solubility and high log Kow, exposure via inhalation route is unlikely and dermal uptake rate may be small, therefore exposure can be controlled by personal protective equipment in normal working conditions. At rubber production sites, where this chemical is used as plasticizer, mist may be released when rubber is treated at elevated temperature.

Although no quantitative data on the content of the substance in the final products is available, a trace level of consumer exposure through skin contact is expected.

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

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1066-33-7
Chemical Name	Ammonium bicarbonate
Structural Formula	NH_4HCO_3

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Ammonium bicarbonate rapidly dissociates in biological fluids to yield ammonium ion (NH_4^+) and bicarbonate ion (HCO_3^-). Ammonia and ammonium ions are integral components of normal metabolic processes and play an essential role in the physiology of man and other species, the toxicological profile of the substance is assumed to be due to the free ammonia rather than to the ionized form.

It is noted that ammonium bicarbonate, as a human food ingredient is generally recognized as safe (GRAS) by the US FDA. Most of the data related to acute toxicity endpoints come from secondary data sources. Original studies could not be found. These data indicate that the acute oral LD_{50} in rats is LD_{50} is ca. 1576 mg/kg bw. The dermal toxicity reported is $\text{LD}_{50} > 5000$ mg/kg bw. Acute inhalation toxicity results are not available but could refer to ammonia produced by ammonium bicarbonate decomposition which increases with the temperature. The calculated value is LC_{50} (inhalation, 1h, mice) ≥ 13.8 mg $\text{NH}_4\text{HCO}_3/\text{L}$ air. Data from secondary data sources also indicate that ammonium bicarbonate is moderately irritating for the skin and eye.

No information could be found on skin sensitization. However, NH_4^+ or HCO_3^- are not known to be sensitizers, and a further study with ammonium chloride gave negative results.

A repeated (6d) dose study in the rat lead to an oral NOAEL of 2.37 g/kg and the NOEL found in sheep was 2.7 g/kg. Rats exposed continuously for 90 days at 127 mg/m³ ammonia had no signs of toxicity.

As only negative results were obtained in *in vitro* mutagenicity tests, ammonium bicarbonate should not be considered as genotoxic.

There is no convincing substantiation of NH_4HCO_3 having carcinogenic effects and it is thus considered not carcinogenic. The long history of safe use in humans likewise supports this conclusion.

There are no indications that ammonium bicarbonate has effects on reproduction.

Environment

Ammonium bicarbonate is a volatile crystalline powder of 1.586 g/cm³ density, which starts to decompose at 30-35°C, below its melting point, achieved by 60°C into CO_2 , H_2O and NH_3 . Vapour pressure is 78.5 hPa at 25°C. The substance is not flammable and explosive.

The water solubility is 174-178g/L at 20°C. As ammonium bicarbonate is an inorganic compound which rapidly

dissociates in water, some physico-chemical endpoints (Henry's law constant, partition coefficient) and biodegradation are not easily applicable. Fate and behavior of ammonium bicarbonate are closely related to nitrogen and carbon cycles in air and water.

Ammonium bicarbonate rapidly dissociates in the environment to yield ammonium ion (NH_4^+), bicarbonate ion (HCO_3^-) and *un-ionized* ammonia (NH_3).

- Among these compounds, *un-ionized* ammonia is the most toxic.
- Ammonia toxicity would depend on the pH and temperature of the media, and on the amount of ammonia already present in the media. Increasing pH, and temperature to a lesser degree, solution results in more *un-ionized* ammonia (percentage of total ammonia present as NH_3 in aqueous solutions at 20°C is 0.039% at pH 6 and 3.82% at pH 8).
- Relevant toxicity results obtained by testing with ammonium bicarbonate or more generally derived from tests relating to NH_3 , expressed in mg N /L at pH 8, gave the following lowest toxicity values for the substance (expressed as mg NH_4HCO_3 /L): an acute LC50 of 41 mg/L for fish (*Onchorynchus mykiss*) or 87.4 mg/L for *Daphnia magna* and a long term EC20 of 7.6mg/L (*Onchorynchus mykiss*) or <8.2 mg/L (*Hyallela azteca*), while ammonium chloride has a 21d NOEC of 14.6 mg/L with *Daphnia magna*, and a 28d to 44d NOEC of 8.0 to 23.9 mg/L with fish.

No substance relevant data is available for algae, but the reported value is in agreement with other ammonium salts like ammonium chloride (12125-02-9) or sulfate (7783-20-2) and bicarbonates. For ammonium chloride an EC50 value of 1300 mg/L is available for algae (*Chlorella vulgaris*).

According to USEPA (1985), plant species are more tolerant (NOEC 5g/L aspersions of cucumber) than invertebrates or fish. Therefore the results for the two other trophic levels (fish and invertebrates) are more relevant.

Ammonia in the environment is part of the nitrogen cycle and has indirect and long-term effects to the ecosystems, e.g., eutrophication, groundwater pollution, water and soil acidification and can dramatically lower dissolved oxygen in the water resulting in adverse impacts on aquatic organisms. The acidifying effects on soil and water take place when ammonia ions are transformed into nitrate by micro-organisms, a so-called nitrification. In soil, if the nitrate is not absorbed by plants, and instead reaches the surface or groundwater, the acidifying effects increase. In the aquatic environment, ammonia may undergo nitrification, which yields hydrogen and consumes four atoms of oxygen for every atom of nitrogen converted so that, in certain systems, acidification and oxygen depletion may result. These indirect effects of ammonia can result in long-term negative impacts on aquatic organisms.

Exposure

Ammonium bicarbonate is widely used in various sectors as food additive (alone or as component of bicarbonate special), in industrial uses (in cooling baths, in fire extinguishers, in the manufacture of porous plastics and ceramics, dyes, and pigments, in catalyst system for the stiffening of tobacco), in therapeutic and agricultural uses. The present hazard assessment covers ammonium bicarbonate as industrial chemical. Ammonium bicarbonate is a naturally occurring substance. The production and use of ammonium bicarbonate may result in inhalation, dermal and/or oral exposure.

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. However, as the substance degrades in the environment to nitrite, it is recommended that the releases of ammonium bicarbonate are taken into account when assessing the exposure of nitrite and nitrate in drinking water.

Environment: This chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (fish and *Daphnia*). These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure level. However, ammonia has indirect and long-term effects to the ecosystems, e.g. eutrophication, groundwater pollution and soil acidification due to the nitrification of ammonia.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1067-53-4
Chemical Name	Tris(2-methoxyethoxy)vinylsilane (VTMOEOS)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Analog Justification**

VTMOEOS undergoes rapid hydrolysis, which occurs during testing, such that observed toxicity is likely due primarily to the hydrolysis products. The primary hydrolysis products are known to be 2-methoxyethanol (EGME) (CAS No. 109-86-4) and the corresponding vinyltrisilanol (CAS No. 143-48-6). 2-Methoxyethanol and a silanetriol have been used to supplement the existing partition coefficient, water solubility and acute aquatic toxicity (fish, aquatic invertebrate, and algae) data for VTMOEOS. Fugacity modeling of the vinylsilanetriol is also presented. Adequate data for the sponsored substance are presented for the remaining physical chemical properties, environmental fate and mammalian toxicity endpoints. Additional data on EGME are to be made available via the World Health Organization IPCS CICAD process.

Human Health

There are no human studies with VTMOEOS. No data were available on the toxicokinetics, metabolism and distribution of VTMOEOS.

The oral (gavage) LD₅₀ in rats of VTMOEOS was determined using OECD guideline 401 and is greater than 2000 mg/kg bw. Clinical signs included hypoactivity and tremors. Autopsy findings included gastrointestinal abnormalities, slight lung congestion, prominent acini with some mottling of the liver, pale kidneys and slight congestion of the adrenals. When dosed in a vehicle, signs of toxicity included piloerection and lethargy, followed by excessive salivation, sweating, diuresis, diarrhea and blood staining around mouth and nostrils. The dermal LD₅₀ of VTMOEOS in rats was determined using OECD guideline 402 and is greater than 2000 mg/kg bw. Desquamation was noted sporadically during the study. The dermal LD₅₀ of VTMOEOS in rabbits was 1560 mg/kg bw. Covered applications produced necrosis of the skin and when death followed, the lungs were hemorrhagic, livers congested, and kidneys pitted on the surface. VTMOEOS is mildly irritating to the skin (using OECD guideline 404 or similar) and eyes (using OECD guideline 405 or similar). No sensitisation data were available for VTMOEOS.

In a combined oral gavage OECD 422 study in rats there were no test article-related effects on mean body weights, body weight gains or food consumption in the toxicity phase females. Hematological effects were observed in both sexes in the 250 mg/kg/day toxicity phase group. These findings correlated with the microscopic finding of hypocellularity in the sternal bone marrow, in which aggregates of mature granulocytes were absent. Serum

chemistry parameters in the 250 mg/kg bw/day toxicity phase male and female groups were observed. Test article-related macroscopic changes, microscopic changes and/or reductions in organ weights were observed in the 75 mg/kg bw/day group males and the 250 mg/kg bw/day group males and females. The NOAEL for VTMOEOS for male systemic toxicity is 25 mg/kg bw/day. Based on effects on hematology and serum chemistry parameters and effects on lymphoid tissues for females at 250 mg/kg bw/day, which were similar to the effects noted for males, the NOAEL for female systemic toxicity is 75 mg/kg bw/day. Based on decreased fertility at 250 mg/kg/day, macroscopic and microscopic changes with corresponding decreases in weights for the male reproductive organs at 250 mg/kg bw/day and the reduced mean litter size in the 75 mg/kg bw/day group, the NOAEL for VTMOEOS for male and female reproductive toxicity was 25 mg/kg bw/day. The NOAEL for fetotoxicity/developmental toxicity is 75 mg/kg bw/day. A role for developmental toxicity in the reduced postnatal survival at this dose cannot be excluded. The NOAEL for teratogenicity is ≥ 75 mg/kg bw/day.

In vitro, VTMOEOS was negative in bacterial mutagenicity assays (OECD guideline 471 or similar) and did not induce chromosomal aberrations (OECD guideline 473) in CHO cells. No carcinogenicity studies were available for VTMOEOS.

Environment

VTMOEOS is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions. The melting point of VTMOEOS is 30.15°C and the boiling point is 285 °C at 1013 hPa. The vapor pressure is 0.00104057 hPa at 25 °C. The estimated water solubility of VTMOEOS is 1000 g/L; the estimated log Kow is -1.14. The water solubility and log Kow values may not be applicable because the chemical is hydrolytically unstable. The water solubility and partition coefficient of 2-methoxyethanol range from 5 to 1000 g/L and -0.61 to -0.77, respectively. The estimated water solubility and partition coefficient of vinylsilanetriol are 1000 g/L and -2.01, respectively.

The overall OH rate constant is 0.00000000070836 cm³/molecule-sec with an estimated half-life of 0.23 days with a hydroxyl radical concentration of 5.0×10^5 molecule/cm³. Photodegradation as a mode of removal is unlikely as VTMOEOS is hydrolytically unstable. VTMOEOS is reactive and hydrolytically unstable, such that 2-methoxyethanol and vinylsilanetriols are rapidly generated upon contact with water or water vapor. Consequently, reaction with water vapor is likely the predominant degradation process for VTMOEOS in air and the overall reaction half-life in air should include both the oxidation half-life and the hydrolytic half-life. The overall reaction half-life in air is estimated to be less than 0.15 days because of rapid hydrolysis of the material with moisture in the atmosphere. The products resulting from VTMOEOS hydrolysis in the atmosphere are expected to further react with hydroxyl radicals. The overall OH rate constant for vinylsilanetriol is 0.0000000003665 cm³/molecule-sec with an estimated half-life of 0.4 days with a hydroxyl radical concentration of 5.0×10^5 molecule/cm³.

At pH 7 and 25° C, the half-life is 61.5 minutes the hydrolysis products are 2-methoxyethanol and corresponding vinylsilanetriols. Level III fugacity modeling for VTMOEOS, using loading rates for Air, Soil, and Water of 1000 kg/h for each medium, shows the following percent distribution: Air = 0.4%; Soil = 94%; Water = 5.6%; Sediment = 0%. However, VTMOEOS is unlikely to be found in the environment. Level III fugacity modeling for vinylsilanetriol, using loading rates for Air, Soil, and Water of 1000 kg/h for each media, shows the following percent distribution: Air = 0.0%; Soil = 39%; Water = 61%; Sediment = 0.1%. VTMOEOS is readily biodegradable. The biodegradation observed is likely reflective of the hydrolysis product, 2-methoxyethanol. The biodegradation rate for 2-methoxyethanol after 14 days is 100% and after 10 days is 65-77%. Bioaccumulation is not anticipated since this material is hydrolytically unstable.

VTMOEOS undergoes rapid hydrolysis in aquatic media, and thus the exposures to VTMOEOS are likely to be transient. The 96-hour LC50 of VTMOEOS for a freshwater fish (*Brachydanio rerio*) is >100 mg/L. There were no deaths at 100 mg/L, the highest concentration tested. The 96-hour EC50 of 2-methoxyethanol ranges from 15,500 to 16,000 mg/L for *Oncorhynchus mykiss*. 96-Hour LC50 values for 2-methoxyethanol have also been reported for *Lepomis macrochirus* ($>10,000$ mg/L) *Leuciscus idus* (>500 mg/L), *Menidia beryllina* ($>10,000$ mg/L), *Oryzias latipes* (> 89 mg/L) and *Salmo gairdneri* (14,997 mg/L). Studies have been performed with a silanol monomer, trimethylsilanol (CAS No. 1066-40-6). Although this silanol is not a hydrolysis product of VTMOEOS, it has been predicted to be one of the most toxic to aquatic organisms of all the silanols identified to date. A semi-static 96h study with trimethylsilanol and rainbow trout (*Oncorhynchus mykiss*) resulted in a NOEC of 128 mg/L and an LC₅₀ of 271 mg/L. The 48-hour EC50 of VTMOEOS is 314 mg/L for the water flea (*Daphnia magna*) under static conditions. The 48-hour EC50 of 2-methoxyethanol is greater than 85 mg/L for the water flea (*Daphnia magna*). The 48-hour EC50 of trimethylsilanol is 124 mg/L for the water flea (*Daphnia magna*) under semi-static conditions. In an algae study with *Scenedesmus subspicatus* and VTMOEOS, on the basis of biomass, the median

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effective concentration was 72 h EbC50 = 304 mg/L and 72 h EbC10 = 79 mg/L. On the basis of growth rate, a median effective concentration was achieved at (0-72 hr) ErC50 = 611 mg/L; (0-72 hr) ErC10 = 136 mg/L. The NOEC was 75 mg/L. The 48 hr EbC50 is greater than 93 mg/L for 2-methoxyethanol and *Pseudokirchneriella subcapitata*. The most sensitive endpoints for *Pseudokirchneriella subcapitata* exposed to trimethylsilanol were cell density and area under the growth curve (biomass). The 72-hour EC50 value was 555 mg/L with 95% confidence limits of 141 and 612 mg/L. The 72-hour NOEC, based on cell density, area under the growth curve (biomass) and growth rate was 70 mg/L. The 96-hour EbC50 value was 625 mg/L with 95% confidence limits of 555 and 702 mg/L. The 96-hour NOEC, based on area under the growth curve (biomass), was 70 mg/L. Three plant species, *Triticum aestivum* (wheat), *Brassica alba* (mustard), and *Lepidium sativum* (cress) were tested at concentrations of 0, 1, 10 and 100 mg VTMOEOS/kg soil. Five seeds of each species were planted in four replicates. Seedling wet weights were evaluated on day 17. The EC50 for emergence of seedlings and wet weight for wheat, cress and mustard were 29, 94 and >100 mg/kg, respectively; the NOECs for all three species were >100 mg/kg.

Exposure

VTMOEOS undergoes rapid hydrolysis, which occurs during testing, such that observed toxicity is likely due primarily to the hydrolysis product 2-methoxyethanol, with some potential exposure to trisilanols, and silanol oligomers. The alkyl silanols condense to siloxane oligomers; this condensation of silanols is affected by both concentration (the silanetriol has a tendency to condense at concentrations greater than 500 ppm) and pH, and since both change over time it is not feasible to isolate specific silanols for analysis (the structures continue to evolve until they either reach equilibrium or precipitate out of solution).

In the Sponsor Country, production volume of VTMOEOS in 2001 was 285 tonnes with imports of 270 tonnes. In production, this material is handled in closed systems. Necessary engineering controls during production 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 pipe, drums, or tanks rather than in open systems to minimize loss of this material (hydrolysis).

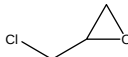
VTMOEOS is bi-functional molecule, containing organo functional groups, which can form strong covalent crosslink with polymers and hydrolysable groups capable of forming strong covalent bonds with the hydroxyl groups on silica surfaces. This functionality allows reaction both with organic and inorganic fillers. It can be used as an adhesive and an accelerant. The major uses of VTMOEOS are in wire and cable, as a pre-treatment for clay filler. VTMOEOS is transported from the production site as the parent silane. The parent silane partially reacts during use by the customer and then completely reacts during curing into the polymer matrix and is no longer available for consumer or worker exposure. VTMOEOS does not volatilize during the cure of crosslinked EPDM or polyolefins. Instead this material hydrolyzes and condenses, producing 3 moles of 2-methoxyethanol and one mole of vinylsilanetriol for each mole of parent silane. Therefore, there is no human exposure to VTMOEOS from use in cross-linked ethylene propylene diene monomer (EPDM) and polyolefin based thermoplastics. Potential routes of exposure for workers include dermal contact and inhalation, although dermal exposures are minimal as chemical protective gloves and/or clothing would be required during handling. There is no known production process that involves aerosolized material or sprayed material. The product is stored on site in tanks, bins, drums and pails. At the customer level, the material is used in closed systems. Open systems as such are not known to be used in the production of treated filler. Industrial customers purchase VTMOEOS in closed vessels (such as Intermediate Bulk Containers) from the manufacturer. The VTMOEOS is pumped from these containers into a treating chamber, where hydrolysis of VTMOEOS occurs. Note that the chamber is not sealed (vapour tight) vessel, but is a closed container with an exhaust system tied into an incinerator. Necessary engineering controls during use are likely to include local ventilation. Exposure due to non-accidental releases are expected to be minimal, and may include dermal and inhalation potential. The treated clay is sold to medium voltage wire and cable manufacturers, for buried utility applications. The wire and cable is formed in an extruder. Industrial customers exposure to 2-methoxyethanol is expected to be negligible as the initial loading rate onto the clay is 0.5 % or less. Contact with the final product (laying buried cable) is small.

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

Human Health: The chemical possesses properties indicating a hazard for human health (reproductive and haematological effects). Due to the rapid hydrolysis to 2-methoxyethanol and the corresponding trisilanol and based on exposure data presented by the Sponsor country, the parent material and its hydrolysis products, including 2-methoxyethanol, will not be available for exposure, and therefore this chemical is currently of low priority for further work. These properties should nevertheless be noted by chemical safety professionals and users.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-89-8
Chemical Name	1-Chloro-2,3-epoxypropane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

In mammals, 1-chloro-2,3-epoxypropane (epichlorohydrin) was absorbed and metabolized rapidly after oral or inhalation exposure. The two primary routes of metabolism of epichlorohydrin were conjugation with glutathione (GSH) with subsequent metabolism to mercapturic acid conjugates that were eliminated in the urine, and hydrolysis of epichlorohydrin to α -chlorohydrin which was further metabolized and exhaled as CO₂ or excreted in urine as a mercapturic acid conjugate. In multiple investigations (oral and inhalation), approximately 25 to 42 percent was exhaled as CO₂ and roughly 50 percent was eliminated via the urine.

Acute oral LD₅₀ values for epichlorohydrin in rats were 175 (female) and 282 (male) mg/kg and the dermal LD₅₀ following a single occluded application to rabbits was 515 mg/kg. The acute inhalation LC₅₀ for a 1-hour exposure of rats was 3617 ppm (13,746 mg/m³) for males and 2165 ppm (8227 mg/m³) for females (values for mice were similar). The LC₅₀ for a 6-hour exposure of male rats was 360 ppm (1361 mg/m³).

In primary irritation studies, epichlorohydrin was corrosive to the skin and eye. Vapors of epichlorohydrin at 1790 ppm or higher also produced damage to the cornea of rats. Epichlorohydrin was considered to be a skin sensitizer based on animal studies. In humans, epichlorohydrin was shown to be a severe irritant and a skin sensitizer.

Subchronic repeated-dose studies indicated that oral or inhalation exposure to epichlorohydrin caused local toxicity (irritation) at the site(s) of contact. Indications of systemic toxicity were principally changes in body weight and food consumption. Except at the site of contact, organ-specific toxicity was minimal for studies of 90 days or longer; increases in kidney weight accompanied by slight histopathological effects were observed at inhaled concentrations of 25 and 50 ppm (95 and 190 mg/m³, respectively). The NOAEL for rats and mice following 90 days of exposure to epichlorohydrin vapors was 5 ppm (18.9 mg/m³). The NOAEL for oral (gavage) dosing following 90 days of exposure was 1 mg/kg bw-day (based on decreases in red blood cell parameters and organ weight changes at higher doses). All of the repeated-dose studies confirm the irritant properties of epichlorohydrin, with localized irritation, often severe, occurring at the site of contact following repeated gavage dosing, at doses greater than approximately 1 mg/kg bw-day, and following inhalation exposure at concentrations greater than approximately 5 ppm (18.9 mg/m³).

Epichlorohydrin was consistently genotoxic in both *in vitro* and *in vivo* assays.

Squamous cell carcinomas of the nasal epithelium in rats were observed following exposure via inhalation of epichlorohydrin at the highest concentration of 30 ppm (113 mg/m³). Squamous cell papillomas and carcinomas of the non-glandular stomach (forestomach) were observed in rats following gavage dosing with epichlorohydrin at the highest concentration of 10 mg/kg bw-day or following drinking water administration at 375 mg/L (approximately 18 mg/kg bw/day) or higher. Based on these findings, epichlorohydrin is considered to be carcinogenic in experimental animals. Carcinogenic effects in humans have not been established in the epidemiology studies of workers either manufacturing or using epichlorohydrin.

In an inhalation fertility study, male rats and rabbits were given doses of 5, 25, and 50 ppm (18.9, 95, and 190 mg/m³, respectively) and mated with untreated females. Male rat infertility was observed at 50 ppm and preimplantation losses were observed at the two highest doses. The resorption rate was significantly increased at

50 ppm. These effects were reversed after 2 weeks of exposure. No effects on counts, motility, viability, and fertility of sperm were observed in the rabbits, nor were any effects observed on number of corpora lutea or resorptions in unexposed females mated to treated males. In a gavage study, male rats were treated with 12.5, 25, and 50 mg/kg bw/day and mated with untreated females. Fertility was assessed only at 50 mg/kg bw/day and was completely impaired. Several parameters related to sperm motility were affected at all doses with dose-dependent trends. Other oral studies also resulted in male infertility and effects on sperm at doses of 20 mg/kg bw/day and higher at exposures of one or more days; effects on fertility reversed in one of these studies, although two studies resulted in retained or abnormal sperm at 10 to 12 weeks after exposure ceased. Reproduction and fertility in female rats was not affected in inhalation and oral studies. Reproductive effects in humans have not been established in the epidemiology studies of workers either manufacturing or using epichlorohydrin.

Developmental toxicity studies were conducted by inhalation at doses of 2.5 and 25 ppm (9.5 and 95 mg/m³) in rats and rabbits and via gavage at doses of 40, 80, and 160 mg/kg bw/day in rats and 80, 120, and 160 mg/kg bw/day in mice. In the gavage study in mice, epichlorohydrin resulted in decreased fetal body weights in mice (7 percent from controls at 120 mg/kg bw/day and 9 percent at 160 mg/kg bw/day). However, no other signs of fetal toxicity were observed in these studies.

Environment

Epichlorohydrin is a liquid with a melting point of -57 °C and boiling point of 116.4 °C. At 20 °C the density is 1.181 g/cm³. The vapour pressure of epichlorohydrin is 22.7 hPa, while the water solubility is 66,000 mg/L at 25 °C. The measured log K_{ow} is 0.45.

The half-life for indirect photooxidation of epichlorohydrin in the atmosphere is 24 days. Based on Level III fugacity modeling, when released to air, epichlorohydrin will primarily remain in air with some transfer to water and soil. When released to water, epichlorohydrin will remain dissolved in water. When released to soil, epichlorohydrin will be primarily dissolved in soil pore water (groundwater). Simultaneous release to air, water and soil is predicted to result in distribution to water and soil compartments. A hydrolysis study (OECD TG 111) revealed half-lives in water of 7.3, 3.9 and 6.8 days at pH 4, 7 and 9 at 20 °C, indicating epichlorohydrin is hydrolyzed in the aquatic environment. Hydrolysis of epichlorohydrin results in the formation of 1-chloro-2,3-dihydroxypropane. Epichlorohydrin was 75% degraded in two days in a biodegradation assay with adapted sludge. On the basis of this study, epichlorohydrin can be considered to be biodegradable. Based on the low log K_{ow} of 0.45, the bioaccumulation potential is expected to be limited.

An acute fish toxicity test with juvenile fathead minnows revealed an LC₅₀ of 10.6 mg/l (nominal concentration) after 96 hours of exposure. An acute toxicity test with water fleas (*Daphnia magna*) resulted in a 48-hour EC₅₀ value of 23.9 mg/l based on nominal concentrations. An OECD guideline study with algae (*Pseudokirchneriella subcapitata*, formerly known as *Selenastrum capricornutum*) resulted in a 72-hour EC₅₀ of 7.1 mg/l and a NOEC value of 1.7 mg/l, both based on biomass and mean measured concentrations. The 72-hour EC₅₀ based on growth rate was 15 mg/l.

Exposure

The annual global production volume of epichlorohydrin is estimated to be about 1 million tonnes per year. The estimated production in the US for 2002 was 480 000 metric tonnes. Releases of epichlorohydrin to the environment from all industries in the United States have been reported as approximately 100 000 kg/year (~100 metric tonnes/year), most of which were released to the atmosphere. The estimated production in Europe for 2002 was 317 000 tonnes. The estimated production in Japan and the Pacific region for 2002 was 365 000 tonnes.

Epichlorohydrin is used only as a chemical intermediate (industrial use). It is used in closed systems with approximately 75% of world consumption of epichlorohydrin used for the production of epoxy resins and 9% used in the production of synthetic glycerin. The remainder is used for the production of miscellaneous products such as elastomers, polyamide-epichlorohydrin resins for wet-strength resin production, glycidyl ethers, glycidyl methacrylate, surfactants, ion exchange resins, polyamide water treatment chemicals, flame retardants and quaternary amines. In the occupational setting, closed system operations allow for the safe handling of epichlorohydrin and personal protective equipment is routinely suggested.

Consumer products are expected to contain only trace levels of epichlorohydrin based on its reactivity and use as an intermediate in polymer and other chemical synthesis since epichlorohydrin is not directly added to consumer

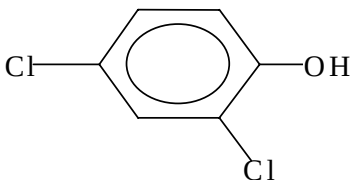
products. The World Health Organization derived a provisional drinking water guideline of 0.4 µg/L (2004). In the sponsor country from a preventive health standpoint, exposures follow the principle of as low as reasonably achievable (ALARA) preferably zero.

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

Human Health: The chemical is a low priority for further work. The chemical possesses properties indicating hazards for human health (skin, eye, and respiratory tract irritation, skin sensitization, genetic toxicity, carcinogenicity, and reproductive effects). Based on data provided by the sponsor country (relating to production by several producers in the United States which account for 42 percent of the global production and relating to the use pattern primarily in the United States), risk management measures are being applied (engineering controls, occupational standards, drinking water standards, Material Safety Data Sheets, and other US regulations). Countries may desire to check their own risk management measures to find out whether there is need for additional measures.

Environment: The chemical has properties indicating a hazard for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However the chemical is of low priority for further work for the environment because environmental exposures are expected to be limited due to its use as a chemical intermediate in closed systems.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	120-83-2
Chemical Name	2,4-Dichlorophenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Free 2,4-dichlorophenol (2,4-DCP) does not accumulate in tissues. 2,4-DCP is a strong uncoupler for oxidative phosphorylation. It is rapidly metabolised into its glucuronate conjugate, its major metabolite, and is mainly excreted in this form via urine.

The acute oral toxicity is low: LD₅₀ 1276-1352 mg/kg b.w. when tested in CD 1 mice. The dermal toxicity is moderate: LD₅₀ in Sprague Dawley rats was 780 mg/kg with molten substance at 40°C. Further occupational deaths have been reported in five cases. Accidents generally occurred in the same way: workers died after being sprayed with molten (60°C) 2,4-dichlorophenol. US-EPA concludes that contact with only 1% of the body surface may lead to death. The skin irritation tests with 2,4-dichlorophenol reports the substance to be "corrosive" to skin and risk of serious damage to the eyes is expected.

The skin sensitisation potential has not been assessed. Its evaluation may be considered as unwanted due to the necessity to avoid contact with corrosive materials. Chloracnea appears at human exposure to a mixture of chlorophenols containing 2,4-dichlorophenol.

The 2-year study (Fischer 344 rat) was chosen to establish an overall NOAEL, after prolonged treatment with 2,4-dichlorophenol, of 440 mg/kg bw/d for male and above 250 mg/kg bw/d for female, which is in agreement with the findings in the other studies. In a 90 days repeated dose toxicity study dietary administration produced bone marrow degeneration at about 800 mg/kg bw/d in females or at 1500 mg/kg bw/d in males; at 3000 mg/kg bw/d these effects were not seen. The general appearance was affected at the top dose of 3000 mg/kg bw/d.

The genetic toxicity is assessed by *in vitro* and *in vivo* studies. *In vitro*, most of the test results were negative. An *in vivo* micronucleus test, an unscheduled DNA synthesis test and two sister chromatid exchange assays were all negative. It is concluded that the material is not genotoxic as the results of the *in vivo* tests are negative.

No evidence of carcinogenic activity was reported in rat and in mouse exposed orally for two years. These results are supported by the conclusion of the IARC: although polychlorophenols and their salts are classified in group 2B, there is evidence suggesting lack of carcinogenicity of 2,4-DCP in experimental animals (IARC, 1999).

In a two-generation study in rat (OECD Guideline 416), effects have been observed at 2000 and 8000 ppm on reproduction parameters such as a slight decrease in mean litter size and mean numbers of implantations. Transient mammary swelling was frequently observed in the F0 and F1 females after weaning of their infants. F1 males treated at 8000 ppm, presented adverse effects (delay in sexual development, increase in relative weight testis). The NOAEL for fertility is 500 ppm (33.4 mg/kg bw/d for males and 49.1 mg/kg bw/d for females).

In a one-generation study, no effect was observed via drinking water at 500 mg/kg bw/d in mice. A non-

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conventional one-generation study with rats using dose levels up to 15 mg/kg bw/d did not show any significant effect on reproduction parameters. The only significant effect was an increase of some hematologic parameters (red blood cell and hemoglobin), in the F1 generation at 15 mg/kg bw/d, observed after a 14 month exposure. *In vitro* studies showed no effect on penetration of sperm in mouse ova.

In an OECD Guideline 414, no teratogenic effect was observed in rats exposed by gavage at doses up to 750 mg/kg bw/d. The NOAEL for maternal effects is <200 mg/kg bw/d, (lowest dose tested) and the NOAEL for foetal effects is 375 mg/kg bw/d.

No teratogenic effect was observed either in the OECD Guideline 416 study but some delay has been observed on pups growth and their differentiation such as eye opening at 8000 ppm. A slight increase in relative uterine weight was observed at 2000 and 8000 ppm in females weanlings, associated with an increased height of the epithelial cells in the uterine horn in F1 weanlings at 8000 ppm. It was concluded that NOAEL for growth and development of the offspring is 500 ppm (33.4 mg/kg bw/d for males and 49.1 mg/kg bw/d for females).

The hormone disruption potential of 2,4-DCP was shown in only one *in vitro* test considered to be invalid. In another *in vitro* tests on estrogenic activity (competitive binding and response to proliferation culture) results were negative. In the 2-generation reproductive toxicity in rat, some findings, such as increased uterine weight in females weanlings, females showing mammary swelling after weanling of their pups, slight delay of the age of sexual development in males and reduced numbers of implantation sites and litters sizes, could coincide with known estrogenic effects. One of the possible interpretations is that 2,4-DCP might alter endogenous sex hormone concentrations by a specific mechanism through which the estrogenic phenotype appears in treated animals. However, the study didn't show any changes in serum concentrations of pituitary or sex steroid hormones (FSH, LH, Prolactin, Estradiol, Progesterone) in the treated females at necropsy after weaning of the offspring. Furthermore, results were also negative in two *in vivo* tests (a uterotrophic assay and a Hershberger assay), thus endocrine disruption potency of 2,4-DCP could not be evidenced.

Environment

2,4-DCP is a white solid in crystal or needle forms. It has a low vapour pressure at room temperature (0.16 hPa at 25 °C). The water solubility of 2,4-DCP is 4.5 g/l at 25 °C, but since the pKa is 7.89, which falls in the pH range of environmental waters (approximately 6-9), the extent of dissociation of 2,4-DCP may vary significantly. The measured log Pow is 3.21-3.25 at 20°C.

Based on its vapour pressure, 2,4-DCP is expected to have a low volatility from dry soil surfaces. In contrast, photodegradation should be an important means of removing 2,4-DCP from clear surface water. Atmospheric oxidation half-life is estimated by QSAR to be 3.6 days. Hydrolysis is not expected to occur: halogenated aromatics and phenols are generally resistant to hydrolysis. Mechanisms other than photodegradation and microbial degradation, as adsorption by organic matter present within the sediments, catalysis at the surface of silica or oxidation, may also be involved in the disappearance of 2,4-DCP from water. Since the pKa is around 7.8, 2,4-DCP will exist in water and sediment in a partially dissociated state which may affect its transport and reactivity. Similarly in soil, the ionised form (in alkaline soil) is poorly adsorbed, whereas the neutral form (acid soil) is expected to undergo more adsorption. Adsorption will also increase with increasing organic matter content.

Biodegradation studies have shown that 2,4-DCP was not readily biodegradable, but it was inherently degradable only in the presence of adapted microflora, both in aerobic and anaerobic conditions. Anaerobic degradation of 2,4-DCP produced 4-chlorophenol as the major product. The BCFs of 7.1 to 69 in carp suggest that bioaccumulation in aquatic organisms is low.

Aquatic effects

In acute toxicity studies, the lowest LC₅₀ values are 1.7 mg/L for freshwater fish and 1.4 mg/l for *Daphnia magna*. For aquatic plants, results on Lemna are available, leading to EC₅₀ (7d) = 1.5 mg/L (endpoint: vegetative frond reproduction). In chronic toxicity studies, a NOEC of 0.29 mg/l for a fish, of 0.41 mg/L for Lemna (endpoint: vegetative frond reproduction) and a NOEC of 0.21 mg/l (endpoint: reproductivity rate) for *Daphnia magna* have been obtained. In a non-standard valid test on net spinning behaviour of the Trichoptera larvae, A LOEC value of 0.0035 mg/l was derived.

Despite the numerous consistent data available on fish, *Daphnia* and algae, issued from acute and chronic toxicity studies, due to the uncertainties on ecological relevance of the endpoint of the Trichoptera study, no final decision

was made regarding PNEC derivation.

Tests with activated sludge resulted in EC50 values of 32 – 73 mg/l. Tests with *Pseudomonas putida* and *Tetrahymena pyriformis* resulted in EC50 values of 133 and 4.5 – 12.6 mg/l, respectively. Test with nitrifying bacteria resulted in a EC50 value of 0.15 mg/l. This latter value could be used for the derivation of a PNEC.

Terrestrial effects

The LC50 for earthworm is 125 mg/kg dw and for plants the EC50 is 316 mg/kg dw. The EC10 in a 34 day test with *Folsomia candida* was 0.7 mg/kg dw.

Exposure

The production volume of 2,4-dichlorophenol was 2000 to 5000 tonnes per year in France.

The use is non-dispersive, as an intermediate for synthesis in chemical industry. The product is not dispersed or transported outside of the site in the Sponsor country, the process functions in a closed system. The principle hazard for manufacturers or users can be burns by accidents at debottlenecking with a temperature higher than 60°C. In closed systems if there is a leak the penetrating odour of 2,4-dichlorophenol gives an alert.

The possible sources of 2,4-DCP in the environment are through the degradation of 2,4-D (2,4-dichlorophenoxy acetic acid, herbicide), or potentially chlorination of phenol-containing water.

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

The chemical possesses properties indicating a hazard for human health (acute toxicity, corrosivity, toxicity to reproduction) and the environment. Based on data presented by the Sponsor country, exposure to humans and the environment 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. The main source for 2,4-DCP measured in the environment appears to be through degradation of the pesticide 2,4-D.

In other programmes: an EU evaluation (in relation to the Community Strategy for Endocrine Disrupters) is ongoing for the environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1333-86-4
Chemical Name	Carbon Black
Structural Formula	Elemental Carbon (C)

The current assessment focuses exclusively on industrially manufactured carbon black which is a generic term for a high purity elemental form of carbon consisting of near spherical colloidal primary particles (10-500 nm in diameter) fused into aggregates of such particles (80-810 nm in diameter) during a totally enclosed production process. The aggregates are tightly bound, forming the primary, dispersible unit of carbon black, and rapidly form agglomerates in the reactor. Carbon black contains less than 1% organic impurities firmly adsorbed to its surface, including polycyclic aromatic hydrocarbons (PAHs).

Other forms of carbon-containing respirable particles that are released from various industrial and other processes, such as the incomplete combustion of carbonaceous materials (e.g. soot or diesel exhaust particles) and which contain higher proportions of adsorbed organic compounds such as PAHs are not covered by this assessment.

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Uptake and retention of carbon black particles in lung macrophages has been observed following inhalation. In rats, clearance of carbon black particles from the respiratory tract is delayed at lung burdens equal or greater than 0.5 – 1.0 mg carbon black / g lung ("lung overload"). Little carbon black is found in Peyer's patches after oral exposure. It is unlikely that the insoluble particles are capable of skin penetration.

The acute oral toxicity of carbon black in animals is very low; no clinical signs of toxicity were noted in rats gavaged with the maximum technically achievable dose (8000-10,000 mg/kg bw). Small inflammatory changes in lung and bronchoalveolar fluid were found in rats after a 7-hour inhalation exposure to a high surface area carbon black (20 nm primary particle size; 1 mg/m³), whilst low surface area carbon black (200 nm primary particle size; 1 mg/m³) had no effect.

Carbon black was not irritating to the skin and eyes of rabbits in tests performed similar to current OECD guidelines. As superficial foreign bodies, carbon black particles may be slightly irritating mechanically and may cause discoloration of lids and conjunctivae in humans. There is no information to suggest that carbon black might be a skin sensitizer.

After repeated inhalation of a high surface area carbon black for 13 weeks, no pathological or biochemical changes were found in the lungs of rats at 1.1 mg/m³ (NOAEL, respirable fraction) but there were clear dose related increases in both biochemical and cellular markers of inflammation and lung damage at the next higher concentration of 7.1 mg/m³ (respirable fraction). By 8 months post-exposure there was substantial clearance of the carbon black retained in the lungs of animals exposed to 1.1 mg/m³, moderate clearance in the mid-exposure group (7.1 mg/m³) and very little at 52.8 mg/m³. Severe lung damage (including lung tumours) was seen in rats of both sexes exposed for 2 years to 2.5 mg/m³ (16 hrs/day, 5 days/week).

In exposed carbon-black production workers, repeated inhalation exposure to carbon black can cause decrements in pulmonary function, increases in reported respiratory symptoms, and, possibly, chest film changes. Based on data from a large European multi-centre study covering 19 plants in 7 countries (UK, 2 plants; France, 3 plants; Germany, 5 plants; Holland, 2 plants; Italy, 3 plants; Spain, 3 plants; and Sweden, 1 plant), predictions suggest that after 40 years exposure to 1 mg/m³ (inhalable fraction, 8-hr TWA) there would be minimal effects on lung function parameters. It has been estimated that exposure to a working lifetime of 40 years to inhalable carbon black at 1, 2 and 3.5 mg/m³ (8-hour TWA) would lead to mean decreases in FEV₁ of 48, 91 and 169 ml,

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respectively. This may be compared to the average age-related decline in FEV₁ in adult males of about 1,200 ml over this 40-year period. A study of production workers in North America covering 22 plants (Canada, 2 plants; United States, 20 plants) yielded similar respiratory function results for 1 mg/m³ 40-year working-life exposures (FEV₁, 28 ml decrease).

In vitro, carbon blacks were non-mutagenic in various Ames tests, whilst organic extracts can exhibit a wide variety of activity, depending on the conditions of extraction. This activity is ascribed to mutagenic organic impurities (mainly polycyclic aromatic hydrocarbons) in the extract. Carbon black was tested negative in a mouse lymphoma assay, and did not induce sister chromatid exchanges in Chinese Hamster Ovary cells. The available evidence strongly suggests that Carbon Black is not directly mutagenic and that mutations are caused by secondary mechanisms such as oxidative stress; for these effects triggered by inflammatory processes, there is a threshold which has been shown to be above 1 mg /m³ respirable for high-surface Carbon Black (e.g. Printex 90). The threshold for low-surface Carbon Black is above this value.

In vivo, exposure of rats to doses of carbon black particles producing significant inflammation was associated with increased mutation in the hypoxanthine-guanine phosphoribosyl transferase gene (hprt) in alveolar type II epithelial cells. Addition of catalase inhibited the increase in mutation frequency implying a role for cell-derived oxidants in this reaction.

Animal carcinogenicity studies demonstrated that carbon black of respirable size could produce lung tumours in rats of both sexes, but not in mice or hamsters. Increases in the incidence of benign and malignant lung tumours were seen at the lowest concentration tested (2.5 mg/m³, 16 hrs/day, 2 years). The lung tumours occurred under conditions that resulted in impaired lung clearance ("overload"). There is also evidence that inflammation and cell proliferation may have contributed to the development of rat lung tumours.

Skin painting studies in mice using a variety of commercial carbon blacks did not induce signs of skin cancer development. Limited lifetime oral studies showed no evidence of dermal carcinogenicity in rats and mice. Studies of the carcinogenic potential of carbon black in workers generally suffer from limitations, and are considered not to reveal clear evidence for a causal role of carbon black in the development of human cancers (IARC 1996).

In relation to lung cancer, various cohort and case-control studies in the US did not show any increases in lung cancer risk in carbon black production workers. Cohort mortality studies of workers exposed to carbon black in the UK found an excess of lung cancer in some, but not all factories included in the study, and there was no association between duration of carbon black exposure and lung cancer mortality, nor were possible confounders such as smoking or past occupational histories taken into account.

A number of cases of skin cancer were identified in carbon black production workers in the US, whilst in a cohort of carbon black workers in the UK no excesses of skin cancer were found. Also, a study in the rubber and tyre manufacturing industry did not reveal an increased risk of squamous cell skin cancer in workers exposed to carbon black contaminated materials.

An excess number of bladder cancer cases were recently reported in dock workers with a history of manually unloading shipments of carbon black. As there is no information on potential confounding factors such as other chemical exposures in this workforce, and shipyard workers at the same harbour but not exposed to carbon black also showed an increase in bladder cancer, a role for carbon black in bladder cancer is unlikely.

Based on available data demonstrating a low bioavailability, the polycyclic aromatic hydrocarbons (PAHs) contained in carbon black are generally considered not play a role in lung cancer of laboratory rats. The lung cancers in rats are considered by some to be the result of a non-genotoxic mechanism secondary to cellular toxicity brought about by lung overloading, inflammation and oxidative stress. The relevance of carbon-black induced lung tumours in rats to human health is uncertain, but it appears that the rat is the most sensitive species to the effects of lung overload.

Carbon black has not been tested in guideline studies for its effects on fertility, reproduction and the developing organism. Based on the available toxicokinetic principles, it is very unlikely that carbon black particles will reach the reproductive organs, the embryo or the fetus under *in vivo* conditions. No adverse effects on reproduction and development would therefore be expected.

Environment

Carbon black is substantially elemental carbon. It has no functional groups that could bring about solubility in water and organic solvents. Its vapour pressure is negligible. It cannot be further degraded by hydrolysis, light or by photodegradation in air or in surface water. These physico-chemical properties are reason why important parameters like water solubility, octanol/water partition coefficient, dissociation constant or adsorption/desorption which are relevant for environmental fate and distribution cannot be analytically measured. Based on these properties it is expected that carbon black will not occur in air or water in relevant amounts. Also potential for distribution via water or air, respectively, can be dismissed. The deposition in soil or sediments is therefore the most relevant compartment of fate of carbon black in the environment, but carbon is widely distributed in nature and an essential element in the components of all living organisms.

Based on the physical-chemical properties of carbon black as an inert solid, its insolubility and stability in water and in organic solvents, diffusion through the gills or through the membranes of the body of the aquatic organisms and bioaccumulation is not expected.

As an inorganic compound with the chemical structure "C", carbon black will not be further biodegraded by microorganisms.

Since carbon black is not soluble in water and a difficult substance in aquatic toxicity testing, the preparation of the test mediums was not always in accordance with the OECD standard test guidelines but was carried out in accordance with the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, published in 2000. Its low toxicity, requiring high concentrations to be tested in order that toxicity might be detected, and the low pH, depending on the type of carbon black, of some aqueous suspensions makes the testing protocol even more difficult. Nevertheless, results with fish tests have established that a fish LC_{50} related to the nominal concentrations were greater than 5000 mg/L for aqueous suspensions, and greater than 10,000 mg/L for water accommodated filtrates. The results in the acute *Daphnia* test from water-accommodated filtrates indicated an EC_{50} of 5600 mg/L related to the nominal concentration which is attributed to the pH of the solution. The algal test results, also from water accommodated filtrates, showed no adverse effects at the highest tested concentration, from a nominal concentration of 10,000 mg/L. In addition, supporting tests with tyre dust filtrates showed $LC_{50} > 58,000$ mg/L, $EC_{50} > 69,000$ mg/L, and EC_{50} of $> 13,000$ mg/L for fish, *Daphnia*, and algae respectively, all related to the nominal concentrations. Because an analytical determination of the carbon black concentration is technically not feasible in the tests medium, and the test substance is present in a biologically unavailable form, the estimation of the true exposure concentration is difficult, therefore the PNEC calculation in the aquatic environment based on the nominal concentrations or loading rates respectively is not realistic. If the fish, *Daphnia*, and algal results were used to calculate a PNEC, an application factor of 1000 would be required. If this were applied to the fish LC_{50} of $> 5,000$ mg/L, then a PNEC of > 5 mg/L would result. However, the fish and invertebrate LC_{50} and EC_{50} data are dominated by physical and pH considerations, and treatment of these results by methodology appropriate to a chemical toxicity mechanism may not be appropriate.

Carbon black is not expected to interfere with the operation of sewage treatment plants, although it was not possible to carry out a sludge respiration study, due to the particulate nature of carbon black. The dehydrogenase activity of sewage treatment organisms has been tested, with an EC_{10} of approximately 800 mg/L nominal concentration of a suspension of carbon black particles.

Although no reliable tests on terrestrial organisms have been carried out with carbon black, earthworm tests have been reported for filtered extractions of tyre dust. These tests, on filtrate from 100g of material, shaken for 24 hours in one litre of water, showed no toxicity. This supports the expected low toxicity of carbon black to terrestrial organisms.

Exposure

Worldwide production capacity of carbon black is of the order of 8 million tonnes (1996) with North America contributing about 1,815,000 tons; Western Europe 1,310,000 tons; Eastern Europe 1,545,000 tons; Asia 2,630,000 tons; South America 480,000 tons, and Africa and Australia 185,000 tons.

Approximately 90% of carbon black is used in rubber applications (70% is used as a reinforcement in tyres for automobiles and other vehicles, 20% for other rubber products such as hoses, gaskets, mechanical and molded goods, and footwear), 9% is used as a pigment in printing inks and surface coatings, and the remaining 1% as an ingredient in hundreds of diverse applications, for instance, in the manufacture of dry-cell batteries. End users of rubber, ink or paint products are not exposed to Carbon Black *per se*, it is bound within the product matrix

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(IARC 1996). Releases into the environment may occur from production and processing. Both shredded tyres, and carbon black have been shown to significantly adsorb organic pollutants. Also, aqueous desorption of adsorbed organics of various polarities from carbon black has been shown to be negligible.

Occupational exposure may occur during production and processing. Geometric mean personal exposure, measured in carbon black-producing plants in Western European countries as the respirable and inhalable dust fractions (approximately 7400 and 8000 samples, respectively) and North America as total, respirable, and inhalable carbon black dust fractions (approximately 4100, 2500 and 1000 samples, respectively) is on average less than 1 mg/m³ on an 8-hour time-weighted average basis. A recent study has demonstrated that occupational exposure to airborne carbon black in carbon black-producing plants is not in the ultrafine or nanoparticle range.

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

Human Health: The chemical is currently of low priority for further work.

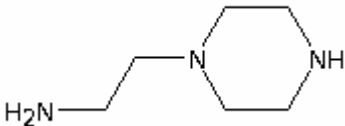
The chemical possesses properties indicating a potential long-term hazard for human health. The relevance of carbon black induced lung tumours in rats to human health is uncertain. IARC classified carbon black as Group 2B *possibly carcinogenic to humans* (1996).

It is noted that from other chemical studies [TiO₂, talc, etc.] that the rat is a species sensitive to lung overload. Judgment as to the interpretation of these data relative to human risk is clearly beyond the SIDS program. The SIAM is aware that such work is in progress. Carbon black, TiO₂ and talc were re-evaluated by IARC in February 2006.

Based on data presented by industry to the Sponsor country, exposure is controlled in occupational settings. Geometric mean personal exposure, measured in production factories in western European countries as respirable and inhalable and North America as total, respirable, and inhalable carbon black is on average less than 1 mg/m³ 8-hr TWA. In most products, carbon black is bound into a matrix. Therefore, exposure is negligible for consumers. Countries may wish to investigate any exposure scenarios that were not represented 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 No.	140-31-8
Chemical Name	Aminoethylpiperazine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No toxicokinetic data are available. The acute oral LD50 in rats is >1000 mg/kg and the 24 hour dermal LD50 in rabbits is 866 mg/kg. Neat aminoethylpiperazine (AEP) is corrosive to the rabbits' skin and causes extensive irritation to the eyes resulting in blindness. Ten percent solution produced moderate irritation in rabbits' skin and produced slight but reversible conjunctivitis in rabbits' eyes. AEP was positive in guinea pig maximization tests and animals sensitized to other structurally similar alkyleneamines may also be sensitized to AEP.

In a 28 day study, rats were dermally exposed to 100, 500 or 1000 mg/kg/day, 6h/day, 5 days/week, resulting in 22 applications. The highest dose corresponded to 25% AEP solution in distilled water. Treatment-related irritation was seen at all doses of males and the two highest doses of females; severity was dose related. No evidence of systemic toxicity was observed. The NOAEL for systemic toxicity was 1000 mg/kg/day.

The test material was negative for point mutation in bacteria (Ames Test) and mammalian cells (CHO HPRT test in Chinese hamster V79 cells). It was negative in L5178Y mouse lymphoma cells for point mutation, chromosomal aberration, human lymphocytes for chromosomal aberration, as well as unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro*. In addition, AEP was negative in the mouse micronucleus test. The positive results in a cell transformation experiment in BALB/3T3 cells were considered to be due to the high pH of the test material.

Because of the severe irritant and corrosive properties and based on current uses, a reproduction or developmental toxicity study is considered inappropriate.

Environment

AEP is a liquid at room temperature with a melting point of -17°C to -19 °C and a boiling point of 220°C to 222 °C. The vapour pressure is 0.051 to 0.075 hPa at 20 °C. Water solubility is >1000 g/L. Partition coefficient (Log Kow) is -1.48.

Hydrolysis is not expected to occur under environmental conditions (pH 5 to 9). AEP has estimated pKa₁, pKa₂ and pKa₃ values of 4.4, 8.6 and 10.1, respectively. AEP would be expected to partition primarily to water (71.4%) and to a lesser extent soil (28.6%) based on Level III Fugacity modeling (equal releases of 1000 kg/hr to air, water, and soil). Available studies indicate AEP is neither readily biodegradable nor inherently biodegradable. Half-life for indirect photolysis is estimated to be 0.6 hours.

The 96-hour LC50 value for fish (*Leuciscus idus*) was 368 mg/L, the 48-hour EC50 for invertebrates (*Daphnia magna*) was 32 mg/L, and 72-hour EC50 for algae (*Pseudokirchneriella subcapitata*) for growth rate was >1000 mg/L and for biomass was 495 mg/L. Studies without a pH adjustment showed higher levels of toxicity than studies with pH adjusted solutions. The EC20 in the one hour activated sludge respiration inhibition test was 1600

mg/L.

Exposure

Total US and Western Europe AEP production is estimated to be 20 000 metric tonnes. AEP is produced in a closed system. Due to its corrosive nature and use of protective equipment, exposure in the workplace is expected to be very low. Aminoethylpiperazine is used as a chemical intermediate and as a curing agent in some epoxy hardener applications.

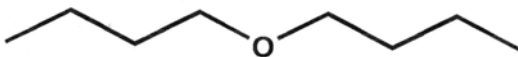
In the US, the National Institute of Health Household Products Database cites one product as being used in automotive and home-repair applications. Both uses are as curing agents (hardeners) containing 5-10% AEP. Consumer used products are sold in small two-part tubes containing equal amounts of epoxy resin and hardener. The curing agents start to react as soon as the epoxy resin and hardener contact each other. Typical set up time ranges from 5-15 minutes. In Sweden, AEP is found in 3 consumer products, all are curing agents. Products are described as containing <5%, 5-15% and 15-25% AEP, respectively. In the Swiss Registry, 10 of 142 products containing AEP are sold into consumer market. Nine of the 10 consumer products contain 1-10% AEP; the remaining product contained 10-50% AEP. The Swiss Registry was asked to review these 10 products. The 10-50% AEP product was no longer on the market, one product contained approximately 10% AEP and the remaining 8 contained 1-4% AEP. All were used as curing agents. Due to the irritating nature of the AEP and the other materials used in epoxy hardener applications as well as the short set up times, exposure is expected to be very low.

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

Human Health: The chemical possesses properties indicating hazard to human health (acute oral and dermal toxicity, corrosive to skin, skin sensitizer and causes extensive irritation to rabbits' eyes resulting in blindness). Based on data presented by the Sponsor Country (relating to production in one country which accounts for an unknown fraction of global production, and relating to the use pattern reported in several OECD member countries), 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: The chemical possesses properties indicating hazard to the environment (acute toxicity to aquatic invertebrates). Based on data presented by the Sponsor Country (relating to production in one country which accounts for an unknown fraction of global production, and relating to the use pattern in one OECD country), exposure to environment 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	142-96-1
Chemical Name	Dibutyl ether
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No experimental data are available regarding the toxicokinetic behavior, and metabolism of dibutyl ether. The appearance of systemic toxicity after oral and inhalative exposure shows the bioavailability of dibutyl ether via these routes.

Dibutyl ether is of low acute toxicity after inhalative (approximate 4-hour LC_{50} rat: 21 600 mg/m³ (4000 ppm)), dermal (LD_{50} rabbit: 7741 mg/kg bw (10.08 ml/kg bw)) and oral exposure (oral LD_{50} rat: 7400 mg/kg bw). Dibutyl ether has no pronounced narcotic potential.

Dibutyl ether is only very slightly irritating to the skin and the eyes of rabbits, as determined in GLP studies performed in accordance with OECD TG 404 and 405, respectively. All symptoms of irritation were completely reversible within 96 and 48 hours, respectively. In humans, a 15 minutes exposure towards 200 ppm (corresponding to 1066 mg/m³) dibutyl ether was reported to be sensory irritating to the eyes and the nose, but not to the throat. In a 28-day inhalation GLP study, performed according to standard guidelines, dibutyl ether at concentrations of up to and including 1500 mg/m³ was not irritating to the respiratory tract of rats. There are no indications of sensitizing properties of dibutyl ether.

No target organ appeared up to and including the highest tested concentration of 1500 mg/m³ in a 28-day inhalation study in rats, performed under GLP according to OECD TG 412 with test concentrations of 0, 150, 500, and 1500 mg dibutyl ether/m³. The repeated exposure to 1500 mg dibutyl ether/m³ caused only a temporary body weight loss in females during the first exposure week. After the first week of exposure and during the 14-day recovery period, growth of high-dose females was comparable to the control group. The treated male rats showed changes in testes, epididymides, liver and brain weights in the low- and mid-dose groups that were not confirmed by data of the high-dose group of 1500 mg/m³. Therefore the findings regarding the low- and mid-dose groups were considered as fortuitous and thus the no observed adverse effect level (NOAEL) was 1500 mg/m³. The temporary effect on body weight seen in female rats is not considered to be a serious adverse effect, and the high-concentration level of 1500 mg/m³ can be regarded as a minimum observed adverse effect level in female rats. Due to the absence of treatment-related changes, the next lower level tested, viz. 500 mg/m³, was considered to be the NOAEL in females.

In vitro, dibutyl ether was neither mutagenic in a bacterial test system (two Ames tests, each performed according to OECD TG 471 (1983)) nor clastogenic in a mammalian test system (chromosomal aberration GLP test according to OECD TG 473 on human peripheral lymphocytes).

There was no data available concerning carcinogenicity.

No specific studies have been performed on the toxicity of dibutyl ether to reproduction. Organ weight determinations and gross and histopathological examinations in a 28-day study revealed no pathological change in reproductive organs (testes, epididymides, prostate, seminal vesicles, coagulating glands, ovaries, uterus, vagina, and mammary glands) when dibutyl ether was administered by inhalation to male and female rats at concentration levels up to and including 1500 mg/m³. No histopathological effects or weight changes were found in testes and

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epididymides of rats treated orally with up to 200 mg/kg bw/day for four weeks in a study specifically designed to detect effects on male reproductive organs. In the latter study, clear testicular effects were produced in a concurrent group of animals treated with 1,6-dimethoxy hexane. This gives confidence that the study was sensitive enough to detect relevant adverse effects on the male reproductive organs, although the duration of treatment was relatively short (4 weeks). In the prenatal developmental toxicity study which is described below, there were no indications on adverse effects on female reproductive organs at doses up to and including 1000 mg/kg bw/day. The data set regarding female fertility is limited and therefore no firm conclusions can be drawn.

In a GLP study performed in accordance with OECD TG 414 on rats with oral administration of dibutyl ether from the 6th to the 19th day of pregnancy, developmental effects (fetal weight reduction, skeletal retardations in form of missing or incomplete ossification of the hyoid, caudal vertebral bodies and 5th metacarpalia, and soft tissue variations in form of dilatation of the 4th cerebral ventricle) were found at the maternally toxic dose level of 1000 mg/kg bw. There was no test item-related increase in the incidence of fetal malformations, or external or skeletal variations. Signs of maternal toxicity at 1000 mg/kg bw/day were piloerection, a reduction in body weight and food intake and an increase in water consumption, absolute and relative liver weights, and plasma aspartate aminotransferase activity. Necropsy revealed no test item-related pathological changes in reproductive organs. Under the conditions of this study the NOAEL for maternal toxicity and developmental toxicity was 300 mg/kg bw/day

Environment

Dibutyl ether has a melting point of - 95.2 °C, a boiling point of 142 °C at 1013 hPa, a water solubility of 113 mg/l, and a vapor pressure of 4.6 hPa at 20 °C. The experimental log K_{OW} is 3.35.

Dibutyl ether is not readily biodegradable under standard test conditions (OECD TG 301 D: 5 % in 28 days, test according to OECD TG 301 C 3 - 4 % in 28 days). However, naturally occurring bacteria enriched in the laboratory as mono-species cultures were used as inoculum and were able to biodegrade dibutyl ether very well, as seen with an aerobic *Gordonia terrae* strain adapted to ethyl t-butyl ether and selected from activated sludge or several *Rhodococcus sp.* and *Terrabacter sp.* strains isolated from various environmental samples like activated sludge, river water, or contaminated soils. In the atmosphere dibutyl ether is expected to undergo rapid indirect photodegradation by the reaction with photochemically produced hydroxyl radicals with a calculated half-life of 15.6 hours. Dibutyl ether does not hydrolyze under environmental conditions. However, dibutyl ether will be degraded in water under favorable environmental conditions (summer, midday) by reaction with OH radicals with calculated half-lives in the range of hours to days. According to a Mackay Fugacity Model Level I calculation dibutyl ether is mainly distributed to air (> 97 %). A high volatility from water to air is also indicated by the calculated values for the Henry's law constant (0.00362 - 0.00472 atm m³/mole). A half-life of 3.5 hours (= 0.15 days) for volatilization of dibutyl ether from river water to air and of 110 hours (= 4.6 days) for volatilization from lake water to air was calculated by EPIWIN v3.12. According to a Mackay Fugacity Model Level III calculation the residence time of dibutyl ether attributable to reaction only is below 28 days when released into air, water, or soil (100 % release into air: < 1 day, 100 % release into water: 25.5 days, 100 % release into soil: 24.4 days, 33.3 % release into air, water and soil: 16.3 days). Measured bioconcentration factors (BCF) in the range of 47 to 83 and 30 to 114 determined in laboratory tests on fish (*Cyprinus carpio*) and the calculated BCF of 76 are indicating a low bioaccumulation potential.

For the aquatic toxicity of dibutyl ether reliable experimental results (based on nominal concentrations) from tests with fish, *Daphnia*, and algae are available. The lowest valid test results were as following:

<i>Oryzias latipes</i> :	48 h-LC ₅₀ = 31 mg/l
<i>Daphnia magna</i> :	48 h-EC ₅₀ = 26 mg/l
<i>Microcystis aeruginosa</i> :	8 d-EC ₅₀ > 50 mg/l (biomass at test end)
(This test measured an EC ₁ with a non standard organism.)	

No valid study with a standard algae species is available. Based on a QSAR calculation the 96 h-EC₅₀ for dibutyl ether is 3.43 mg/l for the green algae *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*).

In an activated sludge respiration inhibition test a 30 min-EC₅₀ > 1000 mg/l was obtained. For protozoa, the lowest toxicity value was determined for *Uronema parduczi* (20 h-EC₅ > 40 mg/l).

The most sensitive species was *Daphnia magna* with a 48 h-EC₅₀ of 26 mg/l. Applying an assessment factor of 1000 according to the EU Technical Guidance Document, a PNEC_{aqua} of 26 µg/l is obtained.

Exposure

The reporting consortium knows about production sites for dibutyl ether in Germany, United Kingdom, the USA,

Japan, and the P.R. of China. The production volumes in Germany and in the USA are both approximately 1000 to 2000 tonnes per year. In Japan, this chemical is produced by at least three manufactures with an annual production volume of 450 tonnes in 2000. No information is available about the world-wide production volume and the world-wide traded volumes.

Dibutyl ether is used as a technical solvent for e.g. fats, oils, organic acids, alkaloids, natural and synthetic resins and as solvent for Grignard syntheses. It is also used as an extractant. Furthermore it is a constituent of catalysts for (co-) polymerization. Recently it has been added to the register of flavoring substance used in or on foodstuffs in the European Union. However, such an application is not known to the reporting consortium.

Releases into the environment may occur during production and processing of the substance. However at the only German production site the release into the environment is minimal under normal conditions, on account of its production and handling in closed systems by the manufacturer. At filling and decanting, state of the art exposure control measures (charcoal absorber) are installed to prevent any releases into the environment and exposures during production are below the detection limit of 2 mg/m³. Also production wastes are minimal because of recovery measures and controlled combustion. During its use in downstream products, e. g. as ingredient in industrial special cleaners (degreasers) or as technical solvent in fats, natural, and synthetic resins releases into the environment and occupational exposure may be higher than those from production, however, quantitative information is not available.

Dibutyl ether is not commonly used in consumer products. Only one single consumer product each is listed in publicly accessible European and US product registers: a degreaser containing 5 % dibutyl ether and a special cleaner, respectively. If dibutyl ether is used as flavoring substance in or on foodstuffs, consumer exposure could occur. However, this kind of application of dibutyl ether is not known to the reporting consortium.

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 (slightly irritating to eyes and upper respiratory system). These hazards do not warrant further work as they are related to reversible, transient effects. They should nevertheless be noted by chemical safety professionals and users.

Environment: The chemical is currently of low priority for further work. The chemical has properties indicating a hazard for the environment (acute aquatic EC₅₀/LC₅₀ values between 1 and 100 mg/l). However the chemical is of low priority for further work for the environment because of its fugacity, its fast photodegradation in the atmosphere, and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1653-19-6
Chemical Name	2,3-Dichlorobuta-1,3-diene
Structural Formula	$\text{CH}_2=\text{CCl}-\text{CCl}=\text{CH}_2$

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

There are no studies available concerning toxicokinetics, metabolism, and distribution of 2,3-dichlorobuta-1,3-diene. Results from toxicity studies with experimental animals show that 2,3-dichlorobuta-1,3-diene is absorbed after inhalation as well as after oral and dermal application.

2,3-Dichlorobuta-1,3-diene is moderately toxic after acute inhalation exposure with an LC_{50} of 408 ppm (2080 mg/m^3)/4 h in rats. After 2 hours exposure the LC_{50} has been calculated as 931 ppm (4750 mg/m^3) for rats and 145 ppm (740 mg/m^3) for mice in a study with limited documentation. There are no dermal LD_{50} data available but limited studies in rats, mice, and rabbits provide evidence for systemic toxicity after dermal application. The oral LD_{50} has been determined as 222 mg/kg bw for rats and 110 mg/kg bw for mice in a study with limited documentation; target organs are the stomach due to the irritant nature of the substance as well as spleen, liver, and kidney.

A 50 % solution of 2,3-dichlorobuta-1,3-diene is not corrosive to the skin of rabbits (4°hours, occlusion). However, data from two unreliable studies suggest that 2,3-dichlorobuta-1,3-diene is irritating to the skin of rabbits. There are no valid studies on eye irritation available. However, according to data given in a monograph, 2,3-dichlorobuta-1,3-diene is irritating to the eyes of rabbits. 2,3-Dichlorobuta-1,3-diene is irritating to the respiratory tract. There are no data available concerning sensitization.

There are no valid dermal or oral repeat dose studies and no standard repeat dose inhalation studies in experimental animals available. However, in the context of a one generation study with 11 weeks of whole body exposure of rats to 2,3-dichlorobuta-1,3-diene vapor it was possible to identify a NOAEC for general toxicity of 5 ppm (25.5 mg/m^3), at the LOAEC of 50 ppm (255 mg/m^3) decreases in body weight, and food efficiency as well as minimal to mild degeneration and regeneration of the nasal olfactory epithelium associated with mild to moderate atrophy of Bowman's glands are observed. Males show generally more severe nasal lesions than pregnant females, which had a 14-day recovery period. The same LOAEC of 50 ppm (255 mg/m^3) is found in a subacute range-finding inhalation study, associated with the one generation reproduction toxicity study, with rats; due to deficiencies in study design it is not possible to define a clear NOAEC from this study. Due to the fact that the substance is a chemical intermediate being manufactured and processed in closed systems exposure to the chemical is negligible. Therefore more in depth examinations of repeated dose toxicity of this substance are not warranted. In humans occupational exposure to 2,3-dichlorobuta-1,3-diene in concentrations of ≤ 2 ppm (≤ 10.2 mg/m^3) is probably not linked to possible health hazards like cardiovascular diseases and respiratory problems.

2,3-Dichlorobuta-1,3-diene is mutagenic in bacteria with and without addition of a metabolic activation system. In a micronucleus assay performed according to OECD TG 474 2,3-dichlorobuta-1,3-diene shows no clastogenic activity *in vivo* after whole body exposure of rats to vapor concentrations of up to 200 ppm (1020 mg/m^3). Overall, 2,3-dichlorobuta-1,3-diene shows a mutagenic activity *in vitro*.

There are no animal carcinogenicity studies with 2,3-dichlorobuta-1,3-diene available. A retrospective cohort mortality study with men occupationally exposed to 2,3-dichlorobuta-1,3-diene during chloroprene production showed no higher risk for them of dying from lung cancer or other causes than the general population. However, these results were based upon a relatively small number of workers and there may not have been sufficient

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statistical power to detect an excess mortality risk, if it had existed.

In a one-generation reproduction toxicity study (OECD TG 415) in rats 2,3-dichlorobuta-1,3-diene shows no impairment of fertility and no adverse effects on the fetus after exposure of the parental generation up to parentally toxic concentrations. The NOAEC for reproductive toxicity and early embryonic development is 50 ppm (255 mg/m³; highest concentration tested) and the NOAEC for toxic effects in P1 rats is 5 ppm (25.5 mg/m³) after 11 weeks inhalation exposure to 2,3-dichlorobuta-1,3-diene. In a teratogenicity study (OECD TG 414) 2,3-dichlorobuta-1,3-diene leads to embryotoxic effects (decreased fetal weight) in the presence of clear maternal toxicity (decreases in maternal body weight, body weight gain and food consumption as well as clinical signs of toxicity during exposure) at the highest concentration tested (50 ppm = 255 mg/m³). Therefore the maternal and fetal NOAECs were both considered to be 10 ppm (51 mg/m³). Overall, 2,3-dichlorobuta-1,3-diene shows no specific effects on fertility or embryonic or fetal development.

Environment

2,3-Dichlorobuta-1,3-diene is a colorless to yellowish, water sensitive liquid with a melting point of -40 °C and a boiling point of 98 °C at 1013 hPa. 2,3-Dichlorobuta-1,3-diene has a relative density of 1.1829 at 20 °C and a vapor pressure of ca. 132.7 hPa at 25 °C. The calculated log K_{OW} is 3.02. The flash point is 13 °C, the auto flammability (ignition temperature) is ca. 420 °C.

2,3-Dichlorobuta-1,3-diene hydrolyzes in water at 50 °C with a half-life of 1.2 hours, forming short chain alcohols and ketones and hydrochloric acid. In the atmosphere 2,3-dichlorobuta-1,3-diene is degraded by photochemically produced OH radicals. The half-life is calculated to be about 3 days.

According to the Mackay fugacity model Level I, the favorite target compartment of the 2,3-dichlorobuta-1,3-diene is air with 99.93 %. The calculated value reflects the properties of the undissociated molecule without taking into account the sensitivity of 2,3-dichlorobuta-1,3-diene towards hydrolysis. A high volatility from water is indicated by the calculated Henry's law constant of 5.16 x 10³ Pa m³/mol at 25 °C.

2,3-Dichlorobuta-1,3-diene is not readily biodegradable as conducted in a respirometry test corresponding to OECD TG 301F with an elimination rate of 1 %.

The bioconcentration factor (BCF) of 42, calculated from the octanol-water partition coefficient, for 2,3-dichlorobuta-1,3-diene, and the low octanol-water partition coefficients for both presumed organic hydrolysis products (calculated log K_{OW} of 0.67 and -1.34 for 2,3-dihydroxybuta-1,3-diene and 2,3-butanedione, respectively), indicate a low potential for bioaccumulation of these compounds. A K_{OC} value of 107 was calculated with PCKOCWIN v. 1.66 suggesting a low sorption potential of 2,3-dichlorobuta-1,3-diene onto the organic phase of soil or sediments.

The lowest reliable toxicity values for aquatic species are (n = nominal concentration; m = measured concentration; c = calculated concentration):

<i>Danio rerio</i> (fish):	96 h-LC ₅₀	=	10 mg/l (n)
Fish (ECOSAR)	96 h-LC ₅₀	=	0.6 mg/l (c)
<i>Daphnia magna</i> (invertebrates):	48 h-EC ₅₀	=	1.5 mg/l (m)
		=	22 mg/l (n)
<i>Desmodesmus subspicatus</i> (algae):	72 h-EC ₅₀ growth rate/biomass	=	> 2.1 mg/l (m)
		=	> 100 mg/l (n).

For bacteria (activated sludge) the lowest available toxicity value determined was a 3 h-EC₅₀ of 1700 mg/l (nominal). For the hydrolysis product 2,3-butanedione, a 40 h-EC₅₀ of 146 mg/l was determined in the protozoa *Tetrahymena pyriformis* (documentation insufficient for assessment).

Since acute test results for 2,3-dichlorobuta-1,3-diene for three trophic levels are available, an assessment factor of 1000 was applied for the derivation of the PNEC_{aqua} according to the EU Technical Guidance Document. The lowest effect concentration of 1.5 mg/l was found for invertebrates (*Daphnia magna*). However, no analytical monitoring was performed during the fish test with this volatile and rapidly hydrolyzing test substance. To further complement the information for this endpoint, a QSAR calculation was performed which yielded an LC₅₀ of 0.6 mg/l. By applying an assessment factor of 1000 on both the lowest measured and calculated concentrations, the PNEC_{aqua} is predicted to be 0.6 µg/l to 1.5 µg/l.

Exposure

2,3-Dichlorobuta-1,3-diene is manufactured by elimination of hydrogen chloride of both 1,2,3,4-tetrachlorobutane and 2,3,4-trichlorobut-1-ene. There are no data on the global production volume of 2,3-dichlorobuta-1,3-diene,

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however, the manufacturing volume is estimated to be 10 000 - 20 000 tons/a. In Germany, the only manufacturer of 2,3-dichlorobuta-1,3-diene has a manufacturing capacity of 1000 - 5000 tons/a and processes all products at the same site.

2,3-Dichlorobuta-1,3-diene is produced and processed in a closed system and is used only as a co-monomer in the manufacturing of polychloroprene rubbers at the production site. In the Sponsor country, these rubbers account for approximately 20 % of the total polychloroprene rubber production volume. No other use pattern is known in the Sponsor country. Depending on the desired quality, the 2,3-dichlorobuta-1,3-diene content of the polymerization mixture may reach up to 10 % of the monomers.

In the Sponsor country during manufacturing and processing in closed systems, virtually no 2,3-dichlorobuta-1,3-diene was emitted into the atmosphere (< 25 kg) and into the aquatic environment in 2004. Due to the high volatility of the substance, occupational exposure to 1,4-dichlorobut-2-ene may occur through inhalation. In the Sponsor country, exposure is well controlled in occupational settings. In the Sponsor country, all 2,3-dichlorobuta-1,3-diene is processed on-site by the manufacturer into solid polychloroprene rubber types. 2,3-Dichlorobuta-1,3-diene is not detectable in these rubbers with a detection limit of 1 mg/kg.

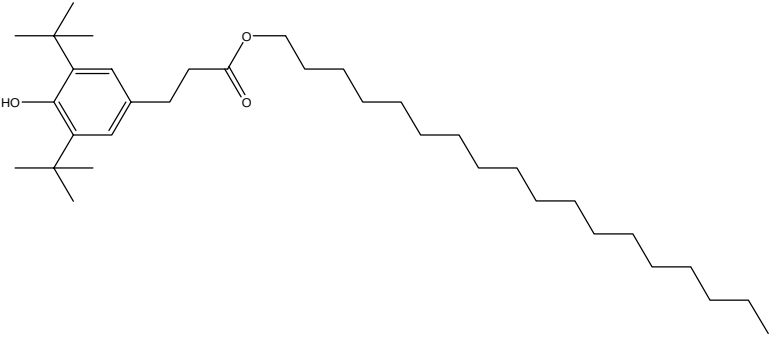
2,3-Dichlorobuta-1,3-diene is not listed in the Nordic and Swiss Product Registers. There is no known route of consumer exposure via the environment. Since no consumer products are known to contain 2,3-dichlorobuta-1,3-diene, consumer exposure to 2,3-dichlorobuta-1,3-diene is not likely to occur.

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

Human Health: The chemical possesses properties indicating a hazard for human health (acute and subacute toxicity, irritation, *in vitro* mutagenicity). Based on data presented by the Sponsor country (relating to production by 1 producer which accounts for approximately 5 % to 50 % of global production and relating to the use pattern in several OECD countries), exposure is well controlled in occupational settings, and exposure of consumers is negligible. 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 and check their own risk management measures to find out whether there is a need for additional measures..

Environment: The chemical possesses properties indicating a hazard for the environment (acute toxicity to fish, algae, and invertebrates). Based on data presented by the Sponsor country (relating to production by 1 producer which accounts for approximately 5 % to 50 % of global production and relating to the use pattern in several OECD countries), emissions into the environment are anticipated to be low. 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2082-79-3
Chemical Name	Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate can be taken up from the gastro-intestinal tract (23-35%) in the rat. After 168 hours 96% of the applied radioactivity was eliminated. No human data on toxicokinetics were available.

The acute oral LD₅₀ of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate in rats is >5000 mg/kg bw. Clinical signs included diarrhoea, sedation, dyspnoea, ruffled fur and hunched posture. For acute dermal toxicity the LD₅₀ was >2000 mg/kg bw. Piloerection and hunched posture were noted. The LC₅₀ for inhalation toxicity is >1811 mg/m³ in the rat. Ruffled fur and ventral posture during exposure were reported. No human data on acute toxicity were available.

Based on tests with rabbits octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate was not considered to be a skin or eye irritant. No human data were available. No sensitization potential was found in the guinea-pig in a Maurer optimisation test. A human patch test confirmed this finding.

Repeated oral exposure to octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate induced effects on the liver (increased weight, hypertrophy), which were most probably related to induction of microsomal enzymes. No effect of duration of exposure and no species differences were observed in the oral studies available; a 28-day study in rats (mainly according to OECD TG 407, NOAEL 30 mg/kg bw/day, a 90-day study in dogs (NOAEL 32-37 mg/kg bw/day) and a 2-year study in rats (NOAEL 64-81 mg/kg bw/day). Therefore the NOAEL for oral toxicity was considered to be 30 mg/kg bw/day. For inhalation toxicity a NOAEL of 543 mg/m³ was derived (the highest concentration tested) from a 21-day study (6h/d; 5 d/wk).

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate was negative in an Ames test and an *in vivo* micronucleus test. There were no indications that octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate possesses genotoxic properties.

In a 2-year dietary carcinogenicity assay in mice no increased tumour incidence was found at any of the dose levels tested (0, 0.6, 5.4 and 56 mg/kg bw/day).

In a two generation study in rats octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (0, 500, 1500 and 5000 ppm) did not show any adverse effects on reproduction based on absence of effects on mating performance, pregnancy rate and gestation duration at 96-111 mg/kg bw/day (1500 ppm). The NOAEL for developmental

toxicity was 32-39 mg/kg bw/day (500 ppm) based on reduced growth and survival of the pups. In teratogenicity studies in rats and mice (0, 150, 500 and 1000 mg/kg bw/day mainly according to OECD TG 414) the NOAEL for maternal toxicity and teratogenicity was 1000 mg/kg bw/day. Decreased foetal weight (2-3% of control) and delayed ossification were reported at 500 and 1000 mg/kg bw/day in rats. These effects were considered not to be toxicologically relevant. Therefore the NOAEL for developmental toxicity was 1000 mg/kg bw.

Environment

Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate is a powder with a melting point of 49-54°C, calculated boiling point of 561°C and a calculated vapour pressure of 5.5E-07 hPa. The substance has a very low solubility in water (2.85 µg/l) and has a calculated log Kow of 13.4.

The substance is not readily biodegradable. However, 32-35% biodegradation was observed in a modified Sturm Test (OECD TG 301 B) over the 28 day study period (CO₂ evolution). In a modified MITI Test (OECD TG 301 C) 21-39% degradation was measured (BOD). Two metabolites were found and identified as 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionic acid and 1-octadecanol. The rate of the acid production amounts to 58-94%. The acid formed was not biodegraded. Although the substance contains an ester bond, hydrolysis is unlikely to be the main abiotic degradation process in waters. Hydrolysis half-life is estimated to be >7 years at pH 7 and 264 days at pH 8 (EPISuite 3.12).

Calculations of the BCF with standard QSARs (EPISuite 3.12, EUSES 2.03) give a wide variation in results depending on the model selected (3 and 25 000). An experimental determination of the BCF is available indicating a low potential for bioaccumulation of the parent substance in fish. However the test was performed at a concentration in excess of the water solubility of the substance in presence of a dispersant. Therefore the available information does not allow concluding that the bioaccumulation is low. Bioaccumulation of degradation products is not assessed.

The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate in air is 3 hours (EPISuite 3.12). Level III fugacity modelling shows that after release to surface water 98% of the substance will partition to sediment. When released to soil 99.9% will remain in this compartment.

For octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate no effects at the water solubility level (2.85 µg/l) were observed in acute fish, daphnia and algae tests. Two static studies in fish according to OECD TG 203 showed no treatment related mortality. The 96-h LC₅₀ for both species (*Lepomis macrochirus*, *Salmo gairdneri*) was >100 mg/l. *Daphnia magna* were exposed to the substance (dispersant used) during 24 hours in a static test (OECD TG 202). No effects on mobility were found at any of the concentrations tested (48-h EC₅₀ is >100 mg/l). A 72h study with the algae *Scenedesmus subspicatus* showed no effect at the highest concentration tested (72-h E_c50 >11.3 mg/l measured; growth rate).

Dry leaves were observed in turnip at 100 mg/kg dry soil weight in a test on seeds of ryegrass, turnip and vetch exposed to octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate at concentrations of 0, 1, 10 and 100 mg/kg dry soil weight.

Exposure

For the year 2004 the global market for octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate was estimated to be 50 000 tonnes. The primary use of the substance is as an antioxidant to prevent the deterioration of polymers. It acts as an inhibitor that reacts with O-centered radicals present in the substrate. Therefore the substance is degraded in complex reactions over the lifetime of the product to some extent.

Limited consumer exposure is expected from the primary use of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate as phenolic antioxidant bound in a polymeric matrix (e.g. packaging materials). Minor uses of Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) are preparations such as adhesives, sealants, paints and lubricants (Swiss Product Register).

There is potential environmental exposure during production and processing of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate and by leaching from waste in landfills.

Occupational exposure might occur during packaging and handling of the additive (e.g. opening of bags, blending or filling operations).

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

Human Health: The chemical is of low priority for further work due to its low hazard potential

Environment: Short-term aquatic toxicity tests at 3 trophic levels were available which show no effects at the water solubility level in any of the tests. However 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionic acid was found as a stable metabolite in a biodegradation study. Therefore the chemical is a candidate for further work. The aquatic hazard of this metabolite should be assessed. If distribution modelling of this metabolite shows that it will end up in the sediment, further testing of the toxicity on sediment dwelling organisms is recommended. Although apparent emissions of the parent substance at manufacturing and processing sites and emissions from the use of the substance in chemical preparations are expected to be low, a more detailed exposure assessment is necessary taking into account the acid formed during aerobic biodegradation of 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2530-87-2
Chemical Name	3-Chloropropyltrimethoxysilane (CPTMO)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

The chemical, 3-chloropropyltrimethoxysilane (CPTMO), undergoes rapid hydrolysis, which results in the production of 3 moles of methanol for each mole of silanetriol. Exposures to CPTMO are likely to be transient and observed toxicity is likely due primarily to the hydrolysis product methanol, with some potential exposure to trisilanols, and silanol oligomers. Methanol (CAS No 67-56-1) was assessed at SIAM 19. The SIAP for methanol is available for review. Use levels are generally less than 1 percent based upon the industrial goods formulation and less than 0.2 percent when used in composites, such that exposure to the hydrolysis products, including methanol is expected to be low.

Human Health

There were no available data on the toxicokinetic, metabolism or distribution of CPTMO. The oral (gavage) LD50 in rats of CPTMO is greater than 2000 mg/kg bw. Additional oral LD50 values in rats include 6.17 mL/kg (female) and 9.51 mL/kg to 10 g/kg (male). The dermal LD50 in rats of CPTMO is greater than 2000 mg/kg bw. Additional dermal LD50 values in rabbits include 2.83 mL/kg (male), 3.36 mL/kg (male) and 3.73 mL/kg (female). 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 guideline 406.

The no-observed-effect-level (NOEL) for male and female rats in a 90 day repeated dose inhalation toxicity study was reported to be 5 ppm (41 mg/m³). Treatment related histopathologic changes in the urinary bladder and kidneys of rats exposed to 100 ppm (814 mg/m³) were observed. Based on these results the lowest observed effect level (LOEL) in the rat was established at 100 ppm (814 mg/m³). In a 28-day repeated inhalation toxicity study with CPTMO, test article-related changes were detected histopathologically in the adrenal glands, kidneys, liver and urinary bladder in some rats from one or more exposure groups at concentrations as low as 10 ppm (81 mg/m³) (the lowest concentration). In an OECD guideline 422 repeated dose inhalation study in rats, 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 article, including effects in the urinary bladder and kidney. Although the effect on the urinary bladder and kidney was not observed in all repeated inhalation exposure studies, the NOAEL for this effect across all studies is considered to be 5 ppm (41 mg/m³). The conclusion has been reached that it is plausible that 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.

CPTMO was not considered to be an inducer of micronuclei *in vivo*, but is mutagenic *in vitro* (positive in

bacterial mutation assays and in the presence of metabolic activation, and in an *in vitro* mouse lymphoma mutagenesis assay). In the *in vivo* micronucleus assays clinical signs included decreases in micronucleated polychromatophilic erythrocyte (NCE) ratios at the 72 hour sampling time among male mice at 1625 mg/kg. Additional clinical observations at both 1000 and 1625 mg/kg doses are ataxia, tremors, prostration, myoclonic jerks and vocalization. There was no available carcinogenicity study for CPTMO.

In an OECD guideline 422 repeated dose inhalation study in rats, exposure to CPTMO up to and including the high concentration of 100 ppm (814 mg/m³) did not result in any signs of reproductive or developmental toxicity. Based on these results the NOEL for general or reproductive toxicity was established at 100 ppm (814 mg/m³).

Environment

The melting point of CPTMO is <-50°C and the boiling point is 196 °C. The vapor pressure is 0.5215 hPa at 25°C. The estimated water solubility of CPTMO is 6.76 mg/L at 25 °C; the estimated log Kow is 0.56. The water solubility and log Kow values may not be applicable because the chemical is hydrolytically unstable. The estimated water solubility of the hydrolysis product of CPTMO, 3-chloropropylsilanetriol, is 65000 mg/L; the estimated log Kow is -1.13. The overall degradation rate constant with OH radicals in the atmosphere is 4.6026 E⁻¹² cm³/molecule-sec with an estimated half-life of 3.5 days with a hydroxyl radical concentration of 5.0×10⁵ molecule/cm³. Photodegradation as a mode of removal is unlikely as CPTMO is hydrolytically unstable. CPTMO is reactive and hydrolytically unstable, such that methanol and silanetriols are rapidly generated upon contact with water or water vapor. Consequently, reaction with water vapor is likely the predominant degradation process for CPTMO in air and the overall reaction half-life in air should include both the oxidation half-life and the hydrolytic half-life. The overall reaction half-life in air is estimated to be 8 hours because of rapid hydrolysis of the material with moisture in the atmosphere. The products resulting from CPTMO hydrolysis in the atmosphere are expected to further react with hydroxyl radicals. The atmospheric oxidation was determined for the hydrolysis product, 3-chloropropylsilanetriol. The overall OH rate constant is 12.4E⁻¹² cm³/molecule-sec with an estimated half-life of 1.3 days.

CPTMO is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions. At pH 7 and 25 °C, the half-life is 53.3 minutes. 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 = 42.1%; soil = 52.5%; water = 5.4%; sediment = 0%. However, CPTMO is unlikely to be found in the environment, as this material is hydrolytically unstable. Level III fugacity modeling, using loading rates for air, soil, and water of 1000 kg/h for each media, shows the following percent distribution for the hydrolysis product, 3-chloropropylsilanetriol: air = 0.0%, soil = 53.5%, water = 46.4 %, and sediment = 0.1 %. CPTMO is readily biodegradable but does not meet the 10 day window. However, the biodegradation observed is likely reflective of the hydrolysis product, methanol, which is readily biodegradable and degraded 76% in 5 days and 95% in 20 days. Bioaccumulation of the parent substance is not anticipated.

CPTMO undergoes rapid hydrolysis, which occurs during testing; exposures to CPTMO are likely to be transient and observed toxicity is likely due primarily to the hydrolysis product methanol, with some potential exposure to trisilanols, and silanol oligomers. The alkyl silanols condense to siloxane oligomers; this condensation of silanols is affected by both concentration and pH, and since both change over time it is not feasible to isolate specific silanols for analysis (the structures continue to evolve until they either reach equilibrium or precipitate out of solution). Data from the hydrolysis product methanol were presented at SIAM 19. The SIAP is available for review. The 96-hour LC50 and LC0 of CPTMO in freshwater fish (*Brachydanio rerio*) are >100 mg/L. Studies have been performed with a silanol monomer, trimethylsilanol. Although this silanol is not expected to be produced following hydrolysis of CPTMO, it has been predicted (using EpiWin) to be one of the most toxic to aquatic organisms of all the silanols identified to date. A semi-static 96h study with trimethylsilanol and rainbow trout (*Oncorhynchus mykiss*) resulted in a NOEC of 128 mg/L and an LC₅₀ of 271 mg/L. The 48 hour EC50 of CPTMO is 869 mg/L for the water flea (*Daphnia magna*) under static conditions. The 48 hour EC50 of trimethylsilanol is 124 mg/L for the water flea (*Daphnia magna*) under semi-static conditions. In an algae study with CPTMO, on the basis of biomass, the median effective concentration was 72 h EbC50 > 883 mg/L and 72 h EbC10 = 241 mg/L. On the basis of growth rate, a median effective concentration was achieved at (0-72 hr) ErC50 >883 mg/L; (0-72 hr) ErC10 = 514 mg/L. The NOEC was 167 mg/L. The most sensitive endpoints for *Selenastrum capricornutum* exposed to trimethylsilanol were cell density and area under the growth curve (biomass). The 72-hour EC50 value was 555 mg/L with 95% confidence limits of 141 and 612 mg/L. The 72-hour NOEC, based on cell density, area under the growth curve (biomass) and growth rate was 70 mg/L. The 96-hour EbC50 value was 625 mg/L with 95% confidence limits of 555 and 702 mg/L. The 96-hour NOEC, based on area under the growth curve (biomass),

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was 70 mg/L.

Exposure

In the Sponsor country, the production volume in 2001 was 10 tonnes. 250 tonnes of CPTMO were imported in the Sponsor country in 2001. Global production volumes are not available.

CPTMO is used as a coupling agent for filled composites and industrial goods (textile goods). Use levels are generally less than 1 percent based upon the industrial good formulation and less than 0.2 percent when used in composites. The substance is reacted during use and loses its chemical identity.

In order to prevent the rapid hydrolysis and subsequent loss of this material in production, it is handled in closed systems. Necessary engineering controls during production include proper ventilation, containment, safety equipment and actual hardware designed to minimize exposure through splashing, or exposure to the air. CPTMO is produced in closed systems. During sampling for analysis (quality control), local ventilation (hoods) is used to prevent worker exposure through inhalation. Dermal exposure is also a possible route of exposure during sampling. Dermal exposures are expected to be minimal as chemical protective gloves and/or clothing would be required during handling. The product is stored on site in standard warehouse conditions, with the product stored under a blanket of nitrogen in sealed containers. CPTMO is transported from the production site as the parent silane or as a blend with other silanes. The parent silane reacts during use by the industrial customer. In composites applications, the substance is added to water. The substance hydrolyzes and its chemical identity no longer exists. In industrial goods applications, the substance is mixed at low levels with polymers, fillers and other ingredients. During the mixing, molding and curing processes, the substance reacts completely and is no longer available for consumer or worker exposure. CPTMO does not volatilize during use. The substance hydrolyzes, releasing methanol.

At the industrial customer level, the material may be used in open or closed systems. Necessary engineering controls during use are likely to 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 minimal, and may include dermal and inhalation exposure during transfer and use.

Consumer products are unlikely to contain any free (unreacted) CPTMO in any application, in that the substance has reacted with the filler and polymer in the composite or rubber.

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

Human Health: The chemical possesses properties indicating a hazard for human health (moderate skin and eye irritation, genotoxicity *in vitro* in bacterial and mammalian systems). Due to the rapid hydrolysis to methanol and the corresponding trisilanol and based on exposure data presented by the Sponsor country, (data on the global production volume were not available) and relating to use pattern in one country 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: The chemical is currently of low priority for further work due to its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2551-62-4
Chemical Name	Sulphur hexafluoride
Structural Formula	SF ₆

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

SF₆ accumulation, distribution and elimination were studied in rats exposed by inhalation. SF₆ was found to distribute widely in the body with a relatively higher affinity for blood and fatty tissues, and to be rapidly eliminated, likely via the exhaled air, suggesting a low accumulation potential.

No significant adverse effects were recorded in several studies in humans acutely exposed to an atmosphere containing up to 80% SF₆, although a slight anesthetic effects and slight signs of discomfort, such as coolness in the upper respiratory tract and the occurrence of voice deepening, were observed.

Limited acute inhalation studies were conducted in rats exposed up to 80% SF₆. No deaths or adverse effects clearly attributable to SF₆ were recorded in these studies.

No cardiac sensitisation was observed in dogs previously injected with adrenaline and exposed up to 20% SF₆ in air. A slight anesthetic potential has been identified for SF₆ in following acute exposure to high SF₆ concentration in rats, dogs and humans. Signs of CNS depression attributable to anesthetic effects were also observed in rats and Guinea pigs exposed to 12,800 ppm and, with lower severity, 1,600 ppm for 4 consecutive months. No adequate studies are available for the assessment of repeated exposure to SF₆ and for the mutagenicity, carcinogenicity and reprotoxicity endpoints. However, its chemical inertness and its very low accumulation potential support the low concern for the toxicity of this substance.

The possible formation of highly toxic breakdown products may occur when SF₆ is subjected to high stress conditions; in particular electrical discharges occurring in the gas-insulated equipments may promote the formation of highly reactive species of toxicological concern.

Environment

SF₆ is a gas with a vapour pressure of 23,676 hPa at 25°C, a water solubility of 0.03 g/l at atmospheric pressure and a Log Kow = 1.68. Fugacity-based Multimedia Environmental Model Level III predicted an almost exclusively partition into the atmosphere following its release into the environment. No experimental data on biotic and abiotic degradation are available. However, due to SF₆ physico-chemical properties, volatilisation is considered the most important process of removal from water. No aquatic ecotoxicological studies are available for SF₆. However, the very low water solubility, the high vapour pressure and the low estimated bio-accumulation potential indicate a low concern for the aquatic compartment. In the atmosphere SF₆ is likely removed by mean of breakdown mediated by the reaction with free electrons, following its advection into the mesosphere, and in a minor amount via Lyman alpha-radiation mediated photolysis. A global atmospheric lifetime of 3200 years is estimated. Its global warming potential relative to CO₂ is 23,900 for a time horizon of 100 years.

Exposure

SF₆ is used in several industrial applications. Among others, the insulation of electrical equipments, the magnesium casting processes and the semiconductor manufacturing are the main applications. Beside the industrial applications, SF₆ is used in medical applications as an ultrasound contrast agent and as a tamponade gas in ophthalmology. Due to the low toxicological concern, occupational exposure to SF₆ is not monitored. However, exposure up to 80% SF₆ and 20 % oxygen is reported in several studies on human volunteers.

The annual global production volumes, based on a survey on global sales, ranged between 5,000 and 7,000

tonnes/year in the period 1999-2001. However, this production figure likely represents an underestimation, since Russian and Chinese sales were not included in the survey.

The atmospheric emission sources mainly concern the industrial applications of SF₆. In particular, 100% of SF₆ used in the casting processes or in the semiconductor manufacturing is considered to be released in the atmosphere. Also, emissions due to leakage and maintenance operations of the existing electrical equipments, as well as release during the filling of new electrical equipments, contribute to atmospheric emissions of SF₆.

Atmospheric emissions of SF₆ from the industrial applications are regularly monitored. Increasing global emissions have been estimated between the '70s and the '90s, with a maximal release of 6,300 tonnes reached in 1997. However, a reverse trend has been registered for the emissions in the last years. The SF₆ atmospheric global mean concentration was estimated to be 4.7 ppt for the year 2000.

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

The chemical is currently of low priority for further work due to its low hazard profile for human health and the environment (fish, daphnia and algae). Its global warming potential is acknowledged and being addressed by other programs.

Human Health:

Environment:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	27813-02-1
Chemical Name	Methacrylic acid, monoester with propane-1,2-diol
Structural Formula	CAS No:923-26-2 70-80% CAS No:4664-49-7 20-30%

SUMMARY CONCLUSIONS OF THE SIAR

A close homologue 2-hydroxyethyl methacrylate (CAS 868-77-9) was evaluated in SIAM13 and published.

Methacrylic acid, monoester with propane-1, 2-diol consists of two isomers. Typical composition of marketed substance is 20-30 % of 2-propenoic acid, 2-methyl, 2-hydroxy-1-methylethylester and 70-80 % of 2-propenoic acid, 2-methyl, 2-hydroxypropylester. CAS number 27813-02-1 is given to the mixture.

CAS 923-26-2 was assigned for a chemical “2-propenoic acid, 2-methyl-, 2-hydroxypropyl ester (I)”. When the chemical is produced industrially or by usual laboratory synthetic method like reaction between methacrylic acid and propylene oxide or methacrylic acid esterification of 1,2 propanediol, the product is normally a mixture of (I) and the isomer “2-propenoic acid, 2-methyl-, 2-hydroxy-1-methylethyl ester (II)” for which CAS 4664-49-7 is assigned. Another CAS number 27813-02-1 has been assigned for this isomer mixture named more generically “methacrylic acid, monoester with propane-2, 2-diole (III)”. (III) contains 70-80 % of (I) and thus some times referred as “methacrylic acid 2-hydroxypropanol ester” or other synonyms of (I) and quoted as CAS 923-26-2. Actually, the purification of the two isomers requires extensive effort and it is supposed no such effort has been taken during data collection otherwise noted. The information collected was made for the CAS number of (III) or (I) however it is reasonable to consider that data is conducted with commercially available substance which is (III).

Human Health

Methacrylic acid, monoester with propane-1, 2-diol is absorbed from the skin. Dermal absorption was studied in male rats for 8 hours with ^{14}C . Fifty-six per cent of dosage evaporated from the application site. The amount absorbed was determined to be 29 % of the radioactivity. Radioactivity was observed in the skin (7 %), carcass (2 %), urine (1 %) and faeces (< 1 %) and as volatile organics (< 1 %). This substance is hydrolyzed to methacrylic acid and 1, 2-propanediol at pH 6.5 and 37 ° C catalyzed by an unspecific esterase *in vitro*.

The oral LD₅₀ is 2000 mg/kg bw and higher in rats, intraperitoneal LD₅₀ is between 500 - 1000 mg/kg bw in rats, and dermal LD₅₀ is 5000 mg/kg bw and higher in rabbits. No acute inhalation studies were found.

This substance is considered to be slightly irritating to the skin and irritating to the eyes of animals. Slight sensitizing potential was demonstrated in guinea pigs in two of four maximization studies. The sensitizing potential was not clearly demonstrated in humans, however cross-sensitization may occur in individuals with prior exposure to other acrylates or methacrylates. Many workers related to dentistry suffered from allergic contact dermatitis; however, the agent that caused sensitisation was not identified, nor was it possible to distinguish between concomitant sensitization and cross reactivity.

A combined oral repeated dose toxicity study with the reproductive/developmental toxicity screening test [OECD TG 422] (0, 30, 100, 300, 1000 mg/kg bw/day) was conducted using SD rats. In males, death in two of the 12 animals, salivation, decreases in locomotor activity, and ptosis were observed at 1000 mg/kg bw/day. At this dose,

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decrease in hematocrit and increase in the relative liver weights were observed. In females, death in one of the 12 animals, salivation, decreases in locomotor activity, and ptosis were observed in 1000 mg/kg bw/day. At 30, 100, and 300 mg/kg bw/day in both sexes, there was no toxicological change in any parameters. The NOAELs for the oral repeated dose toxicity are considered to be 300 mg/kg bw/day for both sexes. No repeat dose dermal or reliable inhalation studies were available.

One *in vitro* reverse mutation study in bacteria [OECD TG 471 and 472] was negative. Another *in vitro* study, chromosomal aberration test [OECD TG 473] was positive with and without metabolic activation. In *in vivo* micronucleus assay to MTD (maximum tolerance dose) [OECD TG 474] by gavage, no evidence of genotoxicity was observed. These data indicate that this substance is not mutagenic *in vivo*.

There is no available carcinogenicity study.

In the above mentioned combined oral repeated dose toxicity study with the reproductive/developmental toxicity screening test [OECD TG 422] (0, 30, 100, 300, 1000 mg/kg bw/day) using SD rats, no adverse effects were observed in any reproductive or developmental parameters. The NOAEL for the reproductive/developmental toxicity is considered to be 1000 mg/kg bw/day.

Environment

Methacrylic acid, monoester with propane-1, 2-diol is a colorless liquid with slight ester-like odor. Water solubility is 130 g/L (25 °C). The hydrolysis depends on pH ($t_{1/2}$ at pH 7 and 9 are 73.3 days and 38.2 hours at 40 °C, not significant at acid pH). The primary hydrolysis products are methacrylic acid and propylene glycol. Both of the hydrolysis products were evaluated for the toxicological properties in SIAM 11, and published in Jan. 2003 and Jul. 2004. Melting point, boiling point, logKow and vapour pressure are -89 °C, ca. 240 °C, 0.97 and ca. 0.1 hPa (20 °C), respectively. Indirect photo-oxidation by hydroxyl radicals in the atmosphere is predicted to occur with a half-life of 4.5 hours. This substance is readily biodegradable under aerobic condition within 28 days by OECD TG 301C (BOD = 81) or by TG 301E (DOC = 94.2 %). This substance is predicted to have low bioaccumulation potential (BCF = 3.2). Fugacity modelling (Mackay level III) predicts that all of this substance released to water or soil will not migrate into other compartments. When this substance is released to air, it is mainly distributed to air (57.1%), water (16.2%), and soil (26.6%).

This substance has been tested in aquatic species (algae, invertebrates and fish). An acute growth inhibition test was performed using green algae (*Pseudokirchneriella subcapitata*, OECD TG 201). Both 72-h EC50s in biomass and growth rate were > 97 mg/L. An acute toxicity test for invertebrates was performed using water fleas (*Daphnia magna*, OECD TG 202). Both 48-h EC0 and 48-h EC50 were more than 140 mg/L. An acute toxicity test for fish was performed using golden orfe (*Leuciscus idus melanotus*). The 48-h LC50 was 490 mg/L which agree with a calculated value for 96 hour LC50 for fathead minnow by QSAR. The most sensitive species for which measurement data is obtainable is green algae (*Pseudokirchneriella subcapitata*), and the 72-h EC50 was more than 97 mg/L. Chronic toxicity data for algae can be obtained from the test performed in accordance with OECD TG 201 using green algae (*Pseudokirchneriella subcapitata*). The NOEC (biomass; 72-h) and NOEC (growth rate; 72-h) were 31 and more than 97 mg/L. A chronic toxicity test for invertebrates was performed using water flea (OECD TG 211, *Daphnia magna*) on reproduction. The 21-d LC50, 21-d EC50, 21-d NOEC, and 21-d LOEC were more than 96, more than 96, 45, and 96 mg/L, respectively.

Exposure

The production volume of methacrylic acid, monoester with propane-1, 2-diol was 850 ton/year in Japan, 2003. The production volume is known to exceed 450 ton/year in US. This substance is an intermediate chemical, and is used extensively in chemical, varnishes, paper textile industry, etc. Environmental exposure may occur at the processing or production sites mainly to the waters where it may be hydrolyzed.

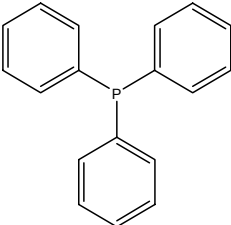
During production and use of this substance at the processing sites, occupational exposure is possible by inhalation and dermal route. This substance is produced in a closed system. The workplace exposures during manufacturing processes are controlled by personal protective equipment to prepare for any accidental exposure. Consumer exposures to this chemical does not occur in normal uses. Because, this chemical is used to produce plastic composite material.

**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 (irritation and potential for skin sensitization). These hazards do not warrant further work. They should nevertheless be noted by chemical safety professionals and users.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	603-35-0
Chemical Name	Triphenylphosphine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Toxicokinetics, metabolism, and distribution of triphenylphosphine have not been studied *in vivo*. According to the results from toxicity studies with experimental animals it can be deduced that triphenylphosphine may be absorbed to some extent after inhalation as well as after oral application, depending on the vehicle employed and/or particle size.

In rats, the 4-hr LC₅₀ of triphenylphosphine was determined to be 12 500 mg/m³ (whole-body exposure). Clinical signs were typical of respiratory irritation. The dermal LD₅₀ was > 2500 mg/kg bw in rats, and > 4000 mg/kg bw in rabbits; no systemic toxicity or local irritation was noted. The oral LD₅₀ of triphenylphosphine in rats was dependent on the vehicle used and ranged from 700 mg/kg bw (in olive oil) to > 6400 mg/kg bw (in aqueous suspension). In mice, the oral LD₅₀ of triphenylphosphine (in olive oil) was 1000 mg/kg bw. Hyperexcitability, followed by atony and transient ataxia were the most prominent toxic signs in rabbits and dogs at sublethal oral doses. In a hen acute delayed neurotoxicity study (US EPA 163) neuropathological changes in the spinal cord and in the sciatic nerve, without clinical signs of neurotoxicity were found at oral doses of 1500 mg/kg bw and above; ataxia was observed at 6000 mg/kg bw. Neurotoxicity was also induced in ferrets after subcutaneous injection of 250 mg/kg bw triphenylphosphine without affecting the neuropathy target esterase (NTE) and acetylcholine esterase (AChE) activities.

Occlusive exposure of a 50 % suspension of triphenylphosphine in ethanol for 20 hours was very slightly irritating to the skin of rabbits. One drop of a 10 % solution of triphenylphosphine in olive oil induced very slight eye irritation in rabbits; 50 mg of the solid substance was irritating. Triphenylphosphine was a skin sensitizer in guinea pigs (Directive 84/449/EEC, B.6).

In rats mild respiratory irritation was the only effect after 2 weeks of inhalation exposure to 2,400 mg/m³. In a 5-week inhalation study on dogs, clinical signs of neurological impairment, ataxia, and pathological changes in the cervical and lumbar spinal cord were found after exposures to 28 mg/m³ (NOAEL: 9.7 mg/m³).

A NOAEL of 6 mg/kg bw/day was found in a 3-month gavage study on rats (OECD TG 408). At 60 mg/kg bw/day changes indicative of liver enzyme induction (decrease in plasma prothrombin time, and a slight increase in liver weight in females and, in both sexes, centrilobular hepatocyte hypertrophy) were found. There were no clinical signs of neurotoxicity up to and including 120 mg/kg bw/day. In dogs, oral doses of 5 mg/kg bw/day, 2 - 5 days/week, induced ataxia, in a 5-week study; 10 or 20 mg/kg bw/day induced axonal degeneration in the spinal cord (NOAEL: 1 mg/kg bw/day). Triphenylphosphine induced severe nervous system disorder also in rabbits at oral doses 100 mg/kg bw/day (lowest tested dose).

Triphenylphosphine was not mutagenic in *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 in the presence and absence of metabolic activation system. In studies with limited validity no mutagenic activity was

detected in *Salmonella typhimurium* TA102 and *Escherichia coli* strains, both in the presence and absence of metabolic activation systems. It was also tested negative in the rec assay in *Bacillus subtilis*, and did not induce chromosomal aberrations in an *in vitro* micronucleus test with Chinese Hamster Lung cells. *In vivo*, triphenylphosphine did not induce micronuclei in bone marrow cells of mice treated intraperitoneally on four consecutive days with doses of up to 80 % of the 4-day LD₅₀ value. Overall, triphenylphosphine showed no mutagenic activity *in vitro* and no clastogenic activity *in vitro* or *in vivo*.

There are no data available as to the carcinogenic potential of triphenylphosphine.

Triphenylphosphine had no effects on reproductive organ weights in a 3-months oral repeat dose toxicity study on rats according to OECD TG 408 (NOAEL: 120 mg/kg bw/day; highest dose tested). No adverse developmental effects were seen in a study performed in accordance with OECD TG 414 on Wistar rats (NOAEL, maternal toxicity: 30 mg/kg bw/day; NOAEL, developmental toxicity: 90 mg/kg bw/day = highest dose tested).

Environment

Triphenylphosphine is an organic solid with a melting point of 80.5 °C, a boiling point of 377.5 °C, and a relative density of 1.194 (at 25 °C). The calculated vapor pressure is 1.4×10^{-5} hPa at 25 °C. Water solubility has been measured (2 studies) to be in the range of 0.09 mg/l to ≤ 0.165 mg/l at 22 – 25 °C. A pH of 6.8 – 7.2 is reported for an aqueous solution of 0.09 mg/l at 25 °C. The log K_{OW} was measured as 5.69, and calculated as 5.02. The Henry's Law constant was calculated as 2.289×10^{-3} Pa x m³/mole (25 °C), the soil adsorption coefficient log K_{OC} as 5.65.

Using a fugacity model (Mackay level I), triphenylphosphine is predicted to appear mainly in the soil compartment (96.3 %), with minor amounts in sediment (2.14 %), water (1.04 %), and air (0.45 %), and negligible amounts in biota (0.011 %). Due to the instability in aqueous solution the calculated distribution is only of theoretical interest and not relevant under environmental conditions.

The half-life for photodegradation was calculated as 2.7 days (24h-day, 0.5×10^6 OH/cm³) and 22 hours (= 1.8 days based on a 12 hr-day and 1.5×10^6 OH/cm³), respectively. Because of its structure, triphenylphosphine is not susceptible to hydrolysis. Triphenylphosphine dissolved in very highly diluted form as available under environmental conditions is oxidized to triphenylphosphine oxide.

The calculated bioconcentration factor (BCF) was 4801. At environmentally relevant low concentrations, triphenylphosphine will be oxidized to triphenylphosphine oxide, whose experimental log K_{OW} was 2.83. Using this log K_{OW} a BCF of 30 was calculated for triphenylphosphine oxide. Triphenylphosphine and triphenylphosphine oxide are not biodegradable as shown in tests according to OECD TG 301F (less than 20 % biodegradation within 28 days each).

Short-term tests with fish, invertebrates, and algae are available. All effect values for aquatic species and bacteria are above the water solubility of triphenylphosphine.

The lowest effect values (based on nominal concentrations) from valid short-term tests are:

Leuciscus idus: 96h-LC₅₀ > 10 000 mg/l

Daphnia magna: 48h-EC₅₀ > 5 mg/l (0.6 mg/l, if tested with a dispersant. For environmental conditions this test result is of limited relevance.)

Desmosdesmus subspicatus: 72h-EC₅₀ growth rate/biomass > 5 mg/l

For bacteria the lowest valid toxicity value determined was a 0.5 h-EC₅₀ > 10 000 mg/l (nominal) for *Pseudomonas putida*.

Tests on terrestrial species are not available.

Exposure

In 2001, between 5000 and 7000 tonnes of triphenylphosphine were produced in Europe. The production volume for Asia (2001) ranged between 1000 and 3000 tonnes, and for the U.S. (2001) between 1000 and 3000 tonnes.

The three producers in Europe have confirmed that triphenylphosphine is produced and used at their sites in closed systems only. Furthermore by the producer in Germany worker exposure is limited by industrial hygiene controls and personal protective measures, regular workplace measurements are not conducted. Exposure could also occur during loading or unloading of tank trucks, railroad tankers, barges, and drums. Dedicated systems are typically used for loading and unloading purposes and procedures should be in place to prevent spills or leaks during transportation. To this end, triphenylphosphine is transported in sealed containers, almost exclusively in the form of pellets or flakes. This also minimizes dust and improves handling and processing. Within the manufacturing site of

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the Sponsor country, triphenylphosphine is transported in pipelines. Workplace measurements from other production and processing sites are not available. There exist no occupational exposure limit values for triphenylphosphine.

Triphenylphosphine is used as chemical intermediate in chemical synthesis, mainly for the synthesis of complexing agents, reducing agents, process regulators, vitamins, and pharmaceuticals. It is the starting material for Wittig reactions (primarily for the synthesis of vitamins and pharmaceuticals), and is used as catalyst ligand in hydroformylation reactions of olefins (oxosynthesis).

Because of the high chemical reactivity of triphenylphosphine, its concentrations in end-products are not expected to exceed trace levels, and exposure of consumers is therefore considered negligible. The SPIN database lists no triphenylphosphine-containing preparations for consumer use on the Nordic market. In the Swiss product register no preparations are listed which are supposed to be used in products for consumers.

Paints containing less than 1 percent of triphenylphosphine are reported to be used by professionals in Norway for ship repairs.

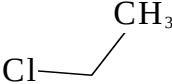
Releases of triphenylphosphine into the environment may occur during manufacturing and processing. At the only manufacturing and processing site in the Sponsor country emissions into the atmosphere are below 25 kg/year. In the waste water treatment plant effluent the concentration of triphenylphosphine as oxide is regularly measured at one production plant in Germany and reported to the responsible authority. As triphenylphosphine is transported in sealed containers, emissions during transport are not expected to occur.

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 (acute and chronic toxicity, neurotoxicity, and sensitization potential) for human health. Based on data presented by the Sponsor country (relating to production by 3 producers in Europe which accounts for 53 to 71% of global production and relating to the use pattern in several OECD countries) exposure of workers during manufacturing is anticipated to be low. Consumer exposure is anticipated to be negligible. As no regular workplace measurements are available, the Sponsor country will develop an occupational exposure limit value (OELV).

Environment: The chemical is of low priority for further work. The chemical has a low water solubility and does not show acute aquatic toxicity at the limit of solubility. For the chemical and its oxidation product no data on chronic toxicity is available. Based on data presented by the Sponsor country (relating to production by 3 producers in Europe which accounts for 53 to 71% of global production and relating to the use pattern in several OECD countries), exposure to the environment 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-00-3
Chemical Name	Chloroethane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Chloroethane is readily absorbed by the lungs. Following a single breath exposure, 30% of the administered radioactivity was eliminated on the breath within 1 hour in humans. 25% of the amount in the blood is localized in the plasma fraction, whereas 75% is found in the cellular fraction. Quantitative species differences were observed with regard to glutathione (GSH) conjugation and oxidation by cytochrome P-450 dependent monooxygenases pathways, revealing higher rates for mice compared to rats. Chloroethane exposure resulted in induction of cytochrome P-450 IIE1 (increase in p-nitrophenol hydroxylase activity) in mice and rats. In the urine of both species S-ethyl-N-acetyl-L-cysteine was detected, and was generally higher in mice than in rats. The non-acetylated S-ethyl-L-cysteine was excreted in mouse urine only. Exposure resulted in a GSH depletion of about 50 % in the lung and uterus of both species, whereas liver and kidney GSH concentrations were not dramatically affected. GSH transferases were not induced. At high exposure concentrations the oxidative pathway (P-450) is saturated and increasing amounts are metabolized via the GSH pathway. The kinetic behaviors for chloroethane metabolism in rats were a combination of saturable and first-order processes. The dechlorination rate for chloroethane under the experimental conditions was low (~ 0.5 %) and found to be inducible by phenobarbital and benzopyrene, but not methylcholanthrene. These results indicate a cytochrome-P-450 dependent enzymatic reaction. The metabolism of chloroethane by microsomes from rats and mice was decreased after pretreatment of animals with phenobarbital or 3-methylcholanthrene. Acetaldehyde was detected as a metabolite.

Chloroethane has been tested for acute toxicity by the inhalation route of exposure. The acute LC₅₀ for rats and mice is greater than 19,000 ppm (50,000 mg/m³). No clinical signs of toxicity were seen. Human exposure has shown that chloroethane vapor is irritating to the eyes, nose and throat. Chloroethane exposure to skin has also resulted in contact dermatitis. In humans, skin sensitization to chloroethane can also occur. In humans, narcosis occurring at very high concentrations was the basis of historic use as a surgical anesthetic.

Repeated dose toxicity studies with chloroethane have been conducted by the inhalation and oral routes of exposure. In general, no compound-related clinical signs or gross or microscopic pathologic effects were seen in any of the repeated dose inhalation studies with rats at concentrations up 10,000 ppm (26,000 mg/m³). Decreased body weight (19000 ppm (50,000 mg/m³) for 13 weeks) and slight but statistically significant increases in liver to body weight ratios was observed for male rats exposed to 4000 (10,470 mg/m³) or 10000 ppm (26,000 mg/m³) for 2 weeks. Similarly, no clinical signs of toxicity have been observed in mice exposed to chloroethane by inhalation up to 19,000 ppm (50,000 mg/m³). An increase in liver weights (absolute and relative to body weight) was observed in some studies. In a 13 week study the liver weight to body weight ratio for female mice exposed to 19000 ppm (50,000 mg/m³) was significantly greater than that for controls, but no microscopic liver changes were observed. An increase in the mean liver weights of both male and female mice exposed to 5000 ppm (13,088 mg/m³), 23 hrs/d for 11 days. Pathological examination revealed an increased liver size in two males and one female exposed to 5000 ppm. A minimal increase in the degree of hepatocellular vacuolization in four of seven mice/sex exposed to 5000 ppm was observed, with a LOAEL of 5000 ppm. Similar effects on the liver were not noted in the remaining studies. Repeated inhalation exposure of chloroethane by rabbits or beagle dogs did not result in the observation of any treatment related effects. NOAELS were 9620 ppm (25.4 g/m³) (rabbit) and 10,000 ppm (26,000 mg/m³) (beagle dogs). There were no treatment related effects in rats and rabbits exposed to chloroethane by the oral route.

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Chloroethane induced gene mutations *in vitro* in both bacterial and mammalian systems, with and without metabolic activation. However, in a mouse micronucleus assay, chloroethane did not induce chromosomal damage *in vivo* at concentrations as high as 25,000 ppm (65,440 mg/m³) and no consistent increase in S-phase DNA synthesis and had no genotoxic activity in a UDS assay. The *in vitro* genotoxicity of chloroethane has not been demonstrated *in vivo*,

There was clear evidence of carcinogenicity for female mice. There was equivocal evidence of carcinogenic activity of chloroethane for male and female rats. A study in male B6C3F1 mice was considered to be inadequate.

There were no compound-related reproductive effects of rats or mice exposed to 15,000 ppm (39,264 mg/m³) for up to two years (NOAEL = 15,000 ppm). Mice exposed to up to 15000 ppm (39,264 mg/m³) chloroethane for 14 consecutive days had significantly longer estrous cycle duration than the pre-exposure duration for the same group and for the corresponding controls; the effect was attributed to a general stress response (NOAEL = 15,000 ppm). However, a direct exposure-related effect of chloroethane on neuroendocrine function cannot be excluded. Developmental toxicity (delayed ossification and supernumary ribs) was observed in mice when exposed at 5000 ppm (13,088 mg/m³) chloroethane vapor for 6 h/d on days 6 through 15 of gestation. The NOAEL for maternal and teratogenicity were >5000 ppm. Weak evidence of developmental toxicity was manifested by very slight fetotoxicity at high concentrations.

Environment

The melting point of chloroethane is -138.7°C and the boiling point is 12.3 °C at 1013 hPa. The vapor pressure is 1347 hPa at 20 °C. The water solubility of chloroethane is 5.74 g/L (20 °C) and the calculated log Kow is 1.43. The Henry's Law Constant is 1.1×10^{-2} atm-cu m/mole.

Chloroethane has an estimated atmospheric half-life (hydroxyl radical oxidation) range of 26.5 to 66.8 days. The hydrolysis half-life is estimated to range between 38 days and 2.6 years. Ethanol and HCl are the hydrolysis products. Results of Mackay Level I distribution modeling at steady state show that chloroethane will partition primarily to the air compartment (99.8%), with a negligible amount partitioning to water (0.19%) and soil (0.01%). Level III modeling using loading rates for air, soil and water of 1000 kg/h predicted the following distribution: air (49.4 %) water (47.3 %), soil (3.2 %) and sediment (0.04%). Using the Henry's Law constant, the volatilization half-lives for a model river and model lake are 50 hours and 3.2 days, respectively. Biodegradation studies suggest that chloroethane is not biodegradable. The calculated BCF is 2.5.

The 96-hour LC₅₀ for bluegill (*Lepomis macrochirus*) exposed to chloroethane under static conditions was 2250 mg/L (measured). Similar results were obtained with largemouth bass (*Micropterus salmoides*), with an LC₅₀ greater than 2000 mg/L (measured). The 48-hour EC₅₀ for *Daphnia magna* exposed to chloroethane was 58 mg/L (measured). The 72-hour ErC₅₀ (growth rate) for *Scenedesmus subspicatus* exposed to chloroethane was 11.8 mg/L (measured). The 72-hour E_bC₅₀ (biomass) for *Scenedesmus subspicatus* was 39 mg/L (measured). Chloroethane possesses properties indicating a hazard for the environment (acute toxicity to invertebrates and algae). However, its volatility and limited potential for bioaccumulation limit the potential for hazard to the environment.

Exposure

In recent years, two previous end uses of chloroethane (i.e. manufacture of tetraethyl lead which was used as an additive anti-knock agent in gasoline, and use as a foam blowing agent) have largely been eliminated in the Sponsor Country. These data show that nearly all of the chloroethane produced for the current US markets goes into consumptive uses, i.e. uses where the chloroethane is a feedstock used to produce different end product chemicals. Only a small volume goes into emissive uses such as foam blowing (2%).

In 2004, 31,624 tonnes of chloroethane were produced in the United States at the only manufacturing site. In production, this material is handled in closed systems. Engineering controls during production 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 pipe systems rather than in open systems to minimize loss of this material (volatilization). At the production site, approximately 175 workers have potential exposure to chloroethane, with measured levels in the range of 0-5 ppm. Chloroethane is transported from the production site to the industrial consumer primarily for consumptive uses. According to information in the USEPA Toxic Release Inventory data base for 2003, chloroethane use was reported at 44 sites, with total reported emissions of 781,700 lbs. (355 tonnes). Changes in end uses have significantly reduced emissions, e.g. in 1989 (a year with typical past end

use activities) 50 sites reported total emissions of 5,200,000 lbs. (23,587 tonnes). In 2003 only one site, where it was used in foam blowing, reported emissions over 100,000 lb/year, whereas the majority of the individual sites (25/44) reported total emissions of less than 1000 lb/year. The American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Time Weighted Average (TWA) for chloroethane is 100 ppm (264 mg/m³) and the US Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) is 1000 ppm (2640 mg/m³) TWA. The USEPA regulates chloroethane under both the Clean Air Act as amended in 1990, Sec. 112 (b)(1) (listed as hazardous air pollutant) and the Clean Water Act (designated as hazardous substance under section 311(b)(2)(A) of the Federal Water Pollution Control Act). Chloroethane is not used in consumer products. Environmental exposure to chloroethane can occur from fugitive and stack emissions at use sites and from its use in foam blowing.

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 (skin sensitisation, genotoxicity *in vitro* which has not been demonstrated *in vivo*, clear evidence of carcinogenicity in female mice and equivocal evidence in rats, weak evidence of developmental toxicity in mice as manifested by very slight fetotoxicity at high concentrations). Based on data presented by the Sponsor country, relating to production volume in one member country, which accounts for an unknown fraction of global production, and relating to the use pattern in several OECD countries, exposure to humans 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 invertebrates and algae). However, the chemical is of low priority for further work for the environment because of its volatility and limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-18-3
Chemical Name	Dimethyl Sulfide
Structural Formula	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array}$

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No reliable toxicokinetic studies were available; however, following acute inhalation exposure (death occurring within 8 minutes), dimethyl sulfide was found widely distributed in tissues of mice.

In rats, the acute 4-h inhalation LC₅₀ was 40250 ppm (102 mg/L). Based on secondary literature, dimethyl sulfide was slightly irritating to rabbit skin and eye. There was no reliable study to determine skin sensitization of dimethyl sulfide.

In a repeated-dose toxicity study, 15 rats/sex were orally dosed for 14 weeks at doses of 0 (corn oil), 2.5, 25, or 250 mg/kg bw /day. No toxicity was observed at the doses tested. Histopathological examination revealed some degree of fatty degeneration of the liver cells and chronic inflammation of lungs and kidneys. These changes were not treatment-related as the incidence and severity of these changes were comparable to the control group. The NOAEL for subchronic exposure was 250 mg/kg bw/day.

Dimethyl sulfide was not mutagenic to *Salmonella typhimurium* or *Escherichia coli* (bacterial reverse mutation assay) *in vitro*, with or without metabolic activation. It was also negative in a DNA damage and repair assay using *Salmonella typhimurium*. Dimethyl sulfide was not mutagenic in an *in vivo* mouse micronucleus study. Overall, dimethyl sulfide was considered not to have mutagenic potential *in vivo* based on available data.

There were no reliable studies to determine the potential carcinogenicity of dimethyl sulfide.

Dimethyl sulfide had no effect on male or female reproductive organs following repeated oral dosing in rats for up to 14 weeks. When pregnant rats were dosed with dimethyl sulfide from gestation days 6 to 19 via gavage at doses as high as 1000 mg/kg bw/day, no maternal toxicity, embryo-fetal or developmental toxicity or teratogenicity was observed. Overall, based on the available animal studies, dimethyl sulfide was not toxic to reproduction or development and was not teratogenic.

There are no known effects of dimethyl sulfide exposure in humans.

Environment

The melting point of dimethyl sulfide is – 98.3°C and the boiling point is 36.2 – 37.3°C at 1013 hPa. The vapor pressure is 559.8 hPa at 20°C. The calculated log Kow is 0.919. The water solubility of dimethyl sulfide is 20 g/L (25°C) and density is 0.8483 g/cm³ at 20°C.

Dimethyl sulfide is photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 2.8 days (calculated). Experimental studies show dimethyl sulfide is rapidly degraded in sunlight (natural and simulated) forming a number of breakdown products including sulfur dioxide. Dimethyl sulfide does not hydrolyze with hydrolysis half-lives of > 1 year at pH 4, 7 and 9.

Fugacity model Level III indicates dimethyl sulfide will distribute in air, water and sediment dependent on the

route of the emission. Fugacity model Level III distribution with 100% of the dimethyl sulfide released to air is: 98.6% (air), 1.3% (water), 0.1% (soil) and <0.01% (sediment); with 100% of the dimethyl sulfide released to water the distribution is: 8.6% (air), 91.2% (water), 0.01% (soil) and 0.2% (sediment); with 100% of the dimethyl sulfide released to soil the distribution is: 39.4% (air), 7.2% (water), 53.4% (soil) and 0.01% (sediment). Fugacity model Level III distribution with equal release of dimethyl sulfide to air, water and soil is: 28.1% (air), 57.2% (water), 14.6% (soil) and 0.1% (sediment)

A low bioaccumulation potential is expected based on the partition coefficient Log Kow of 0.919. Dimethyl sulfide is readily biodegradable (67.4% degraded over 28 days; OECD TG 301D).

The 96-hour LC₅₀ for rainbow trout was 213 mg/L (measured) and the 48-hour EC₅₀ values for *Daphnia magna* in two studies were 29 and 81 mg/L (measured). In two separate studies, the 96-hour EC₅₀ values for biomass and growth rate of algae (*Pseudokirchneriella subcapitata*) ranged from 23 to > 113.7 mg/L.

Exposure

The annual production volume of dimethyl sulfide in the United States is 10,000-15,000 tonnes. Dimethyl sulfide is used as a solvent and chemical intermediate for a wide range of organic materials including the production of dimethyl sulfoxide (DMSO). As one of the simplest organic substances containing sulfur, it is used as a sulfiding agent for catalysts in the refinery and petrochemical manufacturing processes, especially in ethylene manufacturing to control the formation of coke and carbon monoxide and in steel mill furnaces to control metal dusting. It is also used as a food flavoring agent and is listed in the Food Chemical Codex, approved for use by the U.S. FDA.

Dimethyl sulfide is primarily used in closed systems and environmental exposure is expected to be very limited. A small amount of dimethyl sulfide is used in natural gas as an odorant and may be released along with the natural gas in leaks from pipelines and gas facilities. Due to very low odor threshold limits, even small leaks can be detected. Most dimethyl sulfide used as a natural gas odorant would be burned. Other small amounts may be released in its use as a flavor or fragrance additive. Dimethyl sulfide is given off by marine organisms and therefore occurs naturally in marine waters.

A TLV of 10 ppm (25 mg/m³) TWA was adopted by the ACGIH in 2004 for dimethyl sulfide showing irritation as the TLV Basis-Critical Effect(s). Due to the low odor threshold (reported as low as 2.5 ppb) and extremely disagreeable odor, facilities typically limit exposure to well below the TLV to avoid odor complaints. Sampling from U.S. plants indicates that exposures over several years did not exceed the TLV and are generally less than 5 ppm with most exposures less than 1 ppm. The disagreeable odor of dimethyl sulfide provides for additional warning and avoidance of vapors.

The primary sources of consumer exposure to dimethyl sulfide are from leaks of natural gas and from its use as a flavoring agent. Humans can also be exposed to dimethyl sulfide produced naturally (e.g. by marine organisms). Due to its high volatility and odor, residues of dimethyl sulfide in products produced with or from the chemical are unlikely to exist.

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 has properties indicating a hazard for environment (acute aquatic EC/LC₅₀ values between 1 and 100 mg/l for invertebrates and algae). However the chemical is currently 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.	75-37-6
Chemical Name	1,1-Difluoroethane (HFC-152a)
Structural Formula	$F_2 - HC - CH_3$

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No toxicokinetic data for HFC-152a were found.

HFC-152a has low acute inhalation toxicity, with a 4-hour rat approximate lethal concentration (ALC) of 383,000 ppm. No valid acute oral toxicity studies are available. Although no standard test results are available, the repeat dose studies show some potential for irritation.

As with most HFCs, HFC-152a has the potential to produce cardiac sensitization in dogs challenged simultaneously with high exposure concentrations and high doses of exogenous epinephrine. Marked responses, which included a cardiac arrhythmia were observed in 3 of 12 dogs at 150,000 ppm. No response was observed at 50,000 ppm. No sensitization studies were available.

HFC-152a has low repeated dose toxicity. HFC-152a had anesthetic properties at a 100,000 ppm exposure level during a 2-week repeated dose inhalation study in rats. No other clinical, haematological, blood chemistry or histopathology effects were observed during the 2-week inhalation study. No adverse effects were observed in rats following a 3-month inhalation exposure to 25,000 ppm HFC-152a.

HFC-152a was not mutagenic in the *in vitro* bacterial reverse mutation test (Ames test) in *Salmonella typhimurium* and *Escherichia coli* strains. However, HFC-152a showed evidence of weak clastogenicity in an *in vitro* human lymphocyte chromosome aberration test. Further evaluation of the chromosome aberration potential using an *in vivo* micronucleus test produced negative results.

In a 2-year bioassay, HFC-152a was not carcinogenic to rats at inhalation exposure levels up to 25,000 ppm.

In a developmental study, female rats were exposed via inhalation up to 50,000 ppm during days 6 to 15 of pregnancy for 6 hours per day. No compound related maternal and developmental effects were observed at any of the concentrations tested, hence, the NOEL is 50,000 ppm. No histopathological or weight effects on reproductive organs were observed in male and female rats exposed up to 25,000 ppm HFC-152a for 6 hours per day, 5 days per week for 3, 12 or 24 months.

Environment

On the basis of its physical properties HFC-152a may be expected, when released to the environment, to partition almost exclusively into the atmosphere as it is a gas, with a vapor pressure at 25°C of 6065.2 hPa, and it has a water solubility of 2.671 g/l at 25°C. Any HFC-152a, which might be present in aqueous waste streams discharged directly into rivers or lakes would be expected, by analogy with similar compounds, to have a half-life with respect to volatilization of days or at the very most a few weeks. HFC-152a is expected to exist solely in the vapor-phase in the ambient atmosphere.

Vapor-phase HFC-152a is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals with a lifetime of 1.4 years. The atmospheric lifetime of this chemical suggests that it will mix throughout the troposphere with a globally averaged concentration in 2003 of about 2.6 ppt. Because of its IR absorption, it will contribute a very small amount to climate change with a global warming potential (GWP)

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relative to CO₂ of 140 for a time horizon of 100 years.

In addition, some HFC-152a is expected to gradually diffuse into the stratosphere above the ozone layer where it will slowly degrade due to reaction with hydroxyl radicals and direct photolysis from UV-C radiation. The ozone depletion potential (ODP) of HFC-152a has been determined to be negligible.

HFC-152a is not expected to adsorb to sediment or particulate matter. Bioconcentration is expected to be low based on an estimated BCF value of approximately 2 using the measured n-octanol/water partition coefficient (log value is 0.75). A Mackay Level III fugacity model (EPIWIN v.3.05) predicts that HFC-152a will partition mainly to the air (99.9%), with very little going to water (0.111%), and virtually none going to soil or sediment (0.01 and <0.01%, respectively).

Based on the ECOSAR predictions (96-hour LC₅₀ in fish of 733 mg/L 48-hour EC₅₀ in daphnids of 720 mg/L, and 96-hour EC₅₀ in algae of 419 mg/L), actual toxicity test data for the analog chemical HFC-134a (96-hour LC₅₀ in fish of 450 mg/L and 48-hour EC₅₀ in daphnids of 980 mg/L), and the high Henry's Law Constant for these compounds (0.02 atm-m³/mole for HFC-152a), the predicted toxicity of HFC-152a to aquatic organisms is low.

Exposure

The primary uses for HFC-152a are as an aerosol propellant and a foam expansion agent. Other potential uses include refrigeration blends and catalyst regeneration. Production capacities are confidential, but are in excess of 5000 metric tonnes per year. In Korea, it is also used in maintaining of a catalytic activity and estimated usage volume of 1,1-difluoroethane was 4.63, 4.85, and 3.14 tonnes/year in 2003, 2004, and 2005, respectively.

Emissions from HFC-152a manufacturing facilities are small. In the sponsor country, small amounts of HFC-152a are used in a closed system. HFC-152a is treated with steam and emitted to wastewater plant. Fluorine is below the detection limit (1 mg/L) in discharged water. There are no reported natural sources of HFC-152a. HFC-152a used in propellant and foaming applications will be emitted to the atmosphere.

Industrial hygiene monitoring data during manufacture and industrial use show exposure to be well under acceptable exposure limits. The current AIHA WEEL (Workplace Environmental Exposure Limit) and DuPont AEL (Acceptable Exposure Limit) are 1000 ppm, 8-hour TWA (time-weighted average). Though consumer exposure has not been measured directly, modeling based on measurement of similar uses shows consumer exposure to be minimal during intended uses.

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

The chemical is currently of low priority for further work, due to its low hazard profile. Its global warming potential is acknowledged and is being addressed by other programs.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-59-2
Chemical Name	Tetramethylammonium hydroxide
Structural Formula	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{H}_3\text{C}-\text{N}^+-\text{CH}_3 \\ \\ \text{CH}_3 \end{array} \quad \text{OH}^- $

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Tetramethylammonium hydroxide (TMAH) is completely dissociated in the body of animals due to its strong alkaline property, forming tetramethylammonium (TMA) ion. TMA administered to the intestine was rapidly absorbed in rats and most of the absorbed dose was excreted unchanged via the urinary route.

The dermal LD₅₀ value in female rats was 112 mg/kg bw. The oral LD₅₀ value in male rats was between 34 and 50 mg/kg bw [OECD TG 401]. TMAH administered dermally or orally caused, variously, a decrease in locomotor activity, an ataxic gait, hypothermia, incomplete eyelid opening or eyelid closure, salivation, irregular respiration, bradypnea and clonic convulsions. There are no data available for acute inhalation toxicity of TMAH.

The substance is reasonably considered to be strongly irritating or corrosive to the skin and the eye of animals due to its strong alkaline property. There are no test results available for skin or eye irritation of TMAH. There are no data available for sensitisation of TMAH.

In a repeated dose dermal toxicity study, rats were exposed for 4 weeks (6 hours/day, 5 days/week) to TMAH at doses of 0, 5.5, 50, 120 and 250 mg/kg bw/day in male rats and 0, 2.5, 5.5, 10 and 50 mg/kg bw/day in female rats. In addition to erythema, edema and/or scabbing observed at the application sites in all of the treated animals, red ovaries were observed in female rats at 5.5, 10 and 50 mg/kg bw/day, and red lungs, urinary bladder calculus, dark eye and small seminal vesicles in male and/or female rats at 50 mg/kg bw/day. Based on these findings, the NOAELs for repeated dose dermal toxicity were considered to be 5.5 mg/kg bw/day in male rats and 2.5 mg/kg bw/day in female rats. In a repeated dose oral toxicity study in rats [OECD TG 407], TMAH was administered by gavage to male and female rats (5 or 10 animals/sex/group) for 28 days at doses of 0, 5, 10 and 20 mg/kg bw/day. No deaths were observed in either sex. In male rats, decreases in food consumption and relative heart weight were also observed at 10 and 20 mg/kg bw/day. In female rats, decreases in food consumption were also observed at 20 mg/kg bw/day. There was no effect observed on haematological, clinical or histopathological examination at any doses. Based on decreases in food consumption and relative heart weight, the NOAEL for repeated dose oral toxicity was considered to be 5 mg/kg bw/day in males and 10 mg/kg bw/day in females. There are no data available for repeated dose inhalation toxicity of TMAH.

A bacterial reverse mutation assay [OECD TG 471] on TMAH was negative with or 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 is no study available for *in vivo* mutagenicity on TMAH, the chemical is considered to be not mutagenic based on negative outcomes in *in vitro* assays.

There are no data available for carcinogenicity of TMAH.

In a reproductive/developmental toxicity screening test in rats [OECD TG 421], TMAH was administered by gavage at doses of 0, 1, 5 and 20 mg/kg bw/day. No effect of TMAH was observed on any reproductive or

developmental parameters up to 20 mg/kg bw/day, the highest dose tested, while some toxic effects on parental animals (a decrease in food consumption, a decrease in locomotor activity) were observed at 20 mg/kg bw/day. Thus the NOAEL for reproductive/developmental toxicity was considered to be 20 mg/kg bw/day in rats.

Environment

TMAH has a water solubility of 1,000 g/l (estimated), a vapour pressure of 1.55×10^{-6} hPa (estimated), and a log Kow of -2.47 (estimated). Although an estimated Koc of 20.7 indicates a relatively low potential of the substance for adsorption onto soil and sediment, there is a possibility that TMA ion is adsorbed more than expected. A melting point for TMAH pentahydrate is 63°C.

A half life of TMAH by reaction with OH radicals in air was calculated to be 2.1 days (50.7 hr). TMAH has a strong alkaline property and is readily dissociated in water, forming TMA and hydroxyl ions. These physico-chemical properties indicate that TMAH is mainly distributed into the water compartment in the forms of TMA and hydroxyl ions in the environment. In a biodegradation test [OECD TG 301C], TMAH is readily biodegradable (BOD 96% after 14 days; the 10-day window was met). A bioconcentration factor of TMAH was calculated to be 3.16, indicating that the bioaccumulation potential of the substance is low.

The acute toxicity of TMA ion to fish was studied with tetramethylammonium chloride (TMAC) as a test substance, resulting in a value of 462 mg/l for the 96-hr LC₅₀ in *Pimephales promelas*. Using the molecular weights of TMAH (91) and TMAC (109), this value is converted to 359 mg/l TMAH, indicating that the toxicity of TMA ion to fish is very low. The acute toxicity of TMAH to invertebrates was studied in *Daphnia magna*, resulting in a value of 3 mg/l for the 48-hr EC₅₀ (pH7.6-9.5). Other studies conducted with *Ceriodaphnia dubia* gave 48-hr LC₅₀ values of 1.3-1.5 mg/l for neutralized TMAH. These results demonstrate that the observed toxicities relate to the TMA ion and are not affected by pH deviations. The acute toxicity of TMAH to aquatic plants was studied in *Pseudokirchneriella subcapitata*, resulting in 72-hr EC₅₀ values obtained on the basis of biomass and growth rate of 13 and 96 mg/l, respectively (pH8.2-11.2).

Chronic toxicity to invertebrates and algae has also been studied. The NOEC of TMAC regarding three brood survival and reproduction in *Daphnia magna* was 0.03 mg/l (converted to 0.02 mg/l TMAH using molecular weights of TMAH (91) and TMAC (109)), showing that TMA ion exerts strong chronic effects on daphnids. 72-hr NOECs of TMAH obtained on the basis of biomass and growth rate in *Pseudokirchneriella subcapitata* were 0.39 and 6.3 mg/l, respectively. No chronic toxicity data on fish are available.

Exposure

The annual production volume of TMAH in Japan was approximately 3,000 tonnes in 2004. The chemical is also produced in the United States and Korea while no data are available on the production volumes in these countries. All of TMAH is used for photolithography processes of semiconductors and liquid crystal panels (>97%) and electronic parts cleaning (<3%).

TMAH is produced in a closed system by electrolysis of aqueous solutions of TMAC or tetramethylammonium carbonate and is distributed to the market as aqueous solutions at various concentrations. In the Sponsor country, there is no process that generates wastewater at the production and formulation sites. Waste residues are derived only from containers and annual maintenance of plants. They are incinerated or biologically treated. Therefore, the release of TMAH into the environment from its manufacturing and formulation plants is minimal. At the user sites, several emission routes of TMAH after use were identified although no detailed information is available on each route. Therefore, the possibility is not excluded that some portion of TMAH used is released into the environment from user sites.

The monitoring data revealed that the TMAH concentrations in workplace atmospheres at a production site were minimal. In addition, workers are obliged to use personal protection equipments such as mask, safety glasses, gloves and protective garment. Thus the actual levels of occupational exposure to the substance via the dermal and inhalation routes are anticipated to be negligible. At the user site, TMAH is treated in a closed system. Although disposal of TMAH solution is the only process that might cause occupational exposure, such occupational exposure levels are considered to be negligible because of the low volatility of TMAH. Furthermore, workers use personal protection equipments such as masks, safety glasses, gloves and protective garment during operations.

Considering that TMAH is only used in the electronics industry as developers or cleaners and is completely washed away from the end products, such as semiconductors, liquid crystal panels and electronic parts, consumer exposure is also anticipated to be negligible.

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

Human Health: The chemical possesses properties indicating a hazard for human health (acute toxicity, corrosiveness and repeated dose toxicity). Based on data presented by the Sponsor country (relating to production in one country which accounts for an unknown fraction of the global production volume and relating to the 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 Sponsor country.

Environment: The chemical has properties indicating a hazard for the environment (acute aquatic toxicity EC/LC50 values between 1 and 100 mg/l). However the chemical is currently of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7632-00-0
Chemical Name	Sodium nitrite
Structural Formula	$\text{O}=\text{N}-\text{O}^- \text{ Na}^+$ NaNO_2

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Sodium nitrite has been reviewed by a number of international organizations: JECFA (Joint FAO/WHO Expert Committee on Food Additives); National Academy of Sciences (NAS); US National Institute of Environmental Health Sciences (NIEHS); National Institute of Public Health and the Environmental Hygiene, Netherlands; US National Toxicology Program (NTP); and California EPA (CAL/EPA).

Nitrite in blood is highly reactive with haemoglobin and causes methaemoglobinemia. Ferrous iron associated with haemoglobin is oxidized by nitrite to ferric iron, leading to the formation of methaemoglobin. Humans are considered to be more sensitive than rats in this respect.

The primary acute effect of sodium nitrite in rats and mice is methaemoglobinemia. Methaemoglobin concentrations in SD rats increased from 45% to 80% over 1 hour after an oral dose of sodium nitrite at 150 mg/kg bw and they returned to normal levels within 24 hours in surviving rats.

LD₅₀ values by gavage were 214 mg/kg bw (males) and 216 mg/kg bw (females) in mice. In an acute inhalation study (which could not be validated) methaemoglobin levels in female rats were significantly increased after 4 hours exposure to 10 mg/m³ sodium nitrite. The increase was judged not to be haematologically significant. No significant increase was observed in exposed males. There were no toxicologically significant effects on animals maintained for 14 days post exposure. No information on acute dermal toxicity is available.

Based on the available information, sodium nitrite is a moderate eye irritant, but is non-irritant to skin in rabbits. No studies are available investigating the sensitising potential of sodium nitrite in animals. No cases of sensitisation have been reported in humans.

In a repeated dose toxicity study [NTP] male and female F344/N rats were exposed to 0, 375, 750, 1500, 3000 or 5000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 30, 55, 115, 200, or 310 mg/kg bw/day in males and 0, 40, 80, 130, 225, or 345 mg/kg bw/day in females) in drinking water for 14 weeks. Methaemoglobin levels were significantly elevated in all treated groups compared to the controls by the end of the treatment period. For males, mean methaemoglobin levels after 14 weeks were 0.03±0.01, 0.08±0.01, 0.12±0.02, 0.25±0.07, 0.71±0.20 and 3.38±0.80 g/dL at doses of 0, 30, 55, 115, 200, and 310 mg/kg bw/day. For females, mean methaemoglobin levels after 14 weeks were 0.06±0.02, 0.14±0.02, 0.16±0.02, 0.48±0.05, 0.99±0.20 and 2.27±0.54 g/dL at doses of 0, 40, 80, 130, 225 and 345 mg/kg bw/day. The NOAELs were not determined (increased methaemoglobinaemia). The LOAELs for other endpoints were 115 mg/kg bw/day (decreased sperm motility) in males and 225 mg/kg bw/day (increased relative weight of the kidney and spleen) in females.

In a second 14-week repeated dose toxicity study [NTP] male and female B6C3F1 mice were exposed to 0, 375, 750,

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1500, 3000 or 5000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 90, 190, 345, 750, or 990 mg/kg bw/day in males and 0, 120, 240, 445, 840, or 1230 mg/kg bw/day in females) in drinking water. Methaemoglobin levels were not reported however there were no clinical signs of toxicity. The LOAELs were 750 mg/kg bw/day (extramedullary haematopoiesis in the spleen, degeneration of the testis) in males and 445 mg/kg bw/day (extramedullary hematopoiesis in the spleen) in females.

In a two-year chronic toxicity/carcinogenicity study [NTP] male and female F344/N rats were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 35, 70 or 130 mg/kg bw/day in males and 0, 40, 80 or 150 mg/kg bw/day in females) in drinking water. There were no clinical findings related to exposure. Methaemoglobin levels were measured at two weeks and three months. At both 2 weeks and three months, methaemoglobin levels were high at night when the rats were actively feeding and drinking and low during the day when the rats were less active. Methaemoglobin levels tended to increase with increasing dosage.

In a second two-year study [NTP] male and female B6C3F1 mice were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 60, 120 or 220 mg/kg bw/day for males and 0, 45, 90 or 165 mg/kg bw/day for females) in drinking water. There were no clinical findings related to exposure. At 12 months, no significant increase in methaemoglobin level was observed in either sex at any dose.

Based on the two-year studies, the NOAELs for rats were 130 mg/kg bw/day in males and 150 mg/kg bw/day in females. For mice the NOAELs were 220 mg/kg bw/day in males and 165 mg/kg bw/day in females

Sodium nitrite is a direct-acting, base-pair substitution mutagen in organisms ranging from bacteria to mammalian cells *in vitro*. This substance induced chromosomal aberrations in mammalian cells *in vitro*. There is evidence of potential *in vivo* genotoxicity. The substance tested positive in a micronucleus test (peripheral blood) when mice were dosed by gavage at 10 to 20 mg/kg bw (4 times at 24 hrs intervals) but was negative in a second study where mice were dosed via drinking water at dosed up to 900 mg/kg bw/day (females) for 14 weeks. In a chromosomal aberration test, pregnant rats were dosed with 210 mg/kg bw/day for 13 days. Positive results for the induction of chromosomal aberrations in bone marrow of the parents and liver cells of embryos were reported.

In a two-year chronic toxicity/carcinogenicity study [NTP] male and female F344/N rats were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 35, 70 or 130 mg/kg bw/day for males and 0, 40, 80 or 150 mg/kg bw/day for females) in drinking water. The incidences of hyperplasia of the forestomach epithelium in high dose males (44/50) and females (40/50) were significantly greater than those in the control groups (12/50 males, 8/50 females). The incidence of fibroadenoma of the mammary gland was significantly increased in 80 mg/kg bw/day females, and the incidences of multiple fibroadenoma were increased in 40 and 80 mg/kg bw/day females; however these neoplasms occur with a high background incidence and no increase was seen in the high dose group. The incidences of mononuclear cell leukemia were significantly decreased in 70 and 130 mg/kg bw/day males (7/50 and 3/50, respectively) and 80 and 150 mg/kg bw/day females (1/50 and 1/50, respectively) compared with controls (17/50 males, 15/50 females). Under the conditions of this study there is no evidence of carcinogenic activity of sodium nitrite in F344/N rats at approximate doses of up to 130 mg/kg bw/day in males and 150 mg/kg bw/day in females over a two year period.

In another NTP study male and female B6C3F1 mice were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 60, 120 or 220 mg/kg bw/day for males and 0, 45, 90 or 165 mg/kg bw/day for females) in drinking water for two years. The incidences of squamous cell papilloma or carcinoma (combined) in the forestomach of female mice occurred with a positive trend (1/50, 0/50, 1/50 and 5/50 at doses of 0, 45, 90 or 165 mg/kg bw/day, respectively). The incidence of hyperplasia of the glandular stomach epithelium was significantly greater in 220 mg/kg bw/day males (10/50) than in the controls (0/50). Under the conditions of this study there is no evidence of carcinogenic activity of sodium nitrite in male B6C3F1 mice at doses up to approximately 220 mg/kg bw/day over a two year period. There is equivocal evidence of carcinogenic activity in female mice, based on the positive trend of squamous cell papilloma or carcinoma (combined) in the forestomach.

Various other carcinogenicity studies in rats were negative. Moreover, some even showed a reduction in tumor risk (e.g. lymphoma or leukemia). WHO concluded that there was no evidence of carcinogenic activity of sodium nitrite

in rats and mice based on the findings of NTP carcinogenicity studies.

There is evidence for transfer of sodium nitrite to fetuses in rats and mice. Reproductive success in the F1 generation was not affected. Increase in mortality of pre- and postnatal offspring and decrease in body weight of preweaning pups were observed in rat dams given a diet containing sodium nitrite at 0.0125% (10.75 mg/kg bw/day), 0.025% (21.5 mg/kg bw/day) and 0.05% (43 mg/kg bw/day), and the NOAEL was considered to be 10.75 mg/kg bw/day. Reproductive toxicity by continuous breeding in the mice was conducted with drinking water at doses of 125, 260 and 425 mg/kg bw/day, and no adverse effect on reproductive performance or necropsy endpoint were observed. The NOAEL was estimated to be 425 mg/kg bw/day. Sodium nitrite caused maternal anemia and the incidence of abortion and fetal mortality increased when administered to pregnant guinea pigs in drinking water and LOAEL was considered to be at 60 mg/kg bw/day.

From the weight of evidence, sodium nitrite appears to affect erythropoiesis, hematological parameters and brain development resulting in mortality and poor growth of offspring.

In humans, sodium nitrite causes smooth muscle relaxation, methaemoglobinemia, and cyanosis. Infants are particularly sensitive. A large proportion of haemoglobin in infants is in the foetal haemoglobin form, which is more readily oxidised to methaemoglobin than adult haemoglobin. Further, reduced nicotinamide-adenine dinucleotide (NADH)-dependent methaemoglobin reductase, the enzyme responsible for reduction of methaemoglobin back to normal haemoglobin, has only about half the activity in infants compared to adults.

Environment

Sodium nitrite is in the form of white or slightly yellow hygroscopic granules, rod or powder, which is very soluble in water (820 g/L at 20 °C). Melting point, boiling point, vapour pressure and partition coefficient are 271 °C, >320 °C (decomposes), 9.9E-17 hPa (25°C) and log Kow = -3.7, respectively. Fugacity model Mackay level III calculations suggest that the substance will distribute mainly to soil if released to the air or soil compartments separately or to all three compartments simultaneously and almost exclusively to water if released to the water compartment. The estimated value of the Henry's law constant is 2.06E-07 atm.m³/mole. This substance dissociates immediately into sodium and nitrite ions in water. The nitrite ion is a component of the nitrogen cycle. In the environment, bacteria of the genus *Nitrobacter* oxidise nitrites to nitrates. Nitrates are reduced to nitrogen by anaerobic bacteria present in soil and sediment. The estimated BCF is 3.2 and hence bioaccumulation is not significant. Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 82.3 days.

The LC₅₀ values for the acute toxicity of sodium nitrite to fish reported in the literature vary widely between the species tested; LC₅₀ (96h) = 0.54 mg NaNO₂/L for *Oncorhynchus mykiss*; LC₅₀ (96h) = 35 mg NaNO₂/L for *Ictalurus punctatus*; LC₅₀ (96h) = 691.0 mg NaNO₂/L for *Micropterus salmoides*; and LC₅₀ (96h) = 1010.4 mg NaNO₂/L for *Anguilla japonica*, for example. This difference has been attributed to the ability of certain species, such as eels, bass and sunfish to prevent nitrite from crossing the gill membrane and entering the blood, whilst other species such as rainbow trout concentrate nitrite in their blood. The range of toxicity values reported for some species of fish varies widely and is believed to be dependant on the quality of the water used in the test with pH, chloride and calcium ion concentration all having an influence. In particular, chloride ion concentration has been shown to be important, with increasing concentrations leading to a decrease in the toxicity of nitrite. As with fish, there is variation in toxicity between invertebrate species. Sodium nitrite is toxic to invertebrates such as *Cherax quadricarinatus* (LC₅₀ (96h) = 4.93 mg NaNO₂/L and *Thamnocephalus platyurus* (LC₅₀ (24h) = 3.9 mg NaNO₂/L), whereas other species, such as *Procambarus clarkii* (LC₅₀ (96h) = 18.7 mg NaNO₂/L) and *Penaeus paulensis* are much less sensitive (LC₅₀ (96h) = 539.2 mg NaNO₂/L). The presence of chloride ions has been found to mitigate nitrite toxicity in some species. Acute toxicity to green alga (*Desmodesmus subspicatus*) is > 100 mg/L (72-h ErC₅₀ and EbC₅₀) [OECD TG 201].

No data were available for chronic toxicity of sodium nitrite in fish. In invertebrates, an 80-day NOEC of 9.86 mg NaNO₂/L for *Penaeus monodon* was reported. The NOEC value in green alga (*Desmodesmus subspicatus*) was 100 mg/L (72-h for growth rate and biomass) [OECD TG 201].

For other aquatic organisms, the EC₅₀ (48h, deformation) and LC₅₀ (48h) for the protozoa *Spirostomum ambiguum* were 421 and 533 mg NaNO₂/L, respectively; for the microalgae *Tetraselmis chuii* the EC₅₀ (96h, mobility) and NOEC (96h, mobility) were 7886 and 3740 mg NaNO₂/L, respectively.

Exposure

Total production of sodium nitrite in Japan was 10,000 - 50,000 t/year in 2001. Information on the worldwide production volume of sodium nitrite is not available.

This substance is used in closed systems, for non dispersive use, and also for wide dispersive use. Workers are recommended to wear protective gear such as a mask, rubber gloves and goggles to prevent exposure. There are no available official recommendations or regulations for occupational exposure limits to this substance. This substance is widely used in various industries including agricultural, basic chemicals, chemical industry, and others. The use in synthesis includes the use as raw material for the production of caprolactam and others. This substance is used widely as food/foodstuff additive, corrosion inhibitor, and so forth.

The nitrite ion is ubiquitous in the environment, where it forms part of the nitrogen cycle. The source of nitrogen is natural or anthropogenic. Fertilizers are considered to be the main anthropogenic source of nitrogen, although anthropogenic nitrogen oxide and dioxide present in the atmosphere from combustion processes are also sources of nitrite and nitrate in soils and surface waters, delivered via acid rain. Naturally occurring nitrogen oxide and dioxide in the atmosphere are also possible sources of nitrite. It should be noted that although the nitrite ion (NO₂⁻) may be a concern when assessing the potential eutrophication hazard including drinking water quality in certain regions, the use of this substance (NaNO₂) as a fertilizer has not been reported. Therefore this substance has a potential of eutrophication, but its influence is lower than that of the fertilizers.

The most common source of exposure of anthropogenic sodium nitrite to consumers is from its use in cured meat products. Exposure to nitrite also occurs from vegetables and drinking water. Nitrite can be formed in the body through reduction of nitrate by enteric bacteria and mammalian nitrate reductase. The Joint FAO/WHO Expert Committee on Food Additives established an acceptable daily nitrite intake of 0 to 0.07 mg/kg bw/day (2002). Various countries have set limits for nitrite through water quality regulations.

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

The chemical possesses properties indicating a hazard to human health (acute toxicity, irritation, repeated toxicity, mutagenicity, and reproductive toxicity) and the environment (acute toxicity). Given the wide dispersive use of this substance, member countries are invited to perform an exposure assessment, and if necessary a risk assessment for these uses. It is acknowledged that some uses (e.g. as a food additive) as well as the presence in drinking water are already regulated in many member countries. It should be noted that there is no standard acute algae study available, however further study is not warranted. It is recommended that the information on possible total exposure from regulated and non-regulated use be shared between regulatory agencies.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	764-41-0
Chemical Name	1,4-Dichlorobut-2-ene
Structural Formula	Cl-CH ₂ -CH=CH-CH ₂ -Cl

SUMMARY CONCLUSIONS OF THE SIAR

1,4-Dichlorobut-2-ene (CAS No. 764-41-0) consists of a mixture of *cis*-1,4-dichlorobut-2-ene (CAS No. 1476-11-5) and *trans*-1,4-dichlorobut-2-ene (CAS No. 110-57-6). 1,4-Dichlorobut-2-ene available in the US contains 95 - 98 % *trans*-1,4-dichlorobut-2-ene and 2 - 5 % of the *cis*-isomer. During manufacturing, mixtures of different composition may occur.

Human Health

For the toxicological endpoints addressed there have been taken into consideration besides the data for the title substance 1,4-dichlorobut-2-ene (*cis* and *trans*) also toxicity data for the pure isomers *cis*-1,4-dichlorobut-2-ene and *trans*-1,4-dichlorobut-2-ene.

There are no studies available concerning toxicokinetics, metabolism and distribution of 1,4-dichlorobut-2-ene. Results from toxicity studies with experimental animals show that 1,4-dichlorobut-2-ene is absorbed after inhalational, oral and dermal application.

1,4-Dichlorobut-2-ene is very toxic by inhalation with a 4 hours-LC₅₀ of 450 mg/m³ in rats; toxic symptoms are mainly of local nature like salivation, lacrimation and irritation of the respiratory tract. The dermal toxicity is moderate with an LD₅₀ (rabbit) of ca. 735 mg/kg bw in a study with rather limited documentation. After oral application the substance is toxic with an LD₅₀ (rat) ranging from > 120 and < 300 mg/kg bw accompanied by toxic effects like spasms and weakness. 1,4-Dichlorobut-2-ene is corrosive at the skin and eyes and extremely irritating to the respiratory tract. The RD₅₀ in rats was calculated as 179 ppm (900 mg/m³).

There are no valid data available concerning sensitization.

The main toxic effects after repeated exposure of rats to 1,4-dichlorobut-2-ene vapors are irritations of the respiratory tract characterised by flattening and metaplasia of the nasal and tracheal mucosal epithelium. At higher exposure concentrations (≥ 1 ppm; ≥ 5.2 mg/m³) mortality is increased. There is no chronic NOAEC derivable; the LOAEC is 0.1 ppm (0.52 mg/m³; lowest concentration tested). A limited study gave information that repeated oral application of 100 mg/kg bw/day to rats led to discomfort, diarrhea, reduced body weight gain and high mortality. Histopathological effects included lung congestions as well as acute necroses in stomach, liver and spleen.

1,4-Dichlorobut-2-ene is mutagenic to bacteria and yeasts as well as to mammalian cells *in vitro*. *In vivo* a negative result was obtained in a micronucleus assay performed according to OECD TG 474 with inhalation exposure of rats although the highest concentration tested (52 mg/m³) led to systemically toxic effects. In another non-guideline study with limited documentation 1,4-dichlorobut-2-ene showed a clastogenic activity after inhalational exposure of rats. Overall 1,4-dichlorobut-2-ene is mutagenic *in vitro* and there are some indications for a possible clastogenic activity *in vivo*.

1,4-Dichlorobut-2-ene has shown a tumorigenic activity in rats after chronic inhalation exposure leading to the dose-dependent increase of the incidence of benign and malignant nasal tumors. In studies with dermal application of 1,4-dichlorobut-2-ene to mice there is no indication for a tumorigenic potential at the skin. A retrospective cohort study gave no suspicion for any increased cancer risk of exposed employees. Due to the small cohort size no firm conclusion can be drawn concerning the cancer risk to humans exposed to 1,4-dichlorobut-2-ene.

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There are no valid studies available concerning possible impairment of fertility by 1,4-dichlorobut-2-ene. From chronic inhalation studies with rats there are no indications for pathological changes of the male and female sex organs due to 1,4-dichlorobut-2-ene exposure. In a developmental toxicity study with rats 1,4-dichlorobut-2-ene showed no embryotoxic or teratogenic potential. The NOAEC for maternal toxicity is 2.6 mg/m³ based on reduced body weight gain at 26 mg/m³ and the NOAEC for developmental toxicity is 26 mg/m³ (highest dose tested). Overall, 1,4-dichlorobut-2-ene is not anticipated to pose a hazard to fertility and has no specific effect on embryonic or fetal development.

Environment

1,4-Dichlorobut-2-ene is a yellowish liquid. The melting points are -48 (cis-isomer), 1 °C (trans-isomer), and between -48 °C and 1 °C for the mixture. The boiling points at 1013 hPa are 156 (mixture), 152.5 (cis-isomer), and 156.1 °C (trans-isomer). 1,4-Dichlorobut-2-ene (mixture) has a density of 1.189 g/cm³ at 25 °C. The cis-isomer has a relative density of 1.188, and the trans-isomer of 1.183, both at 25 °C. The measured vapor pressure of the isomers mixture is 15.9 hPa, of the cis-isomer 4.4 hPa, and of the trans-isomer 3.9 hPa, all at 25 °C. The measured log K_{ow} of the trans-isomer is 2.18, calculated values for both isomers are 2.6. The solubility of the isomers mixture in water is 1.24 g/l at 20 °C, of the cis-isomer 0.58 g/l at 25 °C, and of the trans-isomer 0.85 g/l at 25 °C. The flash points are 59 °C (mixture), 49.9 °C (cis-isomer), and 53 °C (trans-isomer). The auto flammability (ignition temperature) is approx. 465 °C. 1,4-Dichlorobut-2-ene is flammable.

In the atmosphere 1,4-dichlorobut-2-ene is degraded by photochemically produced OH radicals. The half-life is calculated to be 12 hours for the cis-isomer and 10 hours for the trans-isomer. Due to the low absorption in the UV-B range, no direct photodegradation is expected. In a direct photodegradation experiment in demineralized water a half-life of 1 - 3 h was obtained. Under the same conditions, but in the presence of added hydrogen peroxide, the half-life decreased to t_{1/2} < 30 minutes.

1,4-Dichlorobut-2-ene hydrolyzes in water forming organic hydrolysis products (e.g. 2,5-dihydrofuran) and hydrochloric acid. Hydrolysis half-lives of 1,4-dichlorobut-2-ene were measured as 3.2 days under neutral conditions, suggesting that hydrolysis may be an important fate process in moist soils and water.

According to a Mackay Level I calculation the favorite target compartment of 1,4-dichlorobut-2-ene (mixture and isomers) is air, with 98.1 % of the mixture in the gas phase. Henry's Law Constants, relating to the mixture, cis-, and trans-isomers of 1905 Pa m³/mol were calculated according to the Bond method, and of 54.2 Pa m³/mol according to the Group-method. Henry's Law Constants of 57.4 - 160.3 Pa m³/mol were calculated from the ratio of the vapor pressure to the water solubility, respectively, indicating that the compounds have a high potential for volatilization from surface waters.

1,4-Dichlorobut-2-ene is not readily biodegradable. A closed bottle test in all essential parts identical with OECD TG 301 D was performed under GLP with a concentration of 1,4-dichlorobut-2-ene of 5.5 mg/l. After 28 days 20 % of the test substance had been biodegraded. In a closed bottle test, comparable to the OECD TG 301 D performed with a concentration of 1,4-dichlorobut-2-ene of 6.2 mg/l, no biodegradation was observed after 28 days.

The bioconcentration factor (BCF) of 9.5 for 1,4-dichlorobut-2-ene (mixture, cis-, and trans-isomers), calculated from the octanol-water partition coefficient, indicates that there is a low potential for bioaccumulation in aquatic organisms.

With PCKOCWIN v. 1.66 a K_{oc} of 149 for 1,4-dichlorobut-2-ene (mixture, cis-, and trans-isomers) is calculated. In addition, an adsorption coefficient (K_{oc}) of 215 was obtained experimentally for cis-1,4-dichlorobut-2-ene. These results indicate that 1,4-dichlorobut-2-ene is supposed to have a moderate accumulation potential in soil. However, due to hydrolysis and volatilization, accumulation in soil is not expected.

Concerning the aquatic toxicity of 1,4-dichlorobut-2-ene there are acute test results available. The lowest reliable effect values for aquatic species with 1,4-dichlorobut-2-ene towards fish, *Daphnia*, and algae are (n = nominal concentration; m = measured concentration):

<i>Poecilia reticulata</i> (fish):	14 d-LC ₅₀	=	0.086 mg/l (n)
<i>Daphnia magna</i> (invertebrates):	48 h-EC ₅₀	=	0.156 mg/l (m)
<i>Desmodesmus subspicatus</i> (algae)	72 h-EC _{50Growth rate}	=	2.13 mg/l (m)

For microorganisms the lowest available toxicity value determined was 3 h-EC₅₀ of 573 mg/l (n) (activated sludge). Since acute test results for 1,4-dichlorobut-2-ene for three trophic levels are available, an assessment factor of 1000 was applied for the derivation of the PNEC_{aqua} according to the EU Technical Guidance Document. The lowest effect concentration was found for the fish species *Poecilia reticulata*, 14 d-LC₅₀ of 0.086 mg/l effect concentration,

therefore resulting in a $PNEC_{\text{aqua}} = 0.086 \mu\text{g/l}$.

Exposure

1,4-Dichlorobut-2-ene is manufactured by chlorination of butadiene in closed systems. For 2002, the following 1,4-dichlorobut-2-ene manufacturing capacities were estimated:

USA	68 000 tonnes/a	(1 manufacturer)
EU	71 000 tonnes/a	(2 manufacturers)
Japan	67 000 tonnes/a	(3 manufacturers)
Armenia	3000 tonnes/a	(1 manufacturer)
China	no capacity data available	(2 manufacturers)
Global	> 209 000 tonnes/a	(9 manufacturers).

In Germany, the only manufacturer of 1,4-dichlorobut-2-ene has a manufacturing capacity of 10 000 - 50 000 tonnes/a and processes all products at the same site. 1,4-Dichlorobut-2-ene is used as an intermediate in chemical processes. Like 3,4-dichloro-1-butene, it is an intermediate in the manufacturing of chloroprene, furthermore a starting material in the production of 3-hexenedinitril (which can be hydrogenated to adiponitril, a hexamethylenediamine intermediate), butane-1,4-diole, tetrahydrofuran, and tetrachlorobutane. Essentially 100 % of the manufacturing volume is used for the production of 3,4-dichloro-1-butene and adiponitril.

In the Sponsor country 1,4-dichlorobut-2-ene is manufactured continuously and processed in closed systems. During manufacturing and processing, virtually no 1,4-dichlorobut-2-ene was emitted into the atmosphere (< 25 kg) and into the aquatic environment in 2004.

Due to the high volatility of the substance, occupational exposure to 1,4-dichlorobut-2-ene may occur through inhalation. In the Sponsor country, exposure is well controlled in occupational settings.

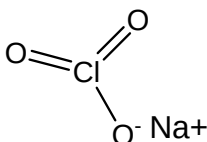
1,4-Dichlorobut-2-ene is not listed in the Nordic and Swiss Product Registers. There is no known route of consumer exposure via the environment. Since no consumer products are known to contain 1,4-dichlorobut-2-ene, consumer exposure to 1,4-dichlorobut-2-ene is not likely to occur.

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

Human Health: The substance is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (acute toxicity, repeated dose toxicity, skin and eye irritation, genotoxicity, carcinogenicity). Based on data presented by the Sponsor country (relating to production by 1 producer which accounts for approximately 5 % to 24 % of global production and relating to the use pattern in several OECD countries), adequate risk management measures are being applied in occupational settings and exposure of consumers is negligible. Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment: The chemical possesses properties indicating a hazard for the environment (acute toxicity to fish, algae, and invertebrates). Based on data presented by the Sponsor country (relating to production by 1 producer which accounts for approximately 5 % to 24 % of global production and relating to the use pattern in several OECD countries), emissions into the environment are anticipated to be low. 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7775-09-9
Chemical Name	Sodium chlorate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Sodium chlorate is rapidly absorbed and distributed throughout the body where after exerting its oxidative action it will be taken up in the chloride pool. Excretion takes place in the urine mainly in the form of chloride. Excretion of unchanged sodium chlorate is only observed during the first day after uptake.

Animal studies with sodium chlorate show a low acute toxicity after inhalation ($LC_{50} > 5.59$ mg/l), dermal ($LD_{50} > 2000$ mg/kg bw) and oral (4950-6250 mg/kg bw) exposure. A handbook reports that doses of 5 to 10 grams can be fatal in adult humans, and doses of 2 grams in children. But also multiple cases are described surviving intakes ranging from 40 g to even 150-200 grams. This is likely related to the possibility of dialysis treatment in case of renal failure after the 1960's. No fatalities were reported in recent years. Despite the low acute toxicity in animals, available data on human lethal effects indicate that sodium chlorate should be classified as harmful.

The primary concern for acute sodium chlorate exposure is oxidative damage to red blood cells and resulting methaemoglobinemia. Acute toxicity of chlorate is mediated by methemoglobin. There are marked species differences in susceptibility to form methemoglobin. Humans are more affected than rodent species.

Experience from exposure of workers in chlorate production plants indicates that eye and respiratory irritation are possible. Also cases were reported of 1st and 2nd grade skin burns related to the possible spontaneous ignition of dried sodium chlorate. Sodium chlorate is only mildly irritating to skin and eyes in rabbit studies. Available data and studies do not indicate that sodium chlorate has a potential for skin sensitization. Concerns for subchronic and chronic chlorate exposures are related to its competitive inhibition of iodide transport through thyroid follicular cells, required for thyroid hormone synthesis. This results in an initial decrease in the T3 and T4 serum levels followed by a compensatory increase of TSH. This in turn results in an increase in thyroid cell proliferation with subsequent restored thyroid hormone production, thus maintaining homeostasis. Thyroid effects were already visible after intake from 4 mg/kg/day in animal (rat) studies. These effects indicate a physiological compensatory mechanism to maintain homeostasis upon the presence of chlorate, and not an adverse effect as such. Human volunteer studies, which also included evaluation of thyroid function parameters, showed no effects up to 36 µg/kg/day for 12 weeks. Sub-chronic and chronic studies do not show a high level of toxicity. A 90-day study on rats resulted in a NOAEL of 100 mg/kg bw/day and a 90-day study on dogs resulted in a NOAEL of 360 mg/kg bw/day, the highest dose tested. In another rat study, a NOAEL of 38 mg/kg was determined when based on the colloid depletion in reaction to decreased iodide transport. In this study, haematological effects (anemia) were also observed at the highest dose (653 mg/kg/day for males and 1021 mg/kg/day for females).

Available studies differ in their reported effects on the thyroid. One study did not show any effect after 90-days up to 1000 mg/kg/day, whereas in NTP studies (2004) hypertrophy was observed from around 40 mg/kg/day. Another 90-day study in rats indicated possible effects of thyroid colloid depletion, and a NOAEL in rats of 38 (males) and 53 mg/kg bw/day (females). A two generation reproduction study on rats indicated a parental NOAEL of 10 mg/kg bw/day for males and 70 mg/kg bw/day for females, based on slight to moderate follicular hyperplasia and signs of slight to moderate hyperactivity of the thyroid gland. Two year chronic NTP studies (2004) in mice and rats indicated thyroid hypertrophy in rats. There seemed to be a concentration related increase in percentage of smaller follicles, often showing colloid depletion, which was visible from 4.5 mg/kg bw/day in males. The seriousness of

long term stimulation of the follicle cells is relatively limited as even at the highest dose levels in this study of 75 to 96 mg sodium chlorate/kg bw/day hypertrophy was clearly present, whereas hyperplasia and follicular cell carcinomas, although exceeding control ranges, were not statistically significant increased.

Although no haematological effects were observed in the chronic NTP studies, the incidence of bone marrow hyperplasia was possibly increased in male rats and female mice, but lowered in male mice.

In a two generation study, there was no indication of either reproductive toxicity of sodium chlorate or developmental toxicity up to 500 mg/kg bw/day in rats. No indication of developmental toxicity was observed up to 475 mg/kg bw/day in rabbits

Sodium chlorate was not mutagenic in the majority of in vitro studies and in all in vivo systems tested. Sodium chlorate did not induce gene mutations in either bacteria or mammalian cells but the results in *Escherichia coli* are suggestive of a primary DNA damage with no requirement for metabolic activation. This effect was not confirmed in mammalian HeLa S3 cells. Sodium chlorate was not considered to be genotoxic.

In the NTP carcinogenicity study, sodium chlorate resulted in a positive trend in the incidences of pancreatic islet cell adenoma or carcinoma in female mice. NTP concluded that it was an equivocal effect. An increase of thyroid neoplasia in male rats (at 75 mg/kg bw/day) was seen. Taking into account the mechanism of action, available data suggest hormone imbalance leads to thyroid tumor formation in rats. The human thyroid is much less sensitive than the rat thyroid for this TSH stimulated effect. Therefore, sodium chlorate was not considered to be a potential human carcinogen.

Environment

Ecotoxicity: Sodium chlorate is a white, odorless, crystalline solid and is highly water soluble. It is a strong oxidant, not combustible but reacts violently with combustible and reducing materials. There is a risk of fire and explosion in dry mixtures with other substances, especially certain organic materials.

Sodium chlorate has a melting point of $255.0 - 259.5 \pm 1^\circ\text{C}$, and decomposes upon further heating. The solubility in water at 20°C is about 802 g/L.

Distribution: Sodium chlorate does not adsorb to soil and will end up in the surface water where it dissociates. Due to its chemical structure, sodium chlorate is considered as stable in water regardless of the pH. Bioaccumulation is not expected. A representative average upon delivery of industrial hypochlorite to bleach formulators is 3 to 5 g/L sodium chlorate in commercial concentrated (15% w/w) hypochlorite product. The total chlorate level amounts to 1.8 g/L in domestic bleach. The predicted environmental input of chlorate from bleach in surface waters is $12.5 \mu\text{g/l}$ (range $0.4\text{--}30 \mu\text{g/l}$) for Europe. There are few data on chlorate levels in brackish or marine waters. In the Baltic Sea, mean values of up to $53 \text{ mg ClO}_3^-/\text{L}$ were recorded in kraft pulp mill effluent discharged into coastal waters in the early 1980s. A few years later the system was improved and the concentration in the Baltic Sea decreased to $2 \mu\text{g/l}$ at a distance of 3 - 4 km from the diffuser.

Fate: As sodium chlorate is an inorganic substance, it cannot be defined as biodegradable on the basis of mineralization of organic matter. However biotic degradation occurred within anaerobic niches in the soil where anaerobic biodegradation occurred via non-obligate anaerobes which mineralise chlorate to chloride generally using the same pathway as for nitrate reduction. In a water-sediment system the DT_{50} s under anaerobic- and aerobic conditions were 8 days in water and less than 3 days in sediment. In soil, sodium chlorate is rapidly degraded under anaerobic conditions, the half-life is 7.5 days. Under aerobic conditions the half-life was at least 39 days. In the presence of glucose or sucrose at a concentration of 10 g carbon/kg soil potassium chlorate is rapidly degradable under aerobic conditions. A concentration of $341 \text{ mg chlorate/kg soil}$ was almost completely decomposed within 4 weeks. In 30 cm soil columns sodium chlorate was found in the leachate, but more than half of the total amount was degraded over a period of 34 days.

Freshwater organisms were not found to be particularly sensitive to sodium chlorate. In the acute studies aquatic algae were found to be most sensitive species tested. For *Selenastrum capricornutum* the E_rC_{50} at 72h was 129 mg/l . The EC_{50} for invertebrates (*Daphnia magna*) was greater than 1000 mg/l . For several fish species an LC_{50} greater than 1000 mg/l was found. Of the chronic aquatic endpoints, the macrophyte, *Lemna minor* was found to be the most sensitive species to sodium chlorate with a NOEC of 10 mg/l . The NOEC for fish (*Danio rerio*) and invertebrates (*Daphnia magna*) were greater than or equal to 500 mg/l (the highest concentration tested in each case). The EC_{50} for aquatic microorganisms was greater than 1000 mg/l .

Sodium chlorate is considered as practically non-toxic to freshwater species ($EC/LC_{50}s > 100$ mg/l). In addition, there is no potential risk of bioaccumulation of sodium chlorate (estimated $\log P_{ow} < -2.9$).

For marine organisms the following tests were performed. The LC_{50} to marine fish was greater than 1000 mg/l. For *Nitzschia closterium* a test with potassium chlorate gave an EC_{50} of 2.8 mg $KClO_3$ /l. This was found to be due to the low nitrate concentration used in the study (<0.005 mg NO_3^- /l).

For terrestrial organisms, several data were found. The 14-day LC_{50} for oligochaetes > 750 mg/kg soil dw. The lowest acute value for arthropods was found for *Typhlodromus pyri* Scheuten with a LR_{50} of 84.4 kg/ha. For worker honey bees, the oral toxicity LD_{50} was greater than 75 μ g/bee. Acute and chronic toxicity to birds was tested. The NOAEL (NOEL) in a 14-day study with ducks was higher than 2510 mg/kg. A 135-day study with *Colinus virginianus* gave a NOEC of 300 ppm (equal to 31.6 mg/kg bw/day).

Exposure

Production: Between 1990 and 2002, the North American sodium chlorate capacity increased from 1,100 to 2,100 ktons/year. The total production capacity in Western Europe was about 700 ktons/year in 2002. Eastern Europe had a production capacity of less than 100 ktons/year in 2002. The total use in the Nordic countries is estimated at 260 to 270 ktons/year. In Japan the total volume consumed in 2005 was 100 ktons.

Use: Up to 95% of all sodium chlorate produced worldwide goes into the pulp and paper industry where it is used to generate chlorine dioxide, a key bleaching agent. The other 5% is mainly used as a herbicide and for uranium manufacture. Use as a non-selective herbicide and defoliant has strongly declined. Sodium chlorate is further used as intermediate in making rocket propellants and dyes, in refining for vanadium and uranium and often as intermediate for other chlorates, in matches, explosives, cosmetics and the pharmaceutical industry. Chlorate is present as a by-product in domestic hypochlorite bleach. In the chlor-alkali industry, producers are switching from mercury-based to membrane cell technology, resulting in the discharge of chlorates instead of mercury. Furthermore it is used as oxidizing agent for acrylic fiber.

Release: Releases into the environment may occur during production, further processing and use of chlorates, as well as from by-product formation during water disinfection with chlorine dioxide, from chlorine production from membrane electrolysis, and presence in hypochlorite bleach.

Occupational exposure: Exposure can occur during production and handling of sodium chlorate. The use of protective suits, boots, gloves, goggles and hardhat with safety visor are mandatory when handling sodium chlorate. Dried sodium chlorate is an ignition hazard in the presence of organic material. The packaging of sodium chlorate powder leads to dust exposure even if workers use personal protective equipment. Epidemiological exposure assessments were not available. A recent survey on the medical status among workers from European sodium chlorate production sites reported no evidence of important health effects related to occupational exposure to sodium chlorate.

Consumer products: Chlorate is present as a by-product in domestic hypochlorite bleach. Sodium chlorate does not form a vapor, therefore exposure of the general public is limited to indirect intake via drinking water and food. From recent literature studies, this intake is expected to be below the WHO TDI of 0.03 mg/kg/day (2005).

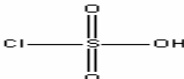
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health. For acute exposure, the oxidative damage to red blood cells and resulting methaemoglobinemia are of concern. For long-term exposure the potential critical effect is on thyroid function. Exposure to humans is anticipated to be low. 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 country.

Environment: The chemical is currently of low priority for further work because of its low hazard profile to freshwater organisms. However, marine tests indicate that chlorate toxicity increases when nitrate concentrations are low. The substance has a high potential of biodegradation in sediment and soil and low potential for

bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7790-94-5
Chemical Name	Chlorosulfuric acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Chlorosulfuric acid undergoes immediate hydrolysis in the water of body fluids after contact with any tissue. The hydrolysis products are hydrogen chloride (HCl; CAS 7647-01-0) and sulfuric acid (H₂SO₄; CAS 7664-93-9); SIDS documents have been prepared for SIAM 11 (H₂SO₄) and SIAM 15 (HCl). For the assessment of effects of the hydrolysis products on human health it is referred to the validated hazard assessment within the OECD HPV Chemical Program.

Toxicity of the hydrolysis products HCl and H₂SO₄ is the result of the hydrogen ion and the local reduction of the pH at the site of contact. Under normal conditions the uptake of hydrogen ions will not change the pH in the body fluids because of the available buffer systems. No hazard is expected from the anions, the chloride and sulfate ions which are normal constituents of the body fluids and enter the body electrolyte pool.

In acute inhalation toxicity studies chlorosulfuric acid and/or the reaction products HCl and H₂SO₄ are extremely irritating to the eyes, mucous membranes and the respiratory tract. They cause rapid destruction of tissues and severe burns. Airways obstruction resulting from tracheal lesions was presumed to be the cause of death. The estimated LC₅₀ (4 h) for male and female rats combined is > 1765 mg/m³. The estimated LC₁₀ (1 h) for male and female rats combined is 926 mg/m³; the NOAEL is 282 mg/m³ following 1-hour exposure. In humans effects of H₂SO₄ aerosols on lung function parameters have been demonstrated at concentrations below 1 mg/m³. No valid data are available on the acute dermal or oral toxicity of chlorosulfuric acid. But, based on the chemical and physical nature of chlorosulfuric acid, it can be concluded that chlorosulfuric acid is corrosive to the skin and mucous membranes and extremely damaging to the eyes.

For chlorosulfuric acid itself no data are available on the following toxicological endpoints: sensitization, toxicity after repeated exposure, genotoxicity, carcinogenicity and toxicity for reproduction. However, data are given for the hydrolysis products. HCl and H₂SO₄ gave no evidence for a sensitizing potential in humans.

The observed effects after repeated inhalation exposure to the hydrolysis products are related to the irritant properties of HCl and H₂SO₄ and are most likely due to decrease in the pH value. The described effects are restricted to alterations in structure and function of the respiratory tract. Potential systemic effects are considered to be a result of the local effects. Laboratory animal studies performed with H₂SO₄ gave LOAELs in the range of 0.3 mg/m³. The LOAEL reported in a subchronic study with HCl on rats and mice was 15 mg/m³; no NOAELs could be determined.

Data on *in vitro* mutagenicity of the hydrolysis products have shown no gene mutagenic activity in the *Salmonella* microsome assay as well as negative results in studies for direct or indirect measurement of DNA damage in bacteria and eucaryotic cells. However, there is some evidence for chromosome aberration in mammalian cells at pH values not inducing general cytotoxicity. Furthermore mutagenic activity has also been detected in the SLRL assay in *Drosophila melanogaster*. No further *in vivo* mutagenicity data are available, but the performance of traditional *in vivo* studies is not considered useful, since systemic genotoxic effects are not expected. Effects including possible genotoxicity due to decreased pH are restricted to the site of first contact. Since the effects are

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related to an exhaustion of the physiological buffer capacity of the target tissue a threshold for the genotoxic effects is also expected.

Carcinogenicity studies with the hydrolysis products on experimental animals do not meet present-day requirements. In an inhalation study using a single dose level HCl induced hyperplasia in the larynx and trachea but no neoplasia. An excess risk for lung cancer was seen in one cohort study on steel-pickling workers exposed to acid mists primarily to HCl mist. No association between exposure to HCl and cancer of the lung was reported in a case-control study. IARC classified HCl in Group 3 (not classifiable as to its carcinogenicity in humans). But data from cohort and case-control studies indicate an association between H₂SO₄ mists and laryngeal cancer. IARC classified strong inorganic acid mists containing sulfuric acid as a Group 1 carcinogen (carcinogenic to humans). However, the mechanism of carcinogenicity is still in discussion. Nongenotoxic mechanisms are suggested and it is assumed that the laryngeal cancer in humans is associated with regenerative cell proliferation at the site of contact.

In a 90 day inhalation study no effects were observed on the gonads of male and female mice and rats at dose levels up to 70 mg/m³ HCl. Because chlorosulfuric acid and the hydrolysis products act at the site of contact due to local reduction of the pH value, effects on reproduction are not expected following exposure by any route.

In a study on developmental toxicity in mice and rabbits borderline effects concerning a certain type of skeletal variation were observed in fetal rabbits at H₂SO₄ aerosol concentrations of 20 mg/m³. The NOEL for developmental toxicity is 5 mg/m³. Local maternal effects were detected in rabbits at 5 mg/m³, the NOEL is below 5 mg/m³. No developmental toxicity was observed in mice. Because chlorosulfuric acid and the hydrolysis products act at the site of contact, prenatal toxicity is only expected secondary to local maternal toxicity of chlorosulfuric acid and/or the hydrolysis products.

Environment

Chlorosulfuric acid is a moisture/water sensitive liquid. It will be hydrolysed in water with explosive violence. The products of hydrolysis are HCl (hydrogen chloride in aqueous solution) and H₂SO₄. The vapour pressure of chlorosulfuric acid is 1.33 hPa at 32 °C, a partition coefficient can not be determined due to hydrolysis. HCl as well as H₂SO₄ are strong mineral acids, which completely dissociate in water into hydrated protons and the corresponding anions. For the assessment of environmental effects of the hydrolysis products it is referred to the validated hazard assessment on HCl (CAS 7647-01-0) and H₂SO₄ (CAS 7664-93-9) within the OECD HPV Chemical Program.

The total ionisation of the hydrolysis products will imply that no absorption to particular matters or surfaces and no accumulation in living organisms take place.

A calculation of the environmental distribution according to a multimedia model of type Mackay level I is not applicable. Taking into account the reactivity of the substance and the nature of the hydrolysis products water can be considered to be the main target environmental compartment for chlorosulfuric acid and its hydrolysis products.

For indirect photodegradation in air due to reaction with OH radicals a half-life of 76.4 days is calculated. However, this reaction can not occur in the presence of moisture since chlorosulfuric acid is then hydrolysed.

As inorganic substance, chlorosulfuric acid does not undergo biodegradation. If it is released into water or moist soil it will be hydrolysed immediately. Biodegradation is therefore not expected to be a significant process.

No data are available on the aquatic toxicity of chlorosulfuric acid itself. Rational: In the presence of water chlorosulfuric acid will be immediately hydrolysed. As chlorosulfuric acid has a proven potential to degrade rapidly in the aquatic environment no classification on the basis of environmental effects is relevant. Aquatic effects of the hydrolysis products are due to acidification and are related to the hydrogen ion concentration (pH value). If chlorosulfuric acid reaches an aquatic ecosystem the decrease in the pH due to the hydrolysis products is influenced by the buffer capacity of the specific ecosystem.

The following aquatic effect data from the three trophic levels are available from studies with HCl:

<i>Cyprinus carpio</i> (fish):	LC ₅₀ (96 h) = pH 4.3 (1.95 mg/l ClSO ₃ H)
<i>Daphnia magna</i> (invertebrates):	EC ₅₀ (48 h) = pH 5.3 (0.195 mg/l ClSO ₃ H)
<i>Selenastrum capricornutum</i> (algae):	ErC ₅₀ (72 h) = pH 5.3 (growth rate) (0.195 mg/l ClSO ₃ H)

In a chronic study on a lake experimentally acidified with H₂SO₄ the following effect values were obtained:

Fish population recruitment	NOEC = pH 5.93 (0.046 mg/l ClSO ₃ H)
Zooplankton population repartition	NOEC = pH 5.59 (0.1 mg/l ClSO ₃ H)
Phytoplankton community structure	NOEC = pH 5.6 (0.098 mg/l ClSO ₃ H)

The quantities of chlorosulfuric acid indicated in brackets are calculated without taking into account the buffer capacity of the aquatic system.

Further chronic laboratory studies on fish (*Jordanella floridae* and *Salvelinus fontinalis*) and invertebrates (*Tanytarsus dissimilis*) have confirmed these values.

No data are available on terrestrial organisms. It is not considered useful to calculate a PNEC for chlorosulfuric acid and/or the hydrolysis products because the buffer capacity of a specific ecosystem is relevant for the effects of the emissions of these acids into the aquatic environment. Further relevant factors are the natural pH and the fluctuation of the pH in a certain ecosystem.

Exposure

Chlorosulfuric acid is produced worldwide. The following production volumes are estimated in the different regions: Europe 30000 – 50000 t/year, NAFTA 50000 – 70000 t/year, Asia 300000 – 500000 t/year. Chlorosulfuric acid is used exclusively as an intermediate in the chemical and pharmaceutical industry. The breakdown of chlorosulfuric acid production according to the end use is the following: detergents (40%), pharmaceuticals (20%), dyes (15%), crop protection agents (10%), ion exchange resins, plasticizers and others (10%).

We assume that also due to its phys-chem properties chlorosulfuric acid is produced and processed in closed systems and is transported under controlled conditions. No emission to the environment has been identified at the specific production site. There is no information about environmental emissions at other production and/or processing sites. If any chlorosulfuric acid is emitted accidentally into the environment it hydrolyses in water to HCl and H₂SO₄. Thus the effects of chlorosulfuric acid itself are not taken into account. After dissociation of the hydrolysis products in water the hydrogen, chloride and sulfate ions occur which are commonly found in the environment.

We can assume that already in the air where certain moisture is present chlorosulfuric acid undergoes hydrolysis but we do not know the percentage of the moisture in the air which can be variable in different regions of the world where the production is taking place. This effects the external concentrations of the substances. Workers may potentially be exposed through the inhalation of vapor/aerosols or dermally by splashing from liquid. However, the production and processing of chlorosulfuric acid takes place in closed systems where the exposure is negligible. Due to efficient personal protective equipment during production, transport and processing of chlorosulfuric acid exposure of operators/workers can be excluded.

No exposure of the general public to chlorosulfuric acid is expected.

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

The data base on chlorosulfuric acid itself is limited. No data are available for a number of endpoints, but the data on HCl and H₂SO₄ have been used as surrogates where available.

Human Health: The chemical is currently of low priority for further work. The chemical possess properties indicating a hazard for human health (corrosivity, skin and eye irritation, potential carcinogenicity caused by mists of sulphuric acid). 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 the sponsor country.

Environment: The chemical is currently of low priority for further work because it hydrolyses rapidly to HCl and H₂SO₄ and therefore environmental releases of chlorosulfuric acid are not expected. The hydrolysis products hydrochloric acid and sulfuric acid have been already assessed within the OECD HPV Chemical Program.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	80-51-3
Chemical Name	4,4'-Oxybis(benzenesulfonyl hydrazide) (OBSH)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No data is available regarding toxicokinetics, metabolism or distribution of 4,4'-Oxybis(benzenesulfonyl hydrazide) (OBSH). The acute oral toxicity of OBSH was studied by two different groups according to OECD TG 401, under GLP. Based on the results of these studies, the LD50 is considered to be higher than 1000 mg/kg bw. No reliable skin/eye irritation and sensitisation studies were available.

In a combined repeated dose toxicity study with the reproduction/development toxicity screening test (OECD TG 422), OBSH was given orally to Sprague-Dawley rats at concentrations of 0, 5, 15, and 45 mg/kg bw/day. The LOAEL for male rats was 5 mg/kg bw/day and the NOAEL for female rats was 15 mg/kg bw/day. These values were based on the increase in salivation and the enlargement of adrenal glands in all male treatment groups and the increase in liver and kidney weights in females and males dosed with 45 mg/kg bw/day, respectively. In another available 28-day repeated dose toxicity study (OECD TG 407), the main target organs were the kidney and the liver. The NOAELs in rats were 10 mg/kg bw/day for both sexes based on the increases in kidney weights for males and decreases in protein contents in urine for females at 30 mg/kg bw/day.

In *in vitro* bacterial reverse mutation tests (OECD TG 471), OBSH showed positive results in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and/or *Escherichia coli* (WP2 *uvrA*) with or without S9 mix. In a chromosomal aberration test (OECD TG 473) with CHL cells and in a DNA repair test with rat and mouse hepatocytes, OBSH elicited positive results. However, in an *in vivo* mammalian erythrocyte micronucleus assay (OECD TG 474), OBSH did not exhibit mutagenic effects in mouse bone marrow cells at doses ranging from 375 to 1,500 mg/kg bw.

No data on carcinogenicity is available.

The reproductive and development toxicities were evaluated using OECD TG 421 and OECD TG 422 in rats. Non-specific signs of intoxication were observed at the highest dose tested. Consideration of the results of these two studies indicates that the NOAEL for reproductive and developmental toxicity is 45 mg/kg bw/day.

Environment

OBSH is an odorless fine white crystalline powder with a melting point of 150 ~ 160 °C. At the melting point, OBSH is decomposed. An experimental water solubility value is 62.5 mg/l at 20 °C. The measured vapor pressure was $\leq 5.43 \times 10^{-6}$ hPa at 80 °C. The vapor pressure and octanol-water partition coefficient ($\log K_{ow}$) were estimated as 8.89×10^{-10} Pa at 25 °C and 0.08, respectively.

The atmospheric half-life of OBSH based on photodegradation (i.e., reaction with hydroxyl radical) is 5.1 days. OBSH is not readily biodegradable (10.9%, TG301C), however, is rapidly hydrolyzed in water. Half-lives of OBSH in water (TG111, 25 °C) were reported as 9.2 hours at pH 4, 7.2 hours at pH 7 and 5.8 hours at pH 9. Identified major degradation products were 4,4'-oxybis(benzenesulfonic acid) and hydrazine (CAS No. 302-01-

2). A bioaccumulation study (TG305) was performed and BCF values ranged from 0.3 to 3.

Following equal releases to air, water, and soil, the fugacity model level III (EQC model) predicts that OBSH will mainly partition to soil (Air = $7.90 \times 10^{-5}\%$; Soil = 98.6%; Water = 1.41%; Sediment = $2.83 \times 10^{-3}\%$). If OBSH is emitted to air or soil, it will mainly partition to soil (99%). If it is released to water, OBSH will remain in water (99.8 %). From the estimated soil adsorption coefficient ($K_{oc} = 8182$) and Henry's law constant (1.28×10^{-12} Pa m³/mole), OBSH has a low potential of mobility in soil and is non-volatile from water. OBSH is not readily biodegradable under aerobic condition. This substance has low bioaccumulation potential (Measured BCF = $0.3 \sim 3$ and Calculated BCF = 3.162).

The following toxicity data for aquatic organisms are available for OBSH (n = nominal concentration; m = measured concentration). It should be noted that these values may reflect toxic effects of degradation products as well as the parent compound.

Fish [<i>Oryzias latipes</i>]:	LC ₅₀ (96 hrs) = 74 mg/L (n) LC ₅₀ (96 hrs) > 6.6 mg/L (m)
Invertebrates [<i>Daphnia magna</i>]:	EC ₅₀ (48 hrs) = 15 mg/L (n) EC ₅₀ (48 hrs) = 2.9 mg/L (m)
Algae [<i>Pseudokirchneriella subcapitata</i>]:	EC ₅₀ (72 hrs) = 6.7 mg/L (Growth rate); (n) EC ₅₀ (72 hrs) = 2.2 mg/L (Biomass) (n) EC ₅₀ (72 hrs) = 3.0 mg/L (Growth rate) (m)

Exposure

In Korea, the production volume of OBSH was 711, 735, and 806 tonnes in 2002, 2003, and 2004, respectively. In the United States, the production volume of OBSH was 453 tonnes in 2000. OBSH is produced at volumes below 100 tonnes/year in the EU, Sweden, and Japan.

OBSH is manufactured by the reaction of 4,4'-oxybis(benzenesulfonyl chloride) and hydrazine in China. OBSH is mainly used as a blowing agent in the manufacturing process of sponge rubber and expanded plastics.

Environmental release to atmosphere may occur during the manufacturing or processing such as drying, handling, mixing, and pulverizing processes. Dusts from manufacturing and processing are controlled by local and general ventilation systems. Monitoring results for total dust containing OBSH in air ranged from 5.2 to 8.0 mg/m³, which were under the emission limit value of 100 mg/m³.

In the production and processing facilities of Korea, workers might be exposed to OBSH dust by inhalation during drying, mixing, pulverizing, and packaging the raw material. Occupational exposure is controlled with personal protective equipments such as dust masks, gloves, glasses, and with ventilation. The 8hr-TWA concentrations of dust for workplace in OBSH were 0.4 ~ 2.0 mg/m³. These values were less than occupational exposure limit of 10 mg/m³ as total dust.

In the sponsor country, a direct consumer exposure is not likely to occur. During the foaming process OBSH decompose into nitrogen and 4,4'-oxybis(benzenesulfonic acid). 4,4'-Oxybis (benzenesulfonic acid) is further transformed into polydithiophenyl ether and polymetric thiosulfonate. Therefore, there are no direct use or consumer products containing this substance.

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

Human Health: This chemical is to be a candidate for further work. The chemical possesses properties indicating hazards for human health (acute repeated dose and *in vitro* but not *in vivo* genetic toxicity). An exposure assessment and, if then indicated, a health risk assessment is recommended.

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard to the environment (acute aquatic toxicity). Therefore, an exposure assessment and, if then indicated, an environmental risk assessment is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	926-57-8
Chemical Name	2-butene, 1,3-dichloro-
Structural Formula	$\text{CH}_3 - \overset{\text{Cl}}{\underset{ }{\text{C}}} = \text{CH} - \text{CH}_2\text{Cl}$

SUMMARY CONCLUSIONS OF THE SIAR

There are no studies available concerning the toxicokinetics, metabolism and distribution of 1,3-dichloro-2-butene (1,3-DCB). However, based on physicochemical properties, structural similarities and expected similar metabolic profiles, data for the analogue substance, 1,3-dichloropropene, typically containing 50% *cis* and 50% *trans*, (DCP; CAS No. 542-75-6;) have been included in the human health section. DCP is considered a suitable analogue for 1,3-dichloro-2-butene (1,3-DCB containing ~20% *cis*-1,3-dichloro-2-butene, CAS No. 10075-38-4, and ~80% *trans*-1,3-dichloro-2-butene, CAS No. 7415-31-8); its structural similarities to DCP suggest the utilisation of the same metabolic pathways.

Because 1,3-DCB is susceptible to hydrolysis, data generated with the major hydrolysis product 3-chloro-2-buten-1-ol (3C2B; CAS No. 40605-42-3) are presented for the ecotoxicity endpoints.

Human Health

1,3-DCB is acutely toxic via the oral and inhalation routes. There are no valid animal dermal LD₅₀ studies available for 1,3-DCB. The oral LD₅₀ for 1,3-DCB was 300 and 414 mg/kg bw in fasted male and female Wistar rats, respectively and 1368 mg/kg bw in the non-fasted male Cr1:CD rat. The inhalation 4-hour LC₅₀ of 1,3-DCB in the male rat ranged from 546 to 756 ppm (2840 to 3930 mg/m³) and the 2-hour LC₅₀ in the mouse was 846 ppm (4400 mg/m³). The structural analogue, DCP, is acutely toxic via the oral (LD₅₀ in rats is 110-170 mg/kg in males and 110-250 mg/kg in females), dermal (LD₅₀ in rats is 800-1300 mg/kg in males and 1300-2000 mg/kg in females) and inhalation [(4-hr LC₅₀ values in rats range from 586 to 666 ppm (2700 to 3070 mg/m³)] routes of exposure.

1,3-DCB is corrosive to the skin of rabbits. Occupational experience shows that 1,3-DCB is also irritating and corrosive to the skin, and that 1,3-DCB vapour is irritating to the eyes and respiratory tract. No eye irritation studies were identified with 1,3-DCB but based on its corrosivity, 1,3-DCB is likely to be severely irritating to eyes. There is no skin sensitization data for 1,3-DCB. The *cis* isomer of DCP showed moderate skin sensitisation in guinea pigs.

Repeated dose inhalation studies in animals indicate that 1,3-DCB may affect the integrity of lung epithelium. Based on histopathological changes, the NOAEL's range from 2 ppm (10 mg/m³) in rats and rabbits exposed over a 5 month period, to 10 ppm (52 mg/m³) in rats exposed for two weeks. Data on the analogue substance, DCP, suggest primarily portal of entry effects with NOEL's being 10 ppm (45 mg/m³) in rats and 30 ppm (136 mg/m³) in mice. By the inhalation route of exposure, degenerative changes in nasal and pulmonary epithelium are potential outcomes of 1,3-DCB exposure. Data from less well documented studies have reported additional 1,3-DCB effects in adrenal tissue, liver, myocardium, kidney, and spleen.

1,3-DCB is not mutagenic in the bacterial reverse mutation assay (Ames test) in *Salmonella typhimurium* strains (TA 98 and TA 1537) but is mutagenic in *Salmonella typhimurium* strains (TA 100 and TA 1535) without metabolic activation and in (TA 100) with metabolic activation. 1,3-DCB gave equivocal results in *Saccharomyces cerevisiae*. *In vivo*, 1,3-DCB does not induce micronuclei in the rat bone marrow assay.

While no carcinogenicity data exist for 1,3-DCB, studies in rats and mice on the analogue chemical indicate that chronic inhalation of DCP (containing epoxidized soya stabilizer) produces non-neoplastic nasal degeneration and

changes in transitional epithelium of the bladder and benign bronchoalveolar adenomas in lungs of male mice. Gavage dosing with technical grades of DCP containing 1% epichlorohydrin produced tumors at the site of application (forestomach adenoma/carcinoma in rats and mice) and remote sites, involving bronchoalveolar adenoma/carcinoma of the lungs and transitional cell carcinomas of the urinary bladder in female mice. Data from DCP suggest 1,3-DCB is a possible carcinogen. The International Agency for Research on Cancer (IARC) has classified DCP (technical grade containing 1% epichlorohydrin) as possibly carcinogenic to humans: Group 2B.

Available data for 1,3-DCB for reproductive toxicity are from acute and short term, repeated-dose inhalation toxicity studies. No toxic effects on the reproductive organs were observed. No data are available for developmental toxicity. A two-generation inhalation study in rats and developmental studies in rats and rabbits with DCP showed no effects on reproduction/development at the highest dose tested [90 ppm (409 mg/m³)]. The NOEL for reproductive toxicity was 30 ppm (136 mg/m³) based on body weight effects and histopathologic changes in the nose and stomach. For developmental toxicity, the maternal NOEL, based on reduced body weight gains was <20 ppm (<91 mg/m³) in rats and 20 ppm (91 mg/m³) in rabbits. No evidence of a teratogenic or embryotoxic response was observed in either species at any exposure level. Evidence for slight fetotoxicity was seen in rats at 120 ppm (545 mg/m³), a level producing maternal toxicity. The NOEL for teratogenicity was greater than 120 ppm (545 mg/m³) in both rats and rabbits.

Environment

The melting point of 1,3-DCB is – 75°C and the boiling point is 128-130°C. The vapor pressure is 13.3 hPa at 25°C. The water solubility of 1,3-DCB cannot be determined due to rapid hydrolysis. The density of 1,3-DCB is 1.161 g/mL at 4°C. The calculated log Kow is 2.84.

1,3-DCB is predicted to be photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of approximately 27 hours (calculated). However, its major path of degradation is hydrolysis, with a measured half-life of 6.0 hrs; the major hydrolysis product being 3-chloro-2-buten-1-ol (3C2B). 3C2B water solubility exceeds 92 mg/L (40,000 mg/L, calculated). Distribution modeling using Mackay Level I for 1,3-DCB indicated that partitioning will occur to air (99.99%), water (0.003%), and soil (0.002%) phases. The fugacity model Mackay Level III predicts that 1,3-DCB will distribute primarily to water (72.4%) with much smaller distributions to air (20%), soil (7.0%) and sediment (0.58%). Based on the formation of 3C2B from the hydrolysis of 1,3-DCB in water, the estimated Mackay Level III fugacity model distribution, assuming emission to water, is almost entirely to water (99.7%) with lesser amounts in air (0.05%), soil (0.02%) and sediment (0.2%). 1,3-DCB is not readily biodegradable (0% degraded in 28 days). Based on an estimated BCF of 30 for 1,3-DCB and an estimated BCF of 1.5 for 3C2B, neither substance is likely to bioaccumulate.

Because 1,3-DCB is susceptible to hydrolysis, data for the major hydrolysis product, 3C2B, are used for the ecotoxicity endpoints. For 3C2B, the 96-hour LC₅₀ for rainbow trout (*Pimephales promelas*) is 4.0 mg/L (measured: ECOSAR 96-hour LC₅₀ 8.4 mg/L for allyl halide and 0.5 mg/L for allyl alcohol), the 48-hour EC₅₀ for *Daphnia magna* is 11 mg/L (measured: ECOSAR 48-hour EC₅₀ 980.4 mg/L) and the 72-hour cell count biomass and growth rate values for algae (*Pseudokirchneriella subcapitata*) are EbC₅₀ equal to 650 mg/L (calculated by probit method) and ErC₅₀ > 650 mg/L (nominal: ECOSAR 72-hour EC₅₀ 104.6 mg/L), respectively

Exposure

There are only three countries producing 1,3-DCB globally (Japan, Germany and USA). Annual global production (2002) of 1,3-DCB totalled approximately 5,000 tonnes. In the USA, 1,3-DCB is produced at one site. It is manufactured by the reaction of 2-chloro-1,3-butadiene with HCl in the presence of a copper chloride catalyst.

Among the producers, 1,3-DCB is produced and used only as a site limited intermediate used only to make 2,3-dichloro-1,3-butadiene, a co-monomer in some grades of polychloroprene synthetic rubber. Consequently, all 1,3-DCB is consumed in the production of polychloroprene. Laboratory scale quantities are available from some commercial specialty-chemical suppliers (e.g., Sigma-Aldrich) as a mixture of the cis and trans isomers.

Occupational exposure to 1,3-DCB may occur through inhalation and/or dermal contact with this compound at workplaces where 1,3-DCB is produced/or used. The total number of workers in manufacturing operations with potential 1,3-DCB exposure is estimated to be less than approximately 200, globally. Since production does not utilize any open vessels and engineering and administrative controls are used in conjunction with personal protective equipment, no significant occupational exposure occurs. .

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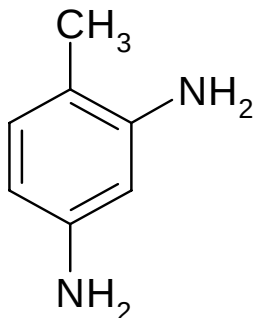
There are no consumer uses of 1,3-DCB. Extensive sampling shows that the amount of residual 1,3-DCB in 2,3-dichloro-1,3-butadiene is less than 0.5 ppm. The end product (polychloroprene rubber) will contain even lower levels of 1,3-DCB since the 2,3-dichloro-1,3-butadiene-containing grades of polychloroprene rubber contain 10% or less 2,3-dichloro-1,3-butadiene. Consequently, potential exposure to 1,3-DCB in consumer products is expected to be negligible (<<50 parts per billion, wt/wt) .

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

Human Health: The chemical possesses properties indicating a hazard to human health (acute toxicity, potential of entry repeated dose toxicity, corrosivity, mutagenicity, possible carcinogen). Based on data presented by the Sponsor country, relating to 50% of global production in a closed-system as a chemical intermediate, and use patterns 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 Sponsor countries.

Environment: The chemical possesses properties indicating a hazard to the environment (acute toxicity to fish and invertebrates). Based on data presented by the Sponsor country, relating to 50% of global production in a closed-system as a chemical intermediate, emissions to the environment are expected to be negligible 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-80-7
Chemical Name	Toluene-2,4-diamine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

The 80/20% mixture of 2,4-TDA/2,6-TDA was used as read across in cases that inhalation data of 2,4-TDA was not available (acute toxicity and repeated dose toxicity).

Toluene-2,4-diamine (2,4-TDA) is almost completely absorbed via the gastrointestinal tract in animals and well absorbed via the skin (54% in monkeys and 24% in humans over an exposure time of 24 h). No data are available on absorption by inhalation. In rats the highest tissue concentrations were measured in liver and kidney after oral or i.p. administration. Concentrations in heart, lungs, spleen, and testes were significantly lower. There are no species-related differences in tissue distribution between mice and rats. In rats, rabbits, and guinea pigs unchanged 2,4-TDA was excreted via urine in concentrations from 0.1 to 3%. 2,4-TDA is mainly hydroxylated at the ring under formation of aminophenols (major pathway) and additionally N-acetylation occurs. Mono- as well diacetyl derivatives were observed in different quantities in the urine of rats, mice, rabbits, and guinea pigs. In dogs, however, only very small amounts of the monoacetyl derivative were detected. Elimination of sulfate conjugates was shown in the 24-hour urine in rats and mice, whereas glucuronic acid conjugates occurred at a higher level in mice than in rats. The excretion of metabolites predominantly occurs via urine in rats and mice.

2,4-TDA has proven to be toxic with oral LD50 values between 73 and 350 mg/kg bw in rats and mice. A dermal LD50 value of 1200 mg/kg bw was detected in rats. No animal nor human data are available on acute inhalation toxicity of 2,4-TDA. A mixture of 80% 2,4-TDA and 20% 2,6-TDA (CAS-No. 25376-45-8) has a similar oral and dermal acute toxicity profile as pure 2,4-TDA (oral LD50 values between 50 and 500 mg/kg bw for rats, mice, rabbits, and cats and a dermal LD50 value of 463 mg/kg bw for rats). Thus results of tests with that 80/20 mixture are used to assess the acute inhalation toxicity of the pure 2,4-TDA. No mortality occurred after a 4 hour inhalation to concentrations of approx. 5.57 mg/l of the 80/20 mixture of 2,4-/2,6-TDA, but all animals appeared in a bad health state.

In a Draize test with rabbits according to OECD TG 404 2,4-TDA did not cause skin irritation. The substance demonstrated only slight conjunctival redness after instillation to the eye in a Draize test with rabbits according to OECD TG 405. In a Magnusson Kligman test with 2,4-TDA (in compliance with OECD TG 406) up to 100% of the guinea pigs demonstrated a positive reaction. Human data demonstrate a possible cross sensitivity to p-phenylenediamine.

Animal studies have shown that main toxic effect associated with dietary exposure of 2,4-TDA is hepatotoxicity. In short-term studies effects were characterized by a decrease in body weight and an increase in the liver: body weight ratios. In long-term studies toxic effects on the liver accelerated the development of chronic renal disease in rats, an

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effect that contributed to a marked decrease in survival. In a 2-year feeding study in rats (doses 5.9 and 13 mg/kg bw/day, OECD TG 452), the lower dose of 5.9 mg/kg bw/d showed toxic effects in the liver and kidneys and increased tumor incidences in the liver (male rats, female rats, female mice), and in the mammary gland (female rats) (LOAEL). An overall NOAEL was not demonstrated. In 28-day inhalation studies of limited test design the 2,4-/2,6-TDA mixture gave 9.5 mg/m³ (approx. 1 mg/kg bw/day) as a NOAEL for systemic effects in rats. At a concentration of 83 mg/m³ (approx. 9 mg/kg bw/d) reduced body weight gain, an increase of the relative weight of the liver, kidneys, and thyroid glands, and a relative lymphopenia were observed. In cats the concentration of 9.5 mg/m³ already caused a slight formation of methaemoglobin (2.1%). At a concentration of 41.6 mg/m³ (approx. 4.5 mg/kg bw/d) cats showed severe methaemoglobinemia (30%), retarded body weight gain, and pathomorphological findings in the lungs, liver, and kidneys.

In vitro 2,4-TDA induces gene mutations in bacteria using standard Ames test conditions (OECD TG 471). Mammalian cell gene mutation tests carried out in various cells according to OECD TG 476 resulted in negative results. In cultivated mammalian cells 2,4-TDA produced chromosomal aberrations and SCE (OECD TG 473, OECD TG 479). 2,4-TDA was positive for induction of UDS (OECD TG 482), and of DNA strand breaks, and DNA adducts. In general, rodent *in vivo* micronucleus tests were negative in bone marrow or peripheral blood (OECD TG 474). A weak positive effect on one rat strain (PVG) was limited to a dose with high acute toxicity. However, in other *in vivo* assays generally weak genotoxic effects were obtained, e.g. gene mutations, UDS, DNA strand breaks and DNA adducts were observed in rodent livers. It cannot be excluded that 2,4-TDA has genetic effects on germ cells.

2,4-TDA is carcinogenic in long-term animal studies similar to OECD TG 453. In F344 rats, liver tumors are produced in both genders and mammary tumors in females after oral administration with doses of 5.9 and 13 mg/kg bw/d. 2,4-TDA was also carcinogenic for female B6C3F1 mice, inducing hepatocellular carcinomas at doses of 15 and 30 mg/kg bw/d. Local sarcomas were demonstrated after subcutaneous application of 25 mg/kg bw/d to SD rats over a 2-year period (doses 8.3 and 25 mg/kg bw/d).

Severe testicular atrophy in rats was shown at 28 mg/kg bw/d in a 15-months study. Inhibited spermatogenesis (66%) associated with a significant reduction in the weights of seminal vesicles and epididymides, morphological damage of Sertoli cells as well as with a diminished level of serum testosterone and an elevation of serum LH was observed at 15 mg/kg bw/d in a 10-week male rat feeding study with dose levels of approx. 5 and 15 mg/kg bw/d.

5 mg/kg bw/d is considered as marginal LOAEL for effects on reproductive organs as it causes a decrease in epididymal sperm reserves. No NOAEL was established.

No valid data are available to assess the endpoint developmental toxicity. Further testing on developmental toxicity is considered to be not necessary, since reduction of occupational risks is effective due to the implemented exposure reduction measures because of genotoxic and carcinogenic properties of the chemicals. Results from human epidemiological studies with various diaminotoluenes concerning reproductive health are inconclusive to assess any developmental impairment by 2,4-TDA.

Environment

2,4-TDA is a clear colourless solid with a boiling point of 288 °C and a melting point of 99 °C. Its density is 1.256 g/cm³. It has a water solubility of 38 g/l at 25 °C, a vapor pressure of 0.017 Pa (at 25 °C) and a measured log K_{OW} of 0.074 (at 25 °C). With a Henry's law-constant of 5.46.10⁻⁵ Pa.m³.mol⁻¹ for 2,4-TDA no significant volatilization from water is expected.

2,4-TDA is not readily biodegradable. In a MITI-II test on inherent biodegradation performed with the 80:20 mixture of 2,4-TDA and 2,6-TDA and unadapted inoculum only 4 % degradation was found after 28 d. However, biodegradation of 2,4-TDA reached 51% of theoretical CO₂ yield over 36 days in the Modified Sturm Test (OECD 301B), using an unadapted inoculum. A Zahn-Wellens-Test conducted with sludge from an industrial sewage treatment plant as inoculum assumed to be adapted to TDA showed elimination of 100 % after 6 days for 2,4-TDA and of 89 % after 28 days for 2,6-TDA. Therefore, it can be concluded that both isomers are inherently biodegradable by adapted inoculum.

Biodegradation studies in soil using ¹⁴C-labelled TDA showed that biodegradation started immediately after mixing with the aerobic soil. The degradation rates indicate that biodegradation slowed down after TDA had formed covalent bounds to humic substances. It is not possible to calculate a half-life for biodegradation of TDA in soil (because of competing reactions with soil organic matter.), but it can be assumed that TDA covalently bound to organic matter is degraded almost similar to the humic acids themselves. A mean half-life of 1000 d can be

assumed for this humified TDA, whereas unbound TDA is rapidly biodegraded in soil.

Based on the molecular structure, hydrolysis of TDA is not expected under environmental conditions. The UV-spectra (λ_{max} at 295 nm for 2,4- TDA indicate that direct photolysis in water may occur. Half-lives in the range of 29 d (summer) to > 1 year (winter) have been calculated. However, under real environmental conditions half-lives should be at least one order of magnitude higher than the calculated half-lives because turbidity and adsorption are not considered.

The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of TDA in air is 2 h (2,4-TDA). This half-life is based on an assumed tropospheric hydroxyl radical concentration of 5×10^5 molecules/cm³.

Experiments with radiolabelled 2,4-TDA revealed that the substances form covalent bonds with the organic fraction in soil. A Koc-value of 9,763 l.kg⁻¹ for 2,4-TDA has been measured. According to a fugacity model (Mackay level I) soil (64 %) and sediment (32 %) are identified as target compartments for TDA in the environment. Measured BCF values in fish of < 5 and < 50 do not indicate a significant potential for bioaccumulation.

Short-term and long-term tests with fish, invertebrates and algae are available for TDA. The lowest effects values from the short-term tests are: *Pagrus major* (marine): 96h-LC₅₀ = 0.161 mg/l (TDA 80:20), *Daphnia magna*: 48h-EC₅₀ = 1.6 mg/l (2,4-TDA), *Selenastrum capricornutum* 96h-EC₅₀ = 9.54 mg/l (2,4-TDA). In a test with *Danio rerio* that investigated the toxicity of TDA 80:20 on the embryo and sac-fry stages a 10d-NOEC of 3.61 mg/l was found for the endpoint behaviour abnormality. In a reproduction test with *Daphnia magna* a 21d-NOEC of 0.282 mg/l was found for TDA 80:20.

Compared to other fish species, *Pagrus major* showed the highest sensitivity to 2,4-TDA and the isomeric mixture (effect values were more than a factor of 1000 lower than for other fish species tested; *Pimephales promelas* (96 h) 1420 mg/l (flow-through; analytical monitoring), 2,4-TDA; *Oryzias latipes* (96 h) 912mg/l (flow-through, analytical monitoring) 2,4-TDA). The reason for this high sensitivity is not clear.

The PNECaqua is derived by applying an assessment factor of 100 to the 96h-LC₅₀ for *Pagrus major* resulting in a PNEC of 1.6 µg/l because in this short-term test a lower effect value was found than in the available long-term tests.

Tests with benthic organisms are available. The effect levels are:

Chironomus riparius: 28d-NOEC of 500 mg/kg dw (TDA 80:20)

Lumbriculus variegatus: 28d-NOEC 12.3 mg/kg dw (TDA 80:20).

For the terrestrial compartment short-term tests with plants and earthworms are available. The following results were obtained: *Lactuca sativa* and *Avena sativa*: 14d-EC₅₀ = 320 mg/kg dw; *Eisenia fetida*: 14d-LC₅₀ > 1000 mg/kg dw. With an assessment factor of 1000, a PNECsoil of 320 µg/kg dw was derived.

Exposure

The total amount of TDA (technical mixture of 2,4- and 2,6-isomers in the ratio 80:20) produced in the EU is about 280 000 t/a for the year 1999/2000. Additionally, about 10,000 t/a are imported. No information is available about export volumes. Therefore, the total volume of TDA handled in the EU amounts to 290,000 t/a.

In the EU, TDA is almost exclusively used as an intermediate in the chemical industry to produce TDI (toluylene diisocyanate). A small volume of 2,4-TDA is processed to dyes.

Releases into the environment may occur from production of TDA and from processing to dyes. During processing to TDI no releases into the wastewater occur as it is a water-free process. From processing of TDA to dyes environmental releases can occur. TDI is not stable in water and hydrolyses to TDA and oligourea.

Diffuse releases can occur from TDA or TDI (after hydrolysis) chemically reacted in polyurethane or epoxy matrices during use and disposal of polymer products. Trace amounts of residual monomers may be released via migration and leaching. No significant releases of TDA into the atmosphere during production and processing to TDI are expected. For a German site, an emission of 10 kg/a is stated, at further sites the exhaust gases are incinerated. A study on the gas phase reaction of TDI with moist air revealed that no TDA was formed. It can be concluded that a relevant TDA exposure does not occur from TDI emissions.

There are no indications for any direct application of 2,4-TDA by consumers.

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 and subacute toxicity, skin sensitisation, genotoxicity, carcinogenicity and reproductive toxicity).

A risk assessment was performed in the context of the EU Existing Substances Regulation. For human health, concerns were identified regarding occupational exposure. For all three TDA scenarios at the workplace (production and further processing as a chemical intermediate, production of 2,4-TDA pastilles and use of 2,4-TDA pastilles for the production of dyes) carcinogenicity in combination with mutagenicity and skin sensitisation lead to concern. Extensive technical and organisational reduction measures have already led to very low levels of exposure. Other member countries are invited to perform an exposure assessment and if necessary a risk assessment for occupational settings. Based on data presented by the Sponsor Country exposure of consumers appears to be negligible.

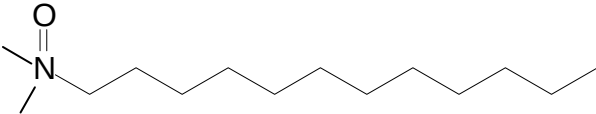
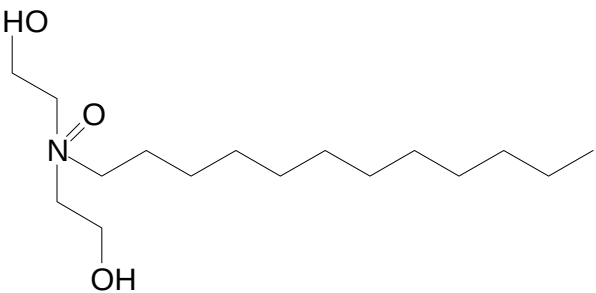
Risks of skin sensitisation are considered to be small. However, because the corresponding risk cannot be quantified or excluded, a general concern for skin sensitisation is expressed. Carcinogenicity risk assessment was conducted with a quantitative approach. Additionally a risk evaluation for this endpoint was done by calculating with different levels of risk acceptance. The specific conclusions for the different occupational exposure scenarios critically depend on the chosen level of risk acceptance. This comparison may be helpful for risk managers in order to evaluate the necessity and priority of further risk reduction measures beyond those that has already been successfully implemented.

Environment: The chemical is a candidate for further work.

The chemical possesses properties indicating hazard for the environment (acute and chronic aquatic toxicity to invertebrates, acute toxicity to fish (*Pagrus major*)) and algae). Other member countries are invited to perform an exposure assessment, and if necessary a risk assessment for the environment.

Note: A risk assessment for this chemical is currently under discussion in the EU in the context of the EU Regulation 793/93. Risk was identified for the generic scenario for process 2,4 TDA to dyes (wastewater treatment plant, surface water and sediment).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1643-20-5 3332-27-2 70592-80-2 68955-55-5 2605-79-0 7128-91-8 2571-88-2 61788-90-7 85408-48-6 85408-49-7 61791-47-7 2530-44-1 14048-77-2 61791-46-6 93962-62-0	1-Dodecanamine, N,N-dimethyl-, N-oxide 1-Tetradecanamine, N,N-dimethyl-, N-oxide Amines, C10-16-alkyldimethyl, N-oxides Amines, C12-18-alkyldimethyl, N-oxides Decanamine, N,N-dimethyl-, N-oxide Hexadecanamine, N,N-dimethyl-, N-oxide Octadecanamine, N,N-dimethyl-, N-oxide Amine oxides, cocoalkyldimethyl Amines, C10-18-alkyldimethyl, N-oxides Amines, C12-16-alkyldimethyl, N-oxides Ethanol, 2,2'-iminobis-, N-coco alkyl derivs., N-oxides Ethanol, 2,2'-(dodecyloxidoimino)bis- Ethanol, 2,2'-(octadecyloxidoimino)bis- Ethanol, 2,2'-iminobis-, N-tallow alkyl derivs., N-oxides Ethanol, 2,2'-[(9Z)-9-octadecenyloxidoimino]bis-
Chemical Category Name	Amine Oxides (AO)	
Structural Formula	Typical structures for amine oxides are as follows: C12 dimethyl amine oxide  C12 dihydroxyethyl amine oxide 	

SUMMARY CONCLUSIONS OF THE SIAR**Category Identification/Justification**

The justification for grouping the amine oxides (AO) into a category is based on their structural and functional similarity. All of the substances in this category are surfactants, consisting of a polar “head” (the amine oxide) and a relatively inert, hydrophobic “tail” (the long alkyl substituent). The structural variations in the category are three-fold: 1) the nature of the second and third substituents on the amine are either methyl groups or hydroxyethyl groups; 2) the long alkyl chain ranges in length from 8 to 20 carbons; and 3) the long alkyl chain may contain one or two double bonds (i.e. unsaturation) as in C18:1 (oleyl) or C18:2 (linoleyl). Alkyl chain lengths range from 8 to 20 with 12 and 14 being predominant. Average chain lengths for the mixtures are 12.9 to 13.5, with the exception

of one tallow-derived compound. The presence of methyl- vs. hydroxyethyl-substituents affects the basicity of the nitrogen only marginally, and the hydroxyethyl group lends more bulk to the hydrophilic head-group of the surfactant. The length of the longest alkyl substituent does not alter the chemical reactivity of the molecule, but does affect its physical properties. The influence of unsaturation in the alkyl chain (as in CAS Nos. 93962-62-0 Ethanol, 2,2'-[(9Z)-9-octadecenylloxidoimino]bis- and 61791-46-6 Ethanol, 2,2'-iminobis-, N-tallow alkyl derivs., N-oxides) is expected to make the molecule prone to reactions as typical for unsaturated fatty alkyl chains. Nevertheless, their overall chemical behavior fits within that of the group of C8-18 alkyl dihydroxy ethyl amine oxides.

Human Health

Substantial data exist for mammalian toxicity by *in vitro* and *in vivo* testing. Amine oxides are produced, and transported in aqueous solutions that are 25-35% concentration and most tests were conducted with aqueous solutions in that concentration range. Sometimes aqueous formulations were tested where the AO was at lesser concentrations than 25-35%. Whatever concentration were tested, results are reported below for the active ingredient, amine oxide, in mg AO/kg bw for dermal and oral acute toxicity results and mg AO/kg bw/day for repeated dose studies.

Toxicokinetic and metabolism studies indicate AO's are extensively metabolized and readily excreted after oral administration. Amine oxide was readily absorbed dermally by rats, mice and rabbits after 24 to 72 hours of exposure. After 8 hours of dermal exposure, humans absorbed <1%.

In rat oral acute toxicity limit tests, no deaths occurred at single doses of 600 mg C₁₀₋₁₆ AO/kg bw or less (for CAS No 70592-80-2). In multi-dose studies, acute oral LD₅₀ values for rats ranged from 846 mg AO/kg bw to 3873 mg AO/kg bw (both values for CAS No 61788-90-7), with several other AO's having rat oral LD50's falling within this range. In single dose acute dermal toxicity limit tests, no deaths occurred at a dose of 520 mg AO/kg bw (CAS No 70592-80-2). This dose was equivalent to 2 mL/kg of a 30% formulation. There were no deaths observed in a rat acute inhalation study to aerosol droplets of a consumer product providing a dose of 0.016 mg AO/L.

In a series of studies on rabbits, AO's of varying chain length showed consistent results and all 1) were not irritating to the skin or eyes at low concentrations (1%), 2) were moderately irritating at 5%, and 3) more severely irritating when tested as produced (e.g., ~30% aqueous solutions). In studies that included rinsing, eye irritation effects diminished with rinsing after 30 seconds of exposure and were slight with rinsing after 4 seconds of exposure. In Draize rabbit eye irritation tests using ~30% AO solutions, rabbits experienced severe to moderate irritation. (The maximum concentration of AO is 10% active in consumer products.) Accidental eye exposure in manufacturing employee incidents and consumer incidents established that eye irritation effects of exposure during manufacturing and use of products containing AO and other surfactants are moderate, transient and reversible.

There is no indication of skin sensitization for the AO category based on the available animal and human data.

In four repeated-dose studies with rats and mice exposed to AO via oral and dermal routes (all with CAS No 70592-80-2), three dermal studies were designed to assess the effect of repeated exposure on skin at maximum doses of 1.5 mg AO/kg-bw/day. Higher doses were tested in a 90-day dietary study with rabbits. No treatment-related clinical chemistry, hematology and histopathological changes were observed. In these studies, LOAELs ranged from 87 to 150 mg AO/kg bw/day with the highest oral NOAEL below the lowest LOAEL as 80 mg AO/kg bw/day. Signs of toxicity observed in the oral study included suppressed mean body weight gain, lenticular opacities and diarrhea; in the dermal studies, local dermal irritation was evident.

In five *in vitro* bacterial (*Salmonella*) mutagenicity studies, AO shows no evidence of mutagenicity either with or without S9 metabolic activation at concentrations up to 250 ug/plate (higher concentrations caused cytotoxicity). Three *in vivo* studies investigated clastogenic effects on a close structural analog of the category, 1-(methyl dodecyl)dimethylamine-N-oxide including: a mouse micronucleus, a Chinese hamster micronucleus and a Chinese hamster cytogenetics study. These studies were all negative showing no increase in micronuclei or chromosome aberrations. An *in vivo* mouse dominant lethal assay showed no evidence of heritable effects. Two AOs (CAS No 1643-20-5 and CAS No 3332-27-2) were negative in an *in vitro* cell transformation assay tested at concentrations up to 20 ug/ml.

The carcinogenic potential of amine oxides has been thoroughly investigated in three carcinogenicity studies in rats or mice by dermal, dietary, or drinking water routes. In all cases the substances demonstrated no evidence of a

carcinogenic response.

No evidence of reproductive toxicity or fertility effects was observed in a study in which rats were given dietary doses of AO in the diet over two generations (CAS No 1643-20-5). No macroscopic or histopathological changes were attributable to treatment with the test substance. The maternal NOAEL from this reproductive study was >40 mg AO/kg bw/day, which was the highest dose tested. At all treatment levels, the rate of bodyweight gain for the F1 and F2 offspring was reduced during the lactation period, however, this reduction was not greater than 10%. This effect appeared to be dose-related, but was not statistically significant until after weaning in the mid and high dose levels. This was not considered an adverse effect since the body weight change only reached statistical significance when the rat pups were getting the majority of their calories from solid food (Developmental NOAEL >40 mg/kg bw/day). In three developmental toxicity studies via gavage in rats and rabbits (with CAS No 1643-20-5 & 70592-80-2), effects such as decreased fetal weight or delayed ossification, were most often observed only at maternally toxic doses and were associated with the irritation effects of AO on the gastrointestinal tract. No decreases in litter size, no changes in litter parameters, no malformations or significant differences in skeletal defects were observed at oral doses up to 25 mg/kg bw/day in rats (based on decreased fetal weight at 100 mg/kg bw/day) and >160 mg/kg bw/day in rabbits (the highest dose tested).

Environment

The chemicals of the amine oxides category do not exist as 'pure' substances, but are produced, transported and used as aqueous solutions, typically within a range of 25-35% AO/water. Experimental values for melting points of C10 to C16 amine oxides range from 125 to 136°C. Amine oxides undergo Cope elimination, i.e., the formation of an olefin and a hydroxylamine by pyrolysis of an amine oxide, in the temperature range 150-200°C, thus decomposition is likely to occur before the melting point is reached, and all boiling points are predicted to be far above the decomposition temperature. Amine oxides are not volatile: predicted vapor pressure values are < 4.6E-7 hPa. Amine oxides are highly water soluble – measured values for a C12.6 average chain length is ~410g/L. Although it is impossible to accurately measure an octanol-water partition coefficient for surface-active agents like amine oxides, an octanol-water partition coefficient (Log value) of < 2.7 has been calculated for amine oxides of chain length C14 and below. The predicted atmospheric oxidation half lives are of the order of 5 hours, indicating a relatively rapid atmospheric degradation potential.

Amine oxides are removed by conventional sewage treatment systems and biodegrade under aerobic and anaerobic conditions. Of the collected data, four amine oxides meet the "readily biodegradable" OECD criterion, two are "ultimately biodegradable," and two are "inherently biodegradable." These studies are conducted on complex mixtures with a high degree of alkyl chain length overlap. Further, biodegradation is not dependent on chain length. Removal of amine oxides in biological wastewater treatment has been studied in laboratory simulation studies (>99.8% removal, OECD 303A study) as well as through monitoring activities in different geographies; the main removal mechanism can be attributed to mineralization and an average removal number of 98% can be assumed as applicable for secondary activated sludge treatment. Level III fugacity modeling, using loading rates for air, soil, and water of 1000 kg/h for each media, shows water receiving compartment receiving 99.5%; the other compartments are negligible. The bioconcentration factor for amine oxides <C14, is predicted to be <87, based on log Kow data, indicating low potential for bioaccumulation in aquatic organisms.

Extensive aquatic toxicity data are available for commercially representative amine oxides (C10 to C18) that are single chain length as well as mixtures. Based on hazard data, freshwater green algae are considered the most sensitive species, for acute and chronic endpoints. Acute toxicity is affected by chain length for fish and invertebrates. Chain length affects hydrophobicity, wherein longer chain-lengths increase the rate of uptake and decrease depuration. All but four supporting AO's have been tested for acute toxicity in fish, daphnia, and algae. The range of acute LC₅₀/EC₅₀/ErC₅₀ values based on a review of the aquatic toxicity data on AO were 0.60-32 mg/L for fish, 0.50-10.8 mg/L for *Daphnia magna* and 0.010-5.30 mg/L for algae. Chronic toxicity data were normalized to a chain length of 12.9 carbon atoms, as this average chain length represents the largest volume product for North America (CAS No 70952-80-2). Chronic toxicity (NOEC, EC20) for an amine oxide of average chain length of C12.9 ranged as follows for the different trophic levels: 0.010-1.72 mg/L for algae, 0.28 mg/L for *Daphnia* (flow through) and 0.31 mg/L for fish (flow through). These are based on geometric mean values, and a dataset of 21 chronic toxicity studies. Based on a chronic periphyton microcosm bioassay that included 110 taxa of algae (most sensitive species), a NOEC value of 0.050 mg/L was derived when normalized for a C12.9 amine oxide.

Exposure

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For the AO category as a whole, current production is approximately 26,000 metric tonnes in the US (sponsor country), 16,000 tonnes in Europe and 6,800 tonnes in Japan. In the production phase, manufacturing processes have been designed to maximize production yield and minimize potential releases. The potential for human exposure to AO is minimized by a water solubility of 409.5 g/L, having volatility below 4.6×10^{-5} Pa and being produced in aqueous solutions. Engineering controls (e.g., closed system operations, exhaust ventilation, dust collection) and personal protective equipment (e.g., protective clothing, eyewear, and gloves) at manufacturing and formulation facilities further mitigate worker exposure. No special engineering controls or additional personal protective equipment are uniquely specified for AO. A limited amount of AO in aqueous solution may be released as a dilute solution from washing and rinsing operations in the manufacturing process and is discharged to wastewater treatment.

Labeling of consumer products containing AO and other surfactants include warnings of the potential for eye irritation and first aid instructions to rinse with water.

Amine oxides are amphoteric surfactants used at active concentrations between 0.1 and 10% in consumer cleaning and personal care products, usually in conjunction with other surfactants. They function as foam stabilizers, thickeners and emollients, emulsifying and conditioning agents in liquid dishwashing and laundry detergents, liquid hard surface cleaners, shampoos, hair conditioners, creams, moisturizers, bar soaps, cleansing and other personal care products. There are no known commercial uses or industrial process intermediate uses of the amine oxides.

Data suggest that inhalation of AO-containing products during use will be low. Spray cleaning products containing AO are designed to produce the large particle sizes needed for efficient delivery of the spray to the surface being cleaned. In laboratory simulations with six spray nozzles representing those used in spray cleaning products, less than 0.1% of the total volume sprayed consists of respirable particles (particles under 10 microns in diameter) and air concentrations in the breathing zone are in the 0.13-0.72 mg/m³ range. Based on these data, it is expected that inhalation exposures to AO in respirable particles are low.

Results of environmental field monitoring in the United States and the Netherlands indicate that surface water concentrations downstream from sewage treatment plant mixing zones range from <0.1 to <1 µg/L. Results of a four season monitoring program in major urban rivers of Japan found concentrations ranging from non-detect (< 0.01 µg/L) to 0.34 µg/L, with a median concentration of 0.04 µg/L.

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

Human Health: This category is currently of low priority for further work. The chemicals in this category present properties indicating a hazard for human health (skin and eye irritation). However, these hazards do not warrant further work as they are related to reversible, transient and non-lasting effects. Nevertheless, these hazards should be noted by chemical safety professionals and users.

Environment: The chemicals in this category are candidates for further work. The chemicals in this category have properties indicating a hazard for the environment (aquatic toxicity <1 mg/L for fish, aquatic invertebrate and/or algae). This category is anticipated to biodegrade and has a limited potential for bioaccumulation. Member countries are invited to perform an exposure assessment and, if necessary, a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	_____
Chemical Name	Bicarbonate special
Structural Formula	NaHCO_3 (CAS No. 144-55-8) Na_2CO_3 (CAS No. 497-19-8) NH_4HCO_3 (CAS No. 1066-33-7)

SUMMARY CONCLUSIONS OF THE SIAR

Bicarbonate special is a substance produced as a result of chemical reactions leading to a composition of 3 existing chemicals, namely sodium bicarbonate (mean: 81 %; range: 78 – 87 %), sodium carbonate (mean: 13 %; range: 5-15 %), and ammonium bicarbonate (mean: 3 %; range: 2-5 %). They are inorganic salts which rapidly dissolve in water and dissociate into their corresponding ions. Based on these similarities, endpoints of bicarbonate special can be assessed based on the available data for sodium bicarbonate, sodium carbonate and ammonium bicarbonate. SIDS Initial Assessment Reports are available for sodium bicarbonate, sodium carbonate and ammonium bicarbonate, which is made available at the same time as this report. The present document is a synthesis of the 3 reports, leading to an estimation of each of the SIDS elements for bicarbonate special.

Human Health

The substance should not be considered as dangerous regarding its acute toxicity by the oral and dermal exposure routes, however it is worth noting that it should be considered harmful if inhaled.

On account of the 5-15% of sodium carbonate, bicarbonate special should be considered as mildly irritating to the skin and to the eyes.

No adverse effects related to chronic treatment with any of the three chemicals were observed in mammals. All the three chemicals of bicarbonate special are considered to be “generally recognized as safe” (GRAS) by the FDA. Therefore, additional testing for repeated dose toxicity is not deemed necessary.

All the mutagenicity tests performed with the three chemicals gave negative results. Therefore, additional mutagenicity testing is not deemed necessary for bicarbonate special.

None of the 3 chemicals has been shown to induce reproductive effects, either if tested with mammals or if not through human experience. Therefore, the substance should not be considered as dangerous for reproductive effects and no further testing is deemed necessary.

According to the conclusions noted for all the above endpoints, bicarbonate special should not be considered as dangerous for human health.

Environment

Bicarbonate Special is a white, quite odourless, crystalline powder. As sodium bicarbonate is the major component (81%) most of the properties are quite similar, but bulk density is 2.14 g/cm³ and water solubility is 100,3 g/L at 20°C. It decomposes starting at 30 - 35°C with first decomposition of ammonium bicarbonate and therefore melting point cannot be determined. The granulometry of particles indicate that 89% are > 45 µm.

The three chemical components of bicarbonate special are inorganic substances which decompose when heated, and are soluble in water where they dissociates into sodium, ammonium, carbonate and bicarbonate ions which are naturally present in the environment. Due to their physico-chemical properties, the vapor pressure, log K_{ow} and

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biodegradation values are not available.

Ammonia is naturally assimilated by most organisms for protein synthesis. Sodium, carbonate and bicarbonate ions are not expected to accumulate in living tissues. However, ammonia is a part of the nitrogen cycle in the environment and has indirect and long-term effects to the ecosystems, e.g. eutrophication, groundwater pollution, water and soil acidification with oxygen depletion. The acidifying effects on soil and water take place when ammonia ions are transformed into nitrate by micro-organisms, a so-called nitrification. In soil, if the nitrate is not absorbed by plants, and instead reaches the surface or groundwater, the acidifying effects increase. In the aquatic environment, nitrification, consuming four atoms of oxygen for every atom of nitrogen converted, can dramatically lower dissolved oxygen in the water resulting in adverse impacts on aquatic organisms.

Among the three components of bicarbonate special, the lowest relevant chronic toxicity value was obtained for ammonium bicarbonate with $EC_{20} = 7.6$ mg/L (*Lepomis macrochirus*, pH 8, 25°C). Sodium bicarbonate and sodium carbonate should not be considered as dangerous for aquatic organisms and only the toxicity of ammonium bicarbonate has to be taken into account. In the composition of bicarbonate special, ammonium bicarbonate is only present at 2-5 % and its contribution in the global toxicity of bicarbonate special would be low.

Because the natural pH, bicarbonate, carbonate and sodium concentrations (and also their fluctuations in time) vary significantly between aquatic ecosystems, it is not considered useful to derive a general PNEC or a $PNEC_{added}$. To assess the potential environmental effect of a bicarbonate special discharge, the variation of pH and the increase in sodium, carbonate, bicarbonate and ammonia should be compared with the natural values and their fluctuations and based on this comparison it should be assessed if the anthropogenic addition is acceptable.

Exposure

The global production of bicarbonate special in closed systems was approximately 5000 tonnes in 2004.

Bicarbonate special is produced for 2 intended uses: treatment of gas from incineration processes or from glass-maker furnaces, and animal feeding: bovine, porcine, ovine, providing sodium to animals.

The production and use of ammonium bicarbonate may result in inhalation, dermal and/or oral exposure.

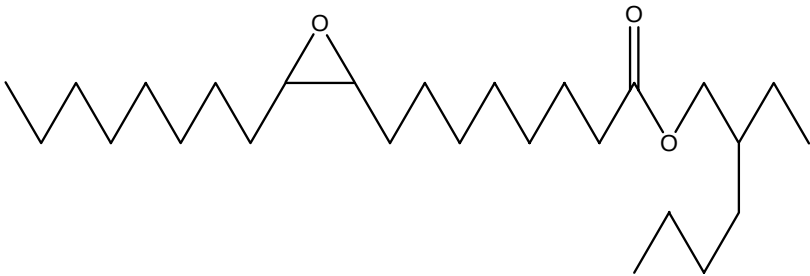
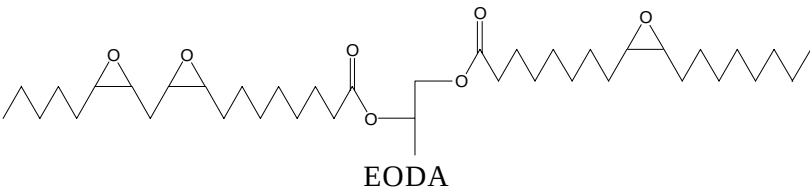
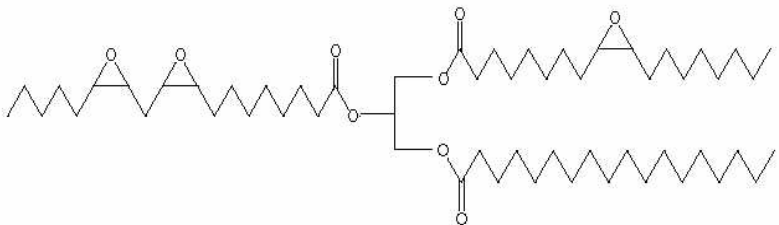
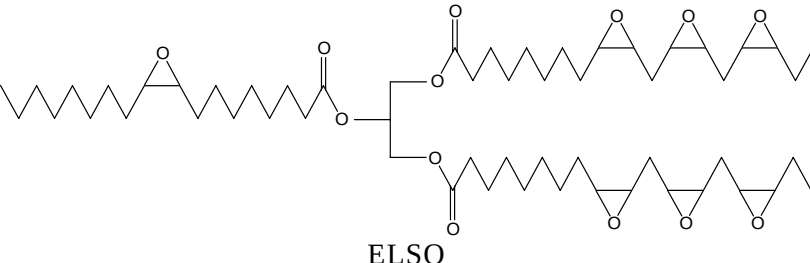
It is obvious that the sodium, ammonium, carbonate and bicarbonate ions, and also ammonia have a wide natural occurrence. Significant direct emissions to the terrestrial environment or atmosphere are not expected during production and use of bicarbonate special. When used for animal feeding, bicarbonate special would be metabolized by animals before reaching soil.

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. Based on the results of aquatic toxicity tests with the 3 chemical components of bicarbonate special, ammonium bicarbonate appears to be the most toxic component. As the concentration of ammonium bicarbonate is very low in bicarbonate special, the latter should not be considered in general as dangerous for the aquatic organisms. However, ammonia has indirect and long-term effects to the ecosystems, e.g. eutrophication, groundwater pollution and soil acidification due to the nitrification of ammonia

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	61789-01-3 Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters (ETP) 68609-92-7 9-Octadecanoic acid (Z)-, epoxidized, ester w/propylene glycol (EODA) 8013-07-8 Epoxidized soybean oil (ESBO) 8016-11-3 Epoxidized linseed oil (ELSO or ELO)
Chemical Category Name	Epoxidized Oils and Derivatives (EOD) Category
Structural Formula	 ETP  EODA  ESBO  ELSO
SUMMARY CONCLUSIONS OF THE SIAR Category Justification The four (4) epoxidized oils and derivatives form the Epoxidized Oils and Derivatives (EOD) Category based on	

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structural and functional similarity. Epoxidized Oils and Derivatives are epoxidized fatty acid esters. The oils from which these products are derived are naturally occurring long chain fatty acid sources, and there is considerable overlap in the composition of the fatty acid portion of these products. They are primarily the C18 acids: oleic, linoleic, and linolenic acid. The alcohols are primary alcohols, diols or triols. This category consists of related fatty acid esters. Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters (ETP) 9-Octadecanoic acid (Z)-, epoxidized, ester w/propylene glycol (EODA) Epoxidized soybean oil (ESBO) Epoxidized linseed oil (ELSO or ELO). ETP is a monoester with 2-ethylhexanol. EODA is a diester with propylene glycol. ESBO and ELSO are triesters with glycerol (triglycerides). These materials are considered a category for purposes of environmental and health hazard screening assessments because of their similarities in metabolism in microbial, aquatic and mammalian systems. Although there are no data regarding metabolism on these materials, it is known that fats are metabolized by esterases, and the materials in this category are fats. Carboxylesterases have been demonstrated to be present in many families of fish and aquatic invertebrates as well as mammals. The action of the esterase will result in a mixture of epoxidized fatty acids and 2-ethylhexanol from ETP, epoxidized fatty acids and propylene glycol from EODA, and epoxidized fatty acids and glycerol from ESBO and ELSO. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category. Following metabolism, the alcohols from each material are a minor constituent of the metabolic products, and not produced in sufficient quantity to influence the toxicity profile of the EOD materials. The alcohols formed as metabolic products have already been assessed at previous SIAMs.

Acute toxicity data for 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO), are considered to be representative of 68609-92-7 (EODA). Hydrolysis data for 61789-01-3 (ETP) is considered to be representative of 68609-92-7 (EODA), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Biodegradation, genetic toxicity, repeated dose, reproductive and developmental data for 61789-01-3 (ETP) and 8013-07-8 (ESBO) are considered to be representative of 68609-92-7 (EODA) and 8016-11-3 (ELSO). The chronic daphnia data for 68609-92-7 (EODA) are considered to be representative of 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO).

Human Health

In mammalian species these materials are expected to be absorbed and metabolized in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides. Lipase is an enzyme that assists in the breakdown and digestion of fat in the body. Pancreatic lipase works at the oil/water interface since triglycerides are insoluble. During metabolism in the GI tract, pancreatic lipase preferentially hydrolyzes triglycerides to release the free fatty acids from the SN-1 and SN-3 (terminal) positions of the glycerol backbone. Other products of metabolism are mono- and diglycerides. The monoglycerides, diglycerides, and fatty acids can be absorbed. In a similar manner, pancreatic lipase and other digestive enzymes have been shown to hydrolyze propylene glycol monoesters and diesters in vitro. The absorption, metabolism and hydrolysis of propylene glycol distearate (which is structurally similar to EODA) were studied in rats using isotopically labelled compounds. These processes for the propylene glycol esters were found to be similar to those of the glycerol esters. So, there is evidence that the propylene glycol esters of fatty acids are hydrolyzed to propylene glycol and fatty acids. The ETP structure is similar to that of the monoglycerides, formed from the ELSO and ESBO. Further hydrolysis can also occur via carboxylesterase activity.

Numerous acute toxicity studies have been conducted with ETP, ESBO and ELSO via the dermal and oral route of exposure. Acute toxicity studies were not available for EODA. The dermal LD50s of ETP, ESBO and ELSO in rabbits range from greater than 16 mL/kg bw (ELSO) to greater than 20 mL/kg bw (ETP and ESBO). The oral LD50s of ETP, ESBO and ELSO in rats range from 14.9 mL/kg bw (ELSO) to greater than 16 mL/kg bw (ETP) up to 41.5 mL/kg bw (ESBO). Similar acute toxicity values would be expected for EODA. There are no valid definitive skin irritation studies for any of the EOD materials, however the results from dermal toxicity studies with ETP, ESBO and ELSO indicate transient erythema and desquamation (no to slight skin irritation), similar effects are anticipated for EODA. Eye irritation studies are available for ETP and ESBO indicating no damage is observed, similar effects (no eye irritation) are expected for ELSO and EODA. Skin sensitization tests with ESBO and ETP indicate the EOD materials are not sensitizers.

Repeat dose studies by the oral route of exposure (gavage or dietary) have been conducted with ETP and ESBO. The NOAEL for ETP in a standard OECD Guideline 422 (rat) study was considered to be 1000 mg/kg bw/d (the highest dose tested). In a 90 day subchronic study, male and female rats were given 0.04, 0.2, 1.0 or 5.0% (5% is approximately 1.25 g/kg bw/d) ESBO. (Liver weights were increased in rats fed ESBO at 1% or 5% in diet. Gross findings indicated a test article-related effect of ESBO on liver and kidney at 1% and 5%. The NOAEL

was 0.2% ESBO; the LOAEL was 1% ESBO. In a 2-year rat feeding study, a LOAEL of 1% ESBO was described based on increased liver and kidney weights. No effects were observed at .5% ESBO. Rats were given diets containing up to 5% ESBO for 15 weeks. Temporary slowed growth and liver and kidney enlargement at concentrations greater than 1.5% was observed. The LOAEL was greater than 1.5% ESBO. Groups of three dogs were fed up to 5% ESBO once per day for one year. Dogs fed 5% ESBO lost weight, and fatty liver changes (fatty infiltration) in one dog given 5% ESBO were observed. Food intake and body weight were decreased at 5% ESBO. The LOAEL was 5% ESBO.

In vitro, ETP and ESBO were negative in bacterial or mammalian gene mutations assays. ETP and ESBO did not induce chromosomal aberrations in Chinese hamster V79 or human lymphocyte cells. EODA and ELSO are not expected to be mutagenic in bacterial or mammalian systems based on the lack of mutagenicity of ETP and ESBO.

Chronic/carcinogenicity studies were conducted with ESBO by the oral route (dietary). ESBO was not carcinogenic when fed to rats at up to 2.5% of the diet. Further, the NOAEL was 2.5% providing an average daily intake of approximately 1.0 g/kg bw in males and 1.4 g/kg bw in females. There were no treatment-related histopathologic lesions and there was no evidence of carcinogenicity of ESBO in groups of male and female rats given ESBO in the diet at 0, 0.1, 0.5, 1.0, 2.5, and 5.0%. A similar lack of carcinogenic response is expected for ETP, EODA and ELSO.

ETP and ESBO have been evaluated for the potential to cause developmental toxicity in rats and were not teratogenic, nor did they demonstrate reproductive toxicity. In a standard OECD Guideline 422 rat study with ETP, there were no adverse effects on reproductive parameters, and the NOAEL (maternal) and NOEL for reproduction was considered to be 1000 mg/kg bw/d. Daily administration of ESBO up to 1000 mg/kg bw/d did not induce any toxic effect in parent male or female animals, did not disturb their capacity for reproduction and did not impair development of the F1 offspring. Based on the lack of reproductive toxicity or developmental effects with ETP and ESBO, EODA and ELSO are not expected to cause developmental toxicity or to demonstrate reproductive toxicity.

Environment

The melting point of the EOD materials range from <-23.2 to -2.2 C. All the EOD materials decompose at 176 – 204C; boiling points are not applicable. The vapor pressures of the EOD materials are less than 0.001 hPa. The reported vapor pressure values are presumed to reflect the influence from minor impurities having relatively low boiling impurities. The estimated water solubilities of the EOD materials range from 0.937 to 6.65 mg/L. It is the nature of the EOD materials to form an emulsion upon mixing in water. They do not dissolve and they do not remain as individual molecules in solution, which reflects the difficulty with which the undissolved microemulsion is separated from true aqueous solution. The actual water solubility if the EOD substances are lower than reported. The log Kow values of these substances are estimated to be all greater than 6.2 according to the OECD Guideline No. 117: HPLC Method.

Estimated half-lives for the indirect photolysis in the atmosphere range from (approximately) 2 to 5 hours for the four materials. Abiotic hydrolysis of these materials is slow in part due to the low water solubility of the materials; the hydrolysis half-life for ETP is greater than one year while the half-life of ESBO could not be determined. Level III Fugacity modeling, using loading rates for soil, and water of 1000 kg/h and 0 kg/h for air (due to the very low vapor pressure of these materials), shows the primary distribution to sediment (ranging from 65-69%) and soil (ranging from 27-32%). Biodegradation studies with ETP and ESBO indicate that these materials are readily biodegradable (70% within 28 days, OECD 301F test). ETP exhibited 70% degradation within 28 days in the OECD 301F test, whereas ESBO exhibited > 79% degradation over 28 days in the OECD 301B test. Previous studies showed lesser extents of biodegradation for these substances (21% of ETP, 0% of ESBO after 20 days). The discrepancy in results among these biodegradation studies can be attributed to differences in inoculum density, and more importantly, the degree to which the insoluble test substance is dispersed in the aqueous test mixtures. Based on data from ETP and ESBO, the EOD category is expected to be readily biodegradable. Whereas the estimated log Kow value of > 6.2 indicates a high potential for bioaccumulation of these substances, their uptake into fish is expected to be hindered by their large molecular size. If taken up by fish, these carboxylate ester-containing substances are expected to be readily metabolized and excreted. Thus, the bioaccumulation potential is expected to be much lower than predicted from log Kow alone.

Acute toxicity tests with fish (48 hr) as well as tests with both freshwater and marine crustacea (24 hr), and algae (72 hr) have been conducted with ESBO. Although the fish and invertebrate studies were conducted for shorter time periods than currently specified in the OECD guidelines, for the time periods examined there was no or minimal evidence of toxicity observed at the limit of water solubility. In the algae study with ESBO, on the basis of biomass, the median effective concentration was 72 h $EbC_{50} > 8$ mg/L and 72 h $NOEC = 2.3$ mg/L. Effects are not expected to be observed below the water solubility of these materials. Based on the physicochemical properties of the category members (very low water solubility, log K_{ow} values > 6.2 , and readily biodegradable), as the substances are unlikely to be bioavailable to aquatic organisms. In preparation to conduct a chronic daphnia study it was demonstrated that there was no water soluble test substance detected above 0.05 mg EODA/L in a Water Accommodated Fraction (WAF) prepared from a loading of 100 mg/L. Therefore, considering the structure and low water solubility of EODA, it was concluded that the WAF is not likely to exert acute measurable effects on daphnids, and a chronic test would not be likely to provide meaningful, quantitative information on such effects. The option of conducting the chronic daphnia test with another member of the EOD family was considered. However, similar results are expected from the WAF preparations for these poorly soluble substances. Further laboratory investigation of the chronic toxicity of this substance to aquatic organisms is therefore deemed not necessary.

Exposure

The production volumes for the sponsor country in 2002 were:

ETP: up to 453 and less than or equal to 4536 tonnes

EODA: up to 453 and less than or equal to 4536 tonnes

ESBO: up to 45359 and less than or equal to 226,796 tonnes

ELSO: up to 453 and less than or equal to 4536 tonnes

ESBO and ELO are approved for use as inert ingredients in pesticides. EODA is a high monomeric epoxy plasticizer, which offers low volatility, low temperature flexibility and high compatibility in polyvinyl chloride systems. EODA is used in semi-rigid and flexible vinyl formulations, vinyl plastisol and organosols, coated fabrics and automotive interiors and moldings. ELSO and EODA are primarily used to keep plastics and rubber soft and pliable in flooring, upholstery, food packaging, hoses, tubing, blood bags and other products. The epoxy functionality provides excellent heat and light stability. ETP is used in flexible low temperature PVC application such as refrigerator gaskets.

These substances are used as plasticizers in PVC for a wide range of applications including food-contact materials where two of these materials have approvals under EU and FDA regulations. Migration does occur from plastics and in the case of ESBO for use in cap seals and use in PVC film a recent EFSA report has shown that the total adult intake is below the TDI, whilst in the case of baby jars the safety margins of the EU regulatory system have been eroded although the use is considered safe and industry is devising techniques to reduce the migration for baby food jars.

Additional dermal exposure may occur at low levels for consumers and this will be the main route of exposure for workers. In this case exposure may occur during filter cleaning operations, but these exposures are limited by appropriate protective clothing. 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 industrial bulk containers, making exposure at this point in the process highly unlikely. Limited dermal exposure may occur with pesticide applicators where ESBO or ELO are used as inert ingredients. Inhalation exposure may occur during manufacture or processing, however these exposures are limited due to the low vapor pressures of these materials.

Some limited potential exists for release of material to the Publicly-Owned Treatment Works after primary biological treatment on site. Materials could potentially reach the primary treatment system as a result of inefficiencies in manufacturing processes. The chemical is stored in closed tanks and transported in tank cars and tank trucks, and smaller amounts are transported in drums or industrial bulk containers. Environmental release during transport is possible in the event of a spill or accident. The materials have very low vapor pressures, making airborne release unlikely.

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

The chemicals in this category are currently of low priority for further work for human health and the environment because of their low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category Name	Long Chain Alcohols (C6-22 primary aliphatic alcohols)			
CAS Nos	Chemical name	CAS no.	Chemical name	CAS no.
	1-Hexanol	111-27-3	Alcohols, C16-18	67762-27-0
	1-Octanol	111-87-5	Alcohols, C14-18	67762-30-5
	1-Decanol	112-30-1	Alcohols, C10-16	67762-41-8
	1-Undecanol	112-42-5	Alcohols, C8-18	68551-07-5
	1-Tridecanol	112-70-9	Alcohols, C14-16	68333-80-2
	1-Tetradecanol	112-72-1	Alcohols, C6-12	68603-15-6
	1-Pentadecanol	629-76-5	Alcohols, C12-16	68855-56-1
	1-Hexadecanol	36653-82-4	Alcohols, C12-13	75782-86-4
	1-Eicosanol	629-96-9	Alcohols, C14-15	75782-87-5
	1-Docosanol	661-19-8	Alcohols, C12-14	80206-82-2
	Alcohols, C12-15	63393-82-8	Alcohols, C8-10	85566-12-7
	Alcohols, C9-11	66455-17-2	Alcohols, C10-12	85665-26-5
	Alcohols, C12-18	67762-25-8	Alcohols, C18-22	97552-91-5
	9-Octadecen-1-ol (9Z)-	143-28-2	Alcohols, C14-18. & C16-18-unsatd	68155-00-0
	Alcohols, C16-18 & C18 Unsaturated	68002-94-8	Tridecanol, branched & linear	90583-91-8
Structural Formula	CH ₃ (CH ₂) _n CH ₂ OH		Linear n = 4 to 20	
	CH₃(CH₂)_nCHCH₂OH (CH₂)_mCH₃		2-Alkyl branched n + m = 3 to 18, and m is predominantly = 0. Present in essentially-linear alcohols	
	CH₃(CH₂)_nCH(CH₂)_mOH CH₃		Other-methyl branching n + m= 9 or 10 Present in essentially-linear Fischer-Tropsch derived alcohols	
	CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇ CH ₂ OH		Unsaturated 9-Z unsaturated components are present in some commercial products.	
SUMMARY CONCLUSIONS OF THE SIAR				
Category Rationale				
This category covers a family of 30 primary aliphatic alcohols within a carbon chain length range of C6-C22. Commercial products generally include several aliphatic alcohol components, with a range of carbon chain lengths				

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present. The family consists of alcohols with varying compositions and structures. Composition depends on the route to manufacture and the related feedstocks. Most of the alcohols have linear carbon chains but certain manufacturing processes create branched structures. Data are also available for eleven other similar substances, which support the category. Non-sponsored alcohols may not be HPV or may not be produced by members of the consortium, but have structures similar to sponsored linear alcohols.

Key points are that the members share:

- The same structural features
- Similar metabolic pathways
- Common mode of ecotoxicological action
- Common levels and mode of human health related effects.

This allows multi-component reaction products to be considered within the Category by the application of validated models of exposure and effects, on the basis of detailed knowledge of the composition. For the environmental end points, this has been done in two ways:

Read-across: this applies to biodegradability, for which sufficient data are available to allow read across from the pattern of degradation across the entire category to fill data gaps directly. For algae, read-across-based expert judgement was applied, taking into account measured and predicted effects in daphnids and fish for the substance of interest.

Modelling: a model of the ideal solubility of the components of the substances has been set up, which allows component and total solubility at any loading rate to be calculated. By use of knowledge of the properties of each component, ecotoxicological effects have been predicted.

Human Health

Considering the manufacturing processes two sub-categories of aliphatic alcohols can be distinguished:

- Linear alcohols: Saturated or unsaturated primary -non-branched- aliphatic alcohols containing an even number of carbon atoms.
- Essentially linear alcohols: Saturated, primary linear aliphatic alcohols and their saturated, mono branched primary alcohol isomers of corresponding carbon chain length

A detailed assessment of the toxicological database of both sub-categories shows that the linear and the essentially linear alcohols are of a low order of toxicity following acute and repeated exposures. The endpoints of skin and eye irritation show a trend within each of the sub-categories with the lower members of the category displaying a more pronounced response than the longer-chained-alcohols. The overall toxicological profile of the sub-categories of linear and essentially linear alcohols is qualitatively and quantitatively similar for all end points assessed. The observed relationship between chain length and toxicological properties is equally present for both sub-categories. Moreover, the mammalian metabolism of the aliphatic alcohols is highly efficient and proceeds similarly for each of the sub-categories. The first step of the biotransformation the alcohols are oxidised to the corresponding carboxylic acids, followed by a stepwise elimination of C2 units in the mitochondrial β -oxidation process. The metabolic breakdown of mono-branched alcohol isomers is also highly efficient and involves processes that are identical to that of the linear aliphatic alcohols. The presence of a side chain does not terminate the β -oxidation process, however in some cases a single Carbon unit is removed before the C2 elimination can proceed.

Surrogate and supporting substances have been assessed for this category in order to address potential concerns associated with differing degrees of branching and to justify the read-across within the sub-category of the essentially linear alcohols.

Aliphatic alcohols are absorbed by all common routes of exposure, widely distributed within the body and efficiently eliminated. There is a limited potential for retention or bioaccumulation for the parent alcohols and their biotransformation products.

The category of the long-chain aliphatic alcohols as a whole is of a low order of acute toxicity upon inhalational, oral or dermal exposure. The members of this category are generally of a low volatility and the acute lethal

concentration exceeds the saturated vapour pressure. In most cases the acute oral and dermal LD50 values exceed the highest dose tested and, depending on the test protocol, range from >2000 to >10,000 mg/kg.

Overall, the toxicology database shows an inverse relationship between chain length and toxicity. The shorter chain alcohols tend to induce more pronounced effects when compared to materials with a longer chain length. This is illustrated most clearly by the degree of irritation in skin and eye irritation studies in laboratory animal studies. For the aliphatic alcohols in the range C6 – C11 a potential for skin and eye irritation exists, without concerns for tissue destruction or irreversible changes. Aliphatic alcohols in the range C12 – C16 have a low degree of skin irritation potential; alcohols with chain lengths of C18 and above are non-irritant to skin. The eye irritation potential for alcohols with a chain length of C12 and above has been shown to be minimal.

Aliphatic alcohols have no skin sensitisation potential.

Repeated exposure to aliphatic alcohols is generally without significant systemic toxicological findings and this category is therefore regarded to be of a low order of toxicity upon repeated exposure. At the lower end, members of this category induce local irritation at the site of first contact. Other notable findings observed for several members within this group suggest mild changes consistent with low-grade liver effects with the changes in essentially linear alcohols being slightly more pronounced than in branched alcohols. Typical findings include: slightly increased liver weight, in some cases accompanied by clinical chemical changes but generally without concurrent histopathological effects. Special studies demonstrated that this category does not have a potential for peroxisome proliferation. CNS effects were absent upon inhalation or dietary administration, however 1-hexanol and 1-octanol showed a potential for CNS depression upon repeated administration of a bolus dose. Similarly, 1-hexanol and 1-octanol induced respiratory distress upon repeated administration of a bolus dose. Aliphatic alcohols do not have a potential for peripheral neuropathy. Typical NOAEL's recorded for this category range between ca. 200 mg/kg/day to 1000 mg/kg/day in the rat upon sub-chronic administration via the diet.

Several members of the long chain aliphatic alcohol category were used as a vehicle or solvent in chronic skin painting studies. Although the validity of such experiments is limited, there was no evidence of a carcinogenic potential for this category. Long chain aliphatic alcohols do not contain structural elements of concern for potential interaction with DNA and have been shown to be without mutagenic activity, primarily on the basis of Ames assays and mouse micronucleus assays.

On the basis of the lack of adverse findings in the reproductive organs in repeated dose toxicity studies and in screening studies for reproductive effects this category is considered without a potential for adverse effects on fertility and reproductive toxicity. Similarly, developmental toxicity studies in substances belonging to this category and aliphatic alcohols supporting this category studies have confirmed the lack of potential adverse effects on the developing foetus.

Environment

The general trends in the data show properties that vary with carbon chain length in accordance with normal expectations. As carbon chain length increases melting point increases, boiling point increases and vapour pressure decreases; one consequence of this is that flash point temperatures increase at higher molecular weight. Water solubility decreases and the octanol-water partition coefficient increases with increasing carbon chain length.

Physicochemical properties vary, as described, across members of the Category. Ranges of key property values are:

- Melting point: from ca. -50°C (*measured; Hexanol*) to +72.5°C (*measured; Docosanol*)
- Boiling point: from 158°C (*measured; Hexanol*) to ca. 400°C (*upper limit of measured boiling range for C18-22 alcohols, supported by estimated value for Docosanol*)
- Density: from ca. 0.80 g/cm³ to ca. 0.85 g/cm³ (*measured; range across category*)
- Vapour pressure: from 8.2E-08 hPa (*estimated; Docosanol*) to 1.22 hPa (*measured; Hexanol*)
- Water solubility: from ca. 0.001 mg/l (*measured; Octadecanol*) to 5900 mg/l (*measured; Hexanol*)
- Partition coefficient: from 2.03 (*measured; Hexanol*) to >7 (*measured; Eicosanol*)

Environmental Fate

Reliable measured data show that alcohols with chain lengths up to C18 are readily biodegradable (*measured; hexanol, octanol, decanol, dodecanol, tetradecanol, hexadecanol and octadecanol*). At carbon chain lengths up to C16, most tests showed that pass levels for ready biodegradation were reached within the 10-day window, with removal levels up to 100% over the timescale of the test. Chain lengths of C16-18 achieved ready test pass levels (62% to 76% in tests on single chain lengths) but not within the 10 day window. The one test on a single carbon chain length greater than C18 (docosanol) showed degradation of 37%. In additional studies conducted at environmentally realistic concentrations with radiolabelled substances (C12-16), very high rates of degradation have been measured (very rapid rate constants, with ca. 75-85% removed as CO₂ and metabolites). These rates accord with field data for measured concentrations in waste-water treatment plant influent and effluent showing greater than 99% removal for carbon numbers 12 to 18. This summary of degradation is applicable to both linear and branched components of substances in the category. Therefore, the whole category is considered to show very high levels of biodegradability. Rapid degradation is also indicated by the removal rates in the chronic aquatic toxicity tests for the lower solubility substances (C10 to C15), where rapid removal of the substance from the test medium was observed, most likely due to biodegradation by micro-organisms.

All of the alcohols in this group would be expected to be stable in respect of abiotic degradation in water. Photo-oxidation in aqueous systems will not be significant. Alcohols have no hydrolysable groups and are therefore not susceptible to hydrolysis. Oxidation would not be expected under normal environmental conditions.

The substances are susceptible to atmospheric degradation by hydroxyl radicals, with half-lives ranging between ca. 10-30 hours (based on measured and estimated rate constants, for a hydroxyl radical concentration of 5E+05 molecules/cm³). Longer chain lengths have shorter estimated half-lives within this range.

No reliable guideline-standard measured bioconcentration data are available. Bioconcentration factors (BCF) calculated on the basis of log Kow range from 7.0 for C6 to a maximum of 46000 for C16, reducing to 1100 for C22. For hexadecanol, the BCF (Q)SAR estimates a value of 45300 (recalculated from the parabolic Connell and Hawker equation), but a measured value of 56 and a range of values from 507-1550 from two unreliable studies exist; BCF data for alcohols similar to those in this family but with 2.1-2.9 branches per molecule also indicate that BCF (Q)SAR overestimate BCF. Log Kow-based BCF (Q)SAR predictions also take no account of biotransformation/metabolism of alcohols in living organisms, the natural mechanism for their removal. For these reasons it is expected that category members will have a low potential for bioaccumulation.

Fugacity modelling shows that the predicted fate of all of the Category members varies depending on the route of release into the environment. For chain lengths C10 and above, alcohol released to water is predicted to partition into sediment. When alcohols are released to air, for chain lengths C14 and above, less than half of alcohol ultimately present in the environment can be found in air.

The situation for modelling exposure of multi-component substances is complicated by the fact that, given a particular route of exposure, each component will behave independently on release to the environment.

Effects on aquatic organisms

Alcohols in this Category act by non-polar narcosis and demonstrate a similar order of magnitude of toxicity in fish, invertebrates and algae. For pure substances, as chain length increases, lipophilicity increases and aqueous solubility decreases. There is an associated increase in aquatic toxicity up to a limiting chain length, at which very low aqueous solubility limits the bioavailable concentration of the alcohol in the water, resulting in a concentration at which no effects are exerted (the cut-off). Consequently, longer chain lengths show no toxicity. For aquatic organisms the chain length cut-off for acute effects lies at C13 to C14 (depending on the test species). For chronic effects, the cut-off for effects in invertebrates is in the region of C15. [The cut-off for chronic effects is probably not a limitation due solely to solubility, but is due to a limitation of the concentration at the site of action. This is not an artefact of the protocol used for the studies].

Effect concentrations vary, as described, across members of the Category. Ranges of key property values, including lowest and highest measured data as well as lowest estimated values as appropriate, are:

- Acute effects in fish (96h LC₅₀): from 0.48 mg/l (*estimated, C12-14 alcohols*) and 0.7-0.8 mg/l (*nominal, C6-12 alcohols*) to 97 mg/l (*measured, Hexanol*). No effects up to limit of water solubility for single chain lengths >C13-14 and for some multi-component substances.
- Acute effects in invertebrates (EC₅₀): from 0.13 mg/l (*48h estimated, C14-16 alcohols*) and 0.8-1.1 mg/l

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(96 h nominal, 1-undecanol) to 200 mg/l (24h nominal, Hexanol). No effects likely up to the limit of water solubility for single chain lengths >C13 and for some multi-component substances.

- Acute growth rate effects in algae (72 h E_rC₅₀): from ca. 0.1 mg/l (nominal, C10-16 and C12-16 alcohols, and estimated for various substances) to 80 mg/l (measured, Hexanol). No effects likely up to the limit of water solubility for single chain lengths >C14 and for some multi-component substances.
- Chronic effects in invertebrates: 21-day NOEC_{repro} from 0.0098 mg/l (measured, tetradecanol, based on mean measured initial concentration) to 1 mg/l (measured, octanol). No effects are expected for single chain lengths >C15 up to limit of aqueous solubility.

In this assessment, trends between aquatic toxicity and carbon chain length are based on normal (linear) alcohols, since data do not exist on single carbon chain length, essentially-linear, alcohols. However, the comparability of the toxicity of straight chain and essentially linear alcohols is shown by a comparison of commercial products. The data sets for essentially pure substances have been interpreted in terms of conventional (quantitative) structure-activity relationships ((Q)SARs), by correlation of the effect concentrations with octanol-water partition coefficients.

In summary, the ranges of expected environmental behaviours of these substances could be characterised as follows.

- For short chain category members (≤C11): high solubility; acute toxicity to aquatic organisms in the range 1-100 mg/l, chronic toxicity to aquatic organisms in the range 0.1-1.0 mg/l; readily biodegradable;
- For mid-range chain length category members (C11-C13): low solubility; acute toxicity in the range 0.1-1.0 mg/l, well-characterised chronic toxicity to aquatic organisms in the range 0.1-<1.0 mg/l; very high biodegradability (readily biodegradable with extremely high removal in environmentally relevant concentrations);
- For longer chain length category members (C14-15): low solubility limits bioavailability and hence acute effects are unlikely to be expressed, well-characterised chronic toxicity to aquatic organisms in the range 0.01 mg/l – limit of solubility; very high biodegradability (readily biodegradable with extremely high removal in environmentally relevant concentrations);
- For the longest chain category members (≥C16): low solubility limits the dissolved (and hence bioavailable) concentration of the alcohol to the extent that neither acute nor chronic toxicity are likely to be exhibited; also significantly biodegradable (considered equivalent to inherent biodegradation; very extensive removal seen under environmentally relevant conditions) but more adsorbing than the lower homologues.

Exposure

Total global production of these long chain aliphatic alcohols by consortium members in 2002 was estimated as approximately 1580 thousand metric tonnes annually. Approximately 50% of the total production volume is used directly in final products (industrial/commercial products and various consumer/personal care products). The remainder is processed as an intermediate (with approximately 65% of the intermediate volume being site limited).

Exposure could arise in association with production, formulation and industrial use of these substances. Within commercial use, the substances are used principally as synthetic intermediates with low expected release levels. For the 50% of Category members intentionally used directly in industrial/commercial and consumer products, release to the environment can be anticipated (especially via waste water treatment plant effluent after disposal to drain). Monitoring data are available from wastewater treatment plant effluents in USA, Canada, UK, Netherlands, Spain, Italy and Germany. The 90th percentile for individual monitored effluent measurements worldwide, not accounting for treatment type and flow, is 2.121 µg/L and the global average is 1.057 µg/L. Modelled (SIMPLETREAT) mixing zone concentration is estimated at ~ 0.02 µg/L from a manufacturing plant.

These substances are also produced naturally, in all living organisms, from bacteria to man, and thus are widely present throughout the natural world. It is clear that measurements of long chain alcohol in environmental matrices will reflect the combination of both natural and anthropogenic sources. An environmental exposure assessment is available in the Annex and: (http://www.bangor.ac.uk/~oss034/Fatty_Alcohol_Natural_and_Anthropogenic_Sources.doc).

Occupational Exposure: As a rule aliphatic alcohols are manufactured and processed in established chemical

complexes in closed installations; these are usually operated at high temperature and pressure. At these sites standard personal protective equipment is routinely applied to prevent direct skin and eye contact. Generally, aliphatic alcohols are of a low volatility and as a rule engineering controls are available preventing the need for respiratory protection. For non-routine operations involving a break in enclosed systems a higher level of protection is applied. Operations with a potential for significant exposure require a permit to work system and a case-by-case assessment is made for appropriate protective measures. Exposure through the use of products in industry and commerce is mitigated by applying measures aimed to prevent direct skin and eye contact by following the recommendations in the material safety data sheet (MSDS).

Consumer Exposure: Aliphatic alcohols are formulated in consumer laundry, cleaning and personal care products. Product labels reflect the hazard potential of the chemical ingredients in these products and include first aid instructions in case of non-intentional exposure.

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

Human Health: The chemicals of the category of the long chain aliphatic alcohols are of low priority for further work. The members of this category are of a low order of toxicity by all common routes of exposure upon acute or repeated exposure. Overall, the toxicology database for this category shows an inverse relationship between chain length and toxicity. The key human health hazards identified for this category are the irritative properties for skin and eye of aliphatic alcohols with chain lengths of C11 or below. These hazards are well characterized and do not lead to tissue destruction or irreversible changes. They should nevertheless be noted by chemical safety professionals and users.

Environment: The category comprises a homologous series of linear and essentially linear C6 - 22 alcohols. Increasing carbon chain length leads to a predictable pattern in physico-chemical properties; this drives a distinct range of fate behaviours in the environment. Category members all have the same mode of ecotoxicological action. In addition, all of the category members are rapidly biodegradable especially at environmentally relevant concentrations. Alcohols are metabolised/biotransformed in living organisms; this biotransformation suggests that bioaccumulation potentials based on octanol-water partition coefficients may be overestimates. Measured BCF data on a related alcohols Category supports the concept that the bioaccumulation potential of these substances will be lower than estimated from log Kow.

Many of the substances in the category do not present a hazard for the environment (acute aquatic toxicity >100 mg/l, or above water solubility with no effects exhibited) and are of low priority for further work. These category members are CAS Numbers: 36653-82-4, 629-96-9, 661-19-8, 143-28-2, 67762-27-0, 67762-30-5, 97552-91-5, 68155-00-0.

Some of the substances in this category present a hazard for the environment (acute toxicity to fish, daphnids and algae in the range 1 - 100 mg/l). However all of these substances are readily biodegradable. Therefore these subgroup members are of low priority for further work. These subgroup members are CAS Numbers: 111-27-3, 111-87-5, 85566-12-7, 67762-25-8, 68002-94-8.

The remaining substances in the category present a greater hazard for the environment (high acute toxicity to fish, daphnids and algae, in the range 0.1 - 1 mg/l, and/or high chronic toxicity). The substances in this subgroup biodegrade rapidly and environmental monitoring data from seven countries indicates exposures to the environment is anticipated to be low and are included in an Annex to the SIAR. The chemicals in this subgroup that should be candidates for further work by member countries, who are invited to perform an exposure assessment and, if necessary, a risk assessment, are CAS Numbers: 112-30-1, 112-42-5, 90583-91-8, 112-70-9, 112-72-1, 629-76-5, 68603-15-6, 67762-41-8, 68855-56-1, 63393-82-8, 66455-17-2, 68333-80-2, 75782-86-4, 75782-87-5, 80206-82-2, 68551-07-5, 85665-26-5.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	124-41-4 865-33-8
Chemical Name	Category of Methanolates: Sodium methanolate, Potassium methanolate
Structural Formula	$\text{H}_3\text{C-O}^- \text{Na}^+; \text{H}_3\text{C-O}^- \text{K}^+$

SUMMARY CONCLUSIONS OF THE SIAR**Category Justification**

The production and use pattern of sodium and potassium methanolates are comparable. The two chemicals have very similar physical and chemical properties. In contact with water they react very fast, quantitative and exothermic to methanol and the corresponding alkali hydroxides.

One mol of sodium or potassium methanolate (54.02 g or 70.13 g) yields one mol of methanol (32.04 g) and sodium- or potassium hydroxide (40 g or 56.11 g) respectively.

Due to the very high pK_a -value of methanol of 15.5, the equilibrium is on the side of the reaction products. Toxicological and ecotoxicological studies of methanol and sodium and potassium hydroxide are therefore relevant for these products as well. The main toxicological characteristic is the corrosivity to skin and mucous membranes that limits the possibility of exposure to methanol and warrants strict exposure controls. In the environment, both effects through pH-changes by the hydroxides and effects of methanol need to be considered.

For potassium hydroxide SIAM 13, and for sodium hydroxide SIAM 14 concluded: "Environment and Human Health: no further work is recommended if sufficient control measures are in place to avoid significant human and environmental impact, including prevention of accidental exposure. Due to the corrosivity of the substance, no further studies are required under SIDS program."

For methanol, SIAM 19 decided that, in terms of human health, this chemical is a candidate for further work. In the US, further work is being performed regarding the use and refinement of pharmacokinetic models for extrapolating animal data to human. Methanol exhibits potential hazardous properties for human health (neurological effects, CNS depression, ocular effects, reproductive and developmental effects, and other organ toxicity). The effects of methanol on the CNS and retina in humans only occur at doses at which formate accumulates due to a rate-limiting conversion to carbon dioxide. In primates, formate accumulation was observed at methanol doses greater than 500 mg/kg bw (which would require a sodium methanolate dose of more than 840 mg/kg bw and a potassium methanolate dose of greater than 1000 mg/kg bw). Repeated exposure to such high dose levels of methanolates that are already in the acutely toxic range is highly unlikely due to their corrosive properties. The only exposure situation for sodium and potassium methanolate that could perhaps lead to methanol and formate blood levels resulting in acute neurophysiological and visual disturbances would be accidental dermal exposure to corrosive concentrations that could lead at the same time to an uptake of toxic amounts of methanol through the skin. For this exposure situation the post SIDS work for methanol is considered relevant as well and no specific work on sodium and potassium methanolate is considered necessary. In terms of the environment, methanol is currently of low priority for further work, due to its low hazard profile.

Human Health

The predominant effect of sodium and potassium methanolate on humans is their corrosivity to skin and mucous membranes, due to the rapid and exothermic reaction with tissue water yielding alkaline hydroxides. The abiotic hydrolysis of sodium and potassium methanolates with tissue water results in the hydroxides formation of sodium and potassium ions respectively, hydroxide ions and methanol. Exposure to non-irritant levels of methanolates via the dermal or inhalation route is not expected to lead to relevant uptake of the ionic degradation products sodium or potassium ions or hydroxide ions in amounts that would exceed the normal physiological levels.

The sodium ion is a normal constituent of the blood and an excess is excreted in the urine. Uptake of sodium

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following exposure to sodium methanolate can be considered negligible compared to the uptake of sodium via food (3.1 to 6 g/day).

Potassium ions are normal constituents of body fluids. K^+ plays an essential role in human physiology, but starts to be toxic at plasma concentrations of 250 mg/l. Its concentration in blood is regulated principally by renal excretion/re-absorption and controlled by an effective feed-back auto-regulation system. A systemic intoxication by potassium methanolate is not expected as the uptake will be limited by the corrosive properties of the substance.

Exposure to hydroxide ions from sodium or potassium methanolate exposure could potentially increase the pH of the blood and lead to alkalosis. However, the pH of the blood is regulated between narrow ranges pH 7.0 to 7.8 and an excessive pH of the blood is prevented by the bicarbonate buffer system, respiration and renal compensation mechanisms.

SIAM 19 concluded for methanol: "Methanol is readily absorbed by inhalation, ingestion and dermal contact and partitions rapidly and equally throughout the organism in relation to the water content of organs and tissues. A small amount is excreted unchanged by the lungs and kidneys. Half-lives of methanol in the body are roughly 2.5 to 3 hours at doses less than 100 mg/kg bw. At high doses disproportionate increases of the parent compound in blood are obtained in rodents, but not in humans. On the other hand, in humans the metabolite formate accumulates at high doses. This important difference mirrors the different enzymes and enzyme capacities involved in the oxidative pathway from methanol to carbon dioxide. Specifically, two different rate limiting processes have been identified: in rodents, high doses (after inhalation of 2.5 – 3.3 mg/l) lead to the saturation of catalase, resulting in the accumulation of methanol whereas formate levels remain low, whereas in primates (especially humans), the parent compound is well oxidized and does not accumulate, but formate increases disproportionately. From studies in humans and monkeys exposed to concentrations of 0.26 – 2.6 mg/l (administered for 6 to 8 hours), it can be concluded that methanol remains close to 50 mg/l in blood. At inhalation exposures of 2.6 mg/l, rats also exhibit methanol blood levels that are not much higher (at about 80 mg/l), whereas the level in mice was 400 mg/l. At a higher inhalation exposure (6.5 mg/l), humans show the lowest blood methanol level (at 140 mg/l), followed by monkeys, rats, and mice, with the level in mice being more than 10 times higher than humans. Formate accumulation in primates has been observed at methanol doses greater than 500 mg/kg."

The corresponding dose levels for sodium and potassium methanolate that would lead to accumulation of formate in primates would be 840 and 1000 mg/kg bw. Such dose levels are already in the acutely toxic dose range. Due to the corrosive nature of the methanolates it is unlikely that repeated exposure to methanolates could result in an uptake of toxic doses of methanol. The only exposure situation for sodium and potassium methanolate that could perhaps lead to methanol and formate blood levels resulting in acute neurophysiological and visual disturbances would be accidental dermal exposure to corrosive concentrations that could lead at the same time to an uptake of toxic amounts of methanol through the skin. It has been assumed that an inhalation exposure to methanol of 260 mg/m³ for 8 hours does not lead to any adverse effects. This exposure level corresponds to a systemic dose of 2600 mg methanol/d (assuming an inhalation volume of 10 m³ during an 8-hour working day) or 37 mg/kg bw day (for a 70 kg human). It would require doses of 44.4 and 65 mg/kg bw of sodium or potassium methanolate, respectively, to achieve a systemic dose of 2600 mg methanol/d. The rate of dermal uptake for methanol was reported to be 0.192 mg/cm²/min. Accidental exposure of both hands (850 cm²) to sodium or potassium methanolate for one minute resulting in corrosive effects could then theoretically additionally lead to an uptake of methanol exceeding the dose level of 37 mg/kg bw. Such an exposure situation does however not reflect any human exposure situation under normal handling conditions as precautions are taken because of the corrosivity of the substances.

No signs of toxicity were observed in rats exposed to a dust enriched atmosphere of sodium methanolate for 8 hours, the dermal LD₅₀ of a 50 % aqueous solution was > 2000 mg/kg bw in rats. Skin necrosis was observed in this study. After oral administration the acute toxicity is dependent on the local tissue concentration and the dose rate of the substance and its degradation product sodium hydroxide. The LD₅₀ in water or water soluble solvents was between 800 and 1687 mg/kg bw, when administered in corn oil the LD₅₀ was 2037 mg/kg bw. The acute toxicity is consistent with that of sodium hydroxide and it can be assumed that the primary mode of action is local irritation/corrosion at the site of first contact.

For potassium methanolate no data are available, but due to the reaction with water and the liberation of hydroxide ions and the alkaline reaction the mode of action will be the same and the acute toxicity will be comparable to that of sodium methanolate and potassium hydroxide. The acute toxicity of both substances is mediated by their alkalinity and the hydroxide ion.

Sodium methanolate was highly corrosive to rabbit skin and eyes. For potassium methanolate no studies are available. Due to its alkaline reaction and exothermic reaction with water it will be similarly corrosive. Based on the skin and eye irritation data it can be assumed that both methanolates will also cause irritation/corrosion to the

mucous membranes of the upper respiratory tract in case of an exposure via the inhalation route.

As the corrosivity is mediated by the exothermic liberation of sodium or potassium hydroxide the data for the two hydroxides may be important for the evaluation of this endpoint as well. For sodium hydroxide it was concluded that based on the animal data a NaOH solution of 8 % can be considered corrosive. Based on human data concentrations of 0.5 to 4 % were irritating to the skin and concentrations slightly lower than 0.5 % were considered non-irritating. Potassium hydroxide is corrosive at concentrations of about 2 % and higher. Between 0.5 % and 2 % it is irritating.

From the data of the hydrolysis products it can be concluded that sodium and potassium methanolate are not expected to have a notable skin sensitization potential.

No data on repeated dose toxicity of sodium and potassium methanolate are available. The tolerable dose levels will be determined by the corrosive nature of the substances. At non-irritant concentrations, the K^+ or Na^+ ions, and the OH^- ions are unlikely to have any adverse effects. The specific ocular and CNS toxicity of methanol in primates is based on the accumulation of formate in blood. Formate accumulation in primates has been observed at methanol doses greater than 500 mg/kg. The corresponding dose levels for sodium and potassium methanolate that would lead to accumulation of formate in primates would be 840 and 1000 mg/kg bw. Such dose levels are already in the acutely toxic dose range. Due to the corrosive nature of the methanolates it is very unlikely that exposure to methanolates could result in an uptake of toxic doses of methanol.

No data on mutagenicity of sodium or potassium methanolate are available with the exception of one negative Ames assay with a limited number of strains conducted with sodium methanolate. Due to the rapid hydrolysis of methanolates in *in vitro* test systems and tissue water *in vivo*, data for the hydrolysis products are relevant for methanolates as well. For sodium and potassium hydroxide there is no evidence for a mutagenic potential. For methanol the weight of evidence suggests that the substance is unlikely to have any relevant mutagenic activity. Therefore it can be concluded that there is no concern with regard to a mutagenic activity of sodium or potassium methanolate.

No data are available on the carcinogenicity of sodium and potassium methanolate. For potassium hydroxide it was concluded at SIAM 13 that there is no evidence of carcinogenicity in exposure situations that are relevant for humans. There was no evidence for a carcinogenic potential of methanol in two long-term inhalation studies on rats and mice. Based on the available data, there is therefore no concern for carcinogenicity of sodium and potassium methanolates.

No data are available on reproductive or developmental toxicity of sodium and potassium methanolate. For hydroxide, sodium and potassium ions, no relevant reproductive toxicity potential has been identified. For methanol reproductive and developmental toxicity effects have been described in rats, mice and monkeys. Blood methanol concentrations associated with serious developmental effects and reproductive toxicity in rodent studies are in the range associated with formate accumulation. It is unlikely that concentrations associated with serious developmental effects in rodents could be reached by administration of sodium or potassium methanolate to experimental animals, as those dose levels would be in the acutely toxic dose range and associated with massive local irritation at the site of first contact. The maximum tolerated dose in such studies is therefore likely to be below the dose that would result in methanol mediated developmental effects. In addition, for animal welfare reasons, it is not recommended to perform further animal studies with sodium and potassium methanolate.

Environment

Both sodium and potassium methanolate are white to yellowish organic solid salts that decompose above 300 °C (sodium methanolate) or at 300 °C (potassium methanolate). Sodium and potassium methanolate have a calculated vapor pressure of 6.39×10^{-6} hPa. On contact with water both substances decompose rapidly and exothermically under formation of methanol and the corresponding alkali hydroxides, sodium- or potassium hydroxide, respectively.

Photodegradation of methanol by hydroxyl radicals takes place with a half-life of 17 - 18 days. For the partitioning in the environmental compartments the hydrolysis products are of relevance. Sodium and potassium hydroxide are inorganic salts that partition predominantly into the water phase and will not adsorb to particulate matter or surfaces. For methanol it was concluded that based on the Henry's law constant of 0.461 Pa m^3/mol it is not expected to significantly volatilize from the aquatic compartment and adsorption is not expected to be significant due to its high water solubility and low octanol-water partition coefficient. A distribution calculation performed with the Mackay level III model predicts that the air is the target environmental compartment for methanol. After

rapid hydrolysis in water the relevant organic reaction product, methanol is readily biodegradable (76 – 82 % BOD removal after 5 days). As sodium and potassium methanolate react with water under formation of sodium or potassium hydroxide and methanol, an octanol-water partition coefficient cannot be experimentally established and bioaccumulation of the substances themselves is unlikely. Methanol will be the species that distributes into the octanol phase or could be taken up by organisms. For methanol the log K_{ow} was –0,74 indicating a low bioaccumulation potential. This was confirmed by experimental BCF-values below 10 that have been determined in different fish species.

The toxicity of sodium and potassium methanolate to aquatic organisms is mediated by their degradation products due to the rapid reaction with water yielding sodium or potassium hydroxide and methanol. The aquatic toxicity of methanol is low with acute EC_{50} or LC_{50} values $> 10\,000$ mg/l and therefore its contribution to the methanolate toxicity is considered negligible. The limited data available for sodium methanolate are consistent with the aquatic toxicity of the alkali hydroxides. For sodium methanolate the acute toxicity to fish (48-h LC_{50}) for *Leuciscus idus melanotus* was 346 mg/l (equivalent to 256 mg/l of sodium hydroxide). The corresponding 48-h LC_{50} value for sodium hydroxide was 189 mg/l the 96-h LC_{50} for *Gambusia officinalis* was 125 mg/l for sodium hydroxide and 80 mg/l for potassium hydroxide. For invertebrates a 48-h LC_{50} value of 40 mg/l (*Ceriodaphnia dubia*) and toxicity threshold concentrations (TTC) between 40 and 240 mg/l (*Daphnia magna*) were reported for sodium hydroxide. Lethal concentrations to molluscs of sodium hydroxide ranged between 150 mg/l (*Bulinus truncatus*, *Lymnea caillaudi*) and 450 mg/l (*Biomphalaria a. alexandria*), the 48-h LC_{50} values for *Ophryotrocha* (marine polychaete) were between 33 and 100 mg/l. The 24-h EC_{50} for algae (assimilation inhibition) was 302 mg/l for sodium methanolate. However, as concluded for sodium and potassium hydroxide already, acute toxicity data cannot be used to derive a PNEC or a $PNEC_{added}$ for the compounds releasing hydroxide. Aquatic ecosystems are characterized by an alkalinity/pH and the organisms of the ecosystems are adapted to these specific natural conditions. Based on the natural alkalinity of waters, organisms will have different optimum pH conditions, ranging from poorly buffered waters with a pH of 6 or less to very hard waters with pH values up to 9. A lot of information is available about the relationship between pH and ecosystem structure and also natural variations in the pH of aquatic ecosystems have been quantified and reported extensively in ecological publications and handbooks.

Normally a PNEC or a $PNEC_{added}$ has to be derived from available ecotoxicity data. A $PNEC_{added}$ is a PNEC which is based on the added concentrations of a chemical (added risk approach). Based on the available data it is not considered useful to derive a PNEC or $PNEC_{added}$ for the sodium and potassium methanolate as their effect is based on hydroxide ions or a pH change. The natural pH of aquatic ecosystems can vary significantly and the sensitivity of aquatic ecosystems to a change of the pH can vary significantly between aquatic ecosystems. The change in pH due to anthropogenic OH⁻ addition through methanolate releases is influenced significantly by the buffer capacity of the exposed ecosystem.

Although a PNEC or $PNEC_{added}$ was not calculated, there is a need to assess the environmental effect of an OH⁻ release through sodium or potassium methanolate release into the environment. Based on the pH and the buffer capacity of the effluent and receiving water and the dilution factor of the effluent, the pH of the receiving water after discharge can be calculated or its pH can be measured. The change in pH should be compared with the natural variation in pH of the receiving water. Based on this comparison it should be assessed if the pH change is acceptable.

To illustrate the procedure and to get an idea about the order of magnitude for a maximum anthropogenic addition, the maximum methanolate concentration will be calculated for 2 representative cases. According to Dir. 78/659/EEC, the pH of surface water for the protection of fish should be between 6 and 9. The 10th percentile and the 90th percentile of the bicarbonate concentration of 77 rivers of the world were 20 and 195 mg/l respectively. If it is assumed that only bicarbonate is responsible for the buffer capacity of the ecosystem and that an increase of pH to a value of 9 would be the maximum accepted value, then the maximum anthropogenic addition of sodium methanolate would be 1.4 mg/l and 8.2 mg/l (corresponding to 1.0 and 6.1 mg NaOH/l) and for potassium methanolate 1.1 mg/l and 10.4 mg/l (corresponding to 0.86 and 8.3 mg KOH/l) for bicarbonate concentrations of 20 and 195 mg/l respectively.

Sodium methanolate was moderately toxic to bacteria with a 24-hour EC_{50} of 97 mg/l. The toxicity is likely mediated through a pH effect by the release of hydroxide ions.

There is only one study with potassium hydroxide available indicating a low level of terrestrial toxicity (90-day EC_{50} in *Enchytraeus sp.* ($> 95\%$ *Cogentia sphagnetorium*) of 850 mg/l (artificial soil)). The terrestrial toxicity will depend on the buffer capacity of the soil.

Exposure

European production volumes for sodium and potassium methanolate are above 1000 metric tonnes per year. The US-volume of sodium methanolate reported to US-EPA in 2002 by all US manufacturers and importers was

between 4500 and 23 000 metric tonnes on a dry weight basis. Sodium and potassium methanolate are widely used in the chemical industry as intermediates, for example for the production of formic acid or the transesterification of fatty acid esters. One other major use is in biodiesel production as transesterification catalysts. Because of the predominant production and use in chemical industry under controlled conditions, environmental exposure from production and use is considered low. Furthermore due to the sensitivity of the substances to moisture it is unlikely that the products themselves enter the environment during production and use as they are immediately hydrolyzed to methanol and sodium or potassium hydroxide. Theoretically, the environment could be exposed to residues of the catalysts in consumer products. However, given the sensitivity of methanolates to moisture it is likely that any residual levels would rapidly hydrolyze under formation of methanol and sodium and potassium hydroxide.

In production and uses in chemical industry for which descriptions are available, from the process description very low occupational exposure is anticipated. As the majority of the products are used as intermediates in the chemical industry a controlled exposure situation is anticipated.

There is no information on possible consumer exposure for potassium methanolate. The only information available on sodium methanolate is from the Nordic Product Register of 2003, where consumer products are listed for Norway and Sweden (no details available on use or use concentrations). Theoretically, consumers could be exposed to residues of the catalysts in consumer products. However, given the sensitivity of methanolates to moisture it is likely that any residual levels would rapidly hydrolyze under formation of methanol and sodium and potassium hydroxide. Both products are listed in the Inventory of Processing Aids for food as catalysts for interesterified food oils of the Codex Alimentarius with residual levels below 1 mg/kg.

Sodium methanolate is contained in Nordic Product Registers for 2003: In Finland, 7 preparations for manufacture of chemicals and chemical products with a tonnage of 228 tonnes but no consumer products are listed. In Norway, 152 products with a total tonnage of 33.0 tonnes are listed, 6 of which are consumer products with a tonnage of 0.1 tonnes. Industrial uses listed in Norway are manufacture of chemicals and chemical products with a tonnage of 32.9 tonnes,. In Sweden, 6 preparations with a tonnage of 51.0 tonnes are listed with information on industrial use from 2001 (4 preparation with a tonnage of 51.0 tonnes for process regulators), and 2 preparations are consumer preparations in which sodium methanolate is not added intentionally. Potassium methanolate is listed in Nordic Product Registers for Norway and Finland in 2003, but all data are confidential. However, given the sensitivity of methanolates to moisture it is likely that any residual levels would rapidly hydrolyze under formation of methanol and sodium and potassium hydroxide.

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. The human health hazard is characterized by the rapid and exothermic degradation of the chemicals to methanol and the corresponding alkali hydroxides with known corrosivity. Based on data presented by the Sponsor country, exposure is well controlled in occupational settings, and exposure of consumers is negligible. Countries may wish to investigate exposure scenarios with potential human exposure.

Environment: The chemicals in this category are currently of low priority for further work due to their rapid degradation in the environment via hydrolysis. The reaction products (methanol, potassium hydroxide and sodium hydroxide) have been evaluated within the OECD SIDS program for their hazardous properties and have been considered of low priority for further work for the environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	68526-84-1	Alcohols C8-C10-iso, C9 rich
	27458-94-2	Isononyl alcohol
	68526-85-2	Alcohols C9-C11-iso, C10 rich
	25339-17-7	Isodecyl alcohol
	10042-59-8	2-Propylheptan-1-ol
	68526-86-3	Alcohols C11-C14-iso, C13 rich
	27458-92-0	Isotridecan-1-ol
Chemical Category Name	Oxo Alcohols C9 to C13	
Structural Formula	68526-84-1	CH ₃ -CH(CH ₃)-(CH ₂) ₆ -OH (based on a C9 alcohol; general structure; contains essentially methyl branching patterns)
	27458-94-2	CH ₃ -CH(CH ₃)-(CH ₂) ₆ -OH (general structure; contains various methyl and/or ethyl branching patterns)
	68526-85-2	CH ₃ -CH(CH ₃)-(CH ₂) ₇ -OH (based on a C10 alcohol; general structure; contains various methyl branching patterns)
	25339-17-7	CH ₃ -CH(CH ₃)-(CH ₂) ₇ -OH (general structure; contains various methyl branching patterns)
	10042-59-8	CH ₃ -(CH ₂) ₄ -CH(CH ₂ -CH ₂ -CH ₃)-CH ₂ -OH (based on a C10 alcohol general structure; may also contain methyl branching)
	68526-86-3	CH ₃ -CH(CH ₃)-(CH ₂) ₁₀ -OH (based on a C13 alcohol; general structure; contains various methyl branching patterns)
	27458-92-0	CH ₃ -CH(CH ₃)-(CH ₂) ₁₀ -OH (general structure; contains various methyl and/or ethyl branching patterns)

SUMMARY CONCLUSIONS OF THE SIAR**Category Justification**

The Oxo Alcohols C9 to C13 Category is a family of saturated alcohols that are produced from olefins by the hydroformylation or "oxo" process. Hydroformylation is the reaction of an olefin with carbon monoxide and hydrogen to produce an aldehyde, and its subsequent hydrogenation to the alcohol. The number of carbon atoms in the category members ranges from 9 to 13. Category members contain predominantly branched alkyl groups. Each member is a multi-isomeric product, containing saturated primary alcohols of high purity, and having the following basic structure: CH₃-R-CH₂-OH, where R is a branched isomeric structure.

The justification for the Oxo Alcohols C9 to C13 Category is that the members have:

- similar chemical structures,
- similar physico-chemical properties,
- comparable environmental fate,
- the same mode of action.

In general, acute aquatic toxicity of aliphatic alcohols occurs by non-polar narcosis. The mode of action is disruption of biological membrane function. Mammalian metabolic pathways for both linear and branched n-primary alcohols are likely to include similar reactions for all category members and result in structurally similar metabolites.

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The data demonstrate that the category is valid for the SIDS endpoints, and read across was applied where no data were available.

Analogue substances which have similar structure and properties of sufficient similarity are of value in supporting selected endpoints of the Category members. They are Alcohols, C7-11-branched and linear (CAS RN: 85566-14-9 - R length (C number) and structure: C7 to C11 Linear), Nonan-1-ol (CAS RN: 143-08-8; 28473-21-4 - R length (C number) and structure: C9 Linear) and Dodecan-1-ol (CAS RN: 112-53-8 - R length (C number) and structure: C12 Linear). As the analogues are not produced by consortium members, they are not included in this category.

Human Health

Linear and branched chain alcohols exhibit similar patterns of absorption, metabolism, and excretion. Both linear and branched aliphatic alcohols are absorbed through the gastrointestinal tract and are rapidly eliminated from the blood. Plasmatic half-lives are normally difficult to measure since many of the low molecular weight metabolites (e.g. aldehydes, carboxylic acids) are endogenous in humans. Linear and branched chain alcohols are initially oxidized to their corresponding aldehydes and further to their corresponding carboxylic acids by high capacity NAD⁺/NADH-dependent enzymes, which are then metabolized to carbon dioxide via the fatty acid pathways and the tricarboxylic acid cycle. Alcohol dehydrogenase (ADH) enzymes are the cytosolic enzymes that are primarily responsible for the oxidation of alcohols to their corresponding aldehydes. Alcohols also can be oxidized to aldehydes by non-ADH enzymes present in the microsomes and peroxisomes, but these are generally quantitatively less important than ADH. Aldehyde dehydrogenases (ALDH) oxidize aldehydes to their corresponding carboxylic acids. Branched-chain aliphatic alcohols and aldehydes have been shown to be excellent substrates for ADH and ALDH. As carbon chain length increases, the rates of ALDH-mediated oxidation also increase. The metabolism of branched-chain alcohols, aldehydes, and carboxylic acids containing one or more methyl substituents is determined primarily by the position of the methyl group on the branched-chain. Higher molecular weight homologues (> C10), may also undergo a combination of ω -, ω -1 and β -oxidation, and selective dehydrogenation and hydration to yield polar metabolites which are excreted as the glucuronic acid or sulfate conjugates in the urine and, to a lesser extent, in the feces. Thus, the principal metabolic pathways utilized for detoxification of these branched-chain substances are determined primarily by four structural characteristics: carbon chain length, and the position, number, and size of alkyl substituents. Most of the substances in the Oxo Alcohols C9 to C13 category are mixed branched-chain alcohols. Based on the similar metabolism of linear and branched-chain alcohols within this carbon number range, it can be concluded that the members of the Oxo Alcohols C9 to C13 category will undergo metabolism similar to those of the analogue linear substances mentioned above. No pharmacokinetic study was conducted on members of the category.

Members of the Oxo Alcohols C9 to C13 Category have a low order of toxicity by the oral, dermal, inhalation and intraperitoneal routes of exposure. Oral LD₅₀s ranged from > 2000 to 5400 mg/kg bw and dermal LD₅₀s ranged from > 2600 to 5010 mg/kg bw. Inhalation exposure studies conducted at saturated vapor pressures generally produced no deaths. Although the lighter C9 alcohols were an exception, the resulting LC₅₀ was in excess of 3600 ppm. Members of the Oxo Alcohols C9 to C13 Category were moderately irritating to the skin of rabbits and generally irritating (range: non-irritating to severely irritating) to the eyes of rabbits. Additionally, the alcohols C9-C11-iso, C10 rich (CAS RN 68526-85-2) produced moderate upper airway sensory irritation in male mice exposed to vapor atmospheres up to the achievable limit. Based on limited data, there is no indication of skin sensitizing potential for the Oxo Alcohols C9 to C13 Category. No data are available to assess the potential for respiratory tract sensitisation in animals or humans.

Only one category member, 2-propylheptanol, was tested in a subchronic toxicity study. The 90-day study in rats showed the liver to be the main target organ, and resulted in a NOAEL of 150 mg/kg bw/day in males and 30 mg/kg bw/day in females (only one female showed peroxisome proliferation related effects). In 14-day screening studies in rats designed to evaluate the liver and testes, iso-nonanol, iso-decanol, and isotridecanol produced minimal or no effects on the liver, and no testicular effects at doses of 144, 168 and 184 mg/kg bw/day, respectively. The available data suggest that the members of the Oxo Alcohols C9 to C13 Category are likely to demonstrate a low order of subchronic toxicity.

Studies carried out on four members of the Oxo Alcohols C9 to C13 Category in accordance with OECD TG 471, using *Salmonella typhimurium* as well as *Escherichia coli* did not show genotoxic effects, either with or without metabolic activation. One category member, isodecanol, was also tested in an *in vitro* chromosomal aberration assay according to OECD TG 473, using V79 Chinese hamster lung fibroblasts, and no mutagenic effects were found with or without metabolic activation. *In vivo* assays were conducted with two category members and did not show genotoxic effects, although only limited experimental details were available. Additionally, an *in vivo* mouse

micronucleus assay was carried out with the analogue linear alcohol (1-dodecanol) and found no clastogenicity. Based on the lack of effects found in the limited studies available and based on data for similar linear alcohols used as analogues, the members of the Oxo Alcohols C9 to C13 Category are considered to have a low genotoxic potential. No chronic toxicity or carcinogenicity studies have been conducted on Oxo Alcohols C9 to C13 Category members. Based on the negative *in vitro* and *in vivo* genotoxicity data, and the absence of any structural alerts, members of the Oxo Alcohol C9 to C13 Category are unlikely to possess genotoxic carcinogenic potential.

Developmental toxicity studies conducted by the oral route on isononyl alcohols, isodecanol, 2-propylheptanol and isotridecanol demonstrated that these materials do not affect reproductive parameters. Although a slight increase in resorptions was observed in several of the studies, this only occurred in the highest dose group(s) and in the presence of overt maternal toxicity. NOAELs for developmental toxicity ranged from 144-1440 mg/kg bw/day. As supporting information, testing of 1-dodecanol in a combined repeated dose developmental /reproductive study showed no effects to parents or offspring at levels up to 2000 mg/kg bw/day. Furthermore, inhalation exposure to vapors, at levels of 150 and 100 mg/m³ of respectively 1-nonanol and 1-decanol, did not induce any statistically significant changes in reproductive parameters. In the 14-day repeat dose studies of isononanol, isodecanol and isotridecanol, no changes in testicular weight were observed. These data support the conclusion that members of the Oxo Alcohols C9 to C13 category are not selective reproductive toxicants.

Environment

Members of the Oxo Alcohols C9 to C13 Category are liquid at 25°C. Most of their physico-chemical properties were obtained by direct measurement. Values that could not be measured were obtained via calculation using chemical structures that best characterize the range of constituent chemicals. The category members demonstrated relatively similar properties or progressive change across a range of values with melting point ranging from -117°C to -40°C, boiling point ranging from 202°C to 270°C (at 1,013 hPa), density ranging from 0.832g/cm³ to 0.846 g/cm³, vapour pressure ranging from 0.002 to 0.054 hPa at 25°C, water solubility values ranging from 2 mg/l to 240 mg/l, and log K_{ow} values cited as greater than 3.4 and ranging up to 5.5. Henry's Law Constant (HLC), a measure of the potential of a molecule to evaporate from open water, indicates that the category members will not volatilize at an appreciable rate, if released to water (HLCs range from 3.61 to 20.0 Pa.m³/mol).

Results of the environmental distribution model, using a level III fugacity model, suggest a high environmental distribution into the water compartment for alcohols C8-C10-iso, C9 rich, isononanol, isodecyl alcohol, and 2-propyl heptan-1-ol. The model also predicts a high environmental distribution into the sediment compartment for alcohols C11-C14-iso, C13 rich and isotridecanol. Volatilization to the air from aqueous and terrestrial habitats will be negligible because Oxo Alcohols C9 to C13 have low vapor pressure (<0.06 hPa at 25° C). However, in the air, these substances have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals (*OH) with a calculated degradation half-life ranging from approximately 6 to 9 hours (based on 12-hour day) and 18 to 33.6 hours (based on a 24-hour day). Although, Oxo Alcohols C9 to C13 have the potential to degrade at a significant rate in the atmosphere, it is unlikely that degradation in this compartment will occur to an appreciable extent because they have a low potential to partition to this compartment. Aqueous photolysis and hydrolysis will not contribute to the transformation of the Oxo Alcohols C9 to C13 in aquatic environments because they are not susceptible to these reactions.

Biodegradability of the Oxo Alcohols C9 to C13 Category members has been evaluated with standard test guidelines. The results from these studies suggest that the members of the Oxo Alcohols C9 to C13 Category are subject to microbial degradation in the aquatic environment under both aerobic and anaerobic conditions with biodegradation potentials of 60.6% to 90-100% in 28 days, and that they are either readily or inherently biodegradable. The inherently biodegradable materials, although exceeding the criteria of 60% biodegradation in 28 days, did not do so within the 10-day window necessary for a "readily biodegradable" designation. Therefore the predominant mechanism accounting for removal in a wastewater treatment facility is biodegradation, followed by partitioning to sludge, with volatilization accounting for the remaining loss.

Member substances of the Oxo Alcohols C9 to C13 Category have been shown to exhibit moderate to high acute aquatic toxicity, in various organisms covering the three trophic levels. Experimental acute toxicity values for fish and invertebrates range from 0.42 to 11 mg/L, and 0.39 to 17.1 mg/L, respectively. For algae, the experimental 72-hr EC₅₀ range from 1.6 to 19.0 mg/L. Despite some variability, the acute aquatic toxicity data clearly shows that as carbon number increases from a C9 to a C13, toxicity increases as is expected for non-polar narcotics. Experimental chronic toxicity data for category members are not available. Chronic toxicity data for an analogue substance (dodecanol) indicate a low potential to produce chronic toxicity to aquatic invertebrates. The 21-day

NOEL for a daphnid was 1 mg/L. Calculated chronic toxicity values range from 0.03 to 11.1 mg/L for the three trophic levels.

Category members have a low potential to bioaccumulate in aquatic species based on biochemical evidence of biotransformation and on experimentally derived bioconcentration factors (BCF) in fish in the range of 15 to 60.

In the terrestrial environment, category members are expected to exhibit a low order of toxicity based on calculated 16-day earthworm LC₅₀ values ranging from 128 to 374 mg/kg soil.

Exposure

Oxo Alcohols C9 to C13 Category substances are primarily used as chemical intermediates and additional applications can include uses such as co-solvents, anti-foaming agents, solvent extraction and flotation. Based on physical properties, the primary workplace exposure would be through inhalation and dermal contact. The majority of the applications do not contain free alcohols; therefore, minimal consumer exposure is foreseen, since the consumer is only indirectly exposed through the use of the applications and uptake is expected to be low. The SPIN database contains confidential data for category members, alcohols, C8-C10-iso, C9 rich, isononyl alcohol, and 2-propylheptanol. No consumer products are listed for isodecanol, isotridecanol, or alcohols, C11-C14-iso, C13 rich. For alcohols, C9-C11-iso, C10 rich 22 preparations are listed in Sweden and Denmark at 1.1 to 2.0 tonnes/ annum, including consumer products in Sweden used for lubricants and additives. Alcohols, C11-C14-iso, C13 rich is listed for approximately 80 preparations with tonnes/annum of 459, 8, 0.1, and 6.7 in Sweden, Norway, Finland and Denmark, respectively. Intended uses of the preparations include paints, lacquers, varnishes, construction applications, surface-active agents in cleaners, and intermediates in the manufacture of non-metallic mineral products. Isotridecanol has 18 products and 36 preparations listed with levels at or below 1.3 tonnes/ annum in Sweden, Norway and Denmark. These preparations and products have intended uses in paints, lacquers, and varnishes and primarily in the manufacture of textiles and also in the automobile sector. At least four uses listed are for antifoaming agents. Of the 36 preparations listed for isotridecanol, at least 21 list a zero tonnage (*i.e.*, not intentionally added to the preparation). European production capacities (in 2003) for category members are of 200000-500000 t/year.

At production sites, potential exposure to Oxo Alcohols C9 to C13 in the environment is low because there are no direct releases to the environment. There was no information on environmental concentrations for substances in the Oxo Alcohols C9 to C13 Category. Essentially, Oxo Alcohols C9 to C13 released during manufacture enter the wastewater treatment facility (WWTF) where they can be biodegraded rapidly or sorbed to sewage sludge, which in Europe is mainly incinerated and in the United States is either incinerated or landfilled. The latter severely hinders their further migration because oxo alcohols have a low potential to migrate through soil as suggested by their K_{oc} values. Process, storage, and handling operations are conducted in enclosed facilities. Over-spills are collected and treated (via WWTF), and air from production plants and pumping stations is collected and incinerated.

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

Human Health: The chemicals in the Oxo Alcohols C9 to C13 Category are of low priority for further work. They possess properties indicating a low hazard for human health, except for eye and skin irritation. These hazards do not warrant further work as they are related to reversible effects. They should nevertheless be noted by chemical safety professionals and users. Countries are invited to perform an exposure assessment for workers and consumers and if necessary a risk assessment.

Environment: The chemicals with chain lengths of C9 and C10 (CAS No 68526-84-1, 27458-94-2, 68526-85-2, 25339-17-7, 10042-59-8) have properties indicating a hazard for the environment (acute aquatic EC/LC₅₀ values between 1 and 100 mg/l). However they are of low priority for further work for the environment because of their rapid biodegradation and their limited potential for bioaccumulation.

The chemicals with chain lengths of C13 (CAS No 68526-86-3, 27458-92-0) show acute aquatic effects at concentrations below 1 mg/l. Therefore, they should be candidates for further work. Furthermore, member countries are invited to perform an exposure assessment and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	_____
Chemical Name	Primary Amyl Acetate-Mixed Isomers (commercial reaction process-derived mixture of approximately 65% 1-pentyl acetate (CAS No 628-63-7) and 35% 2-methyl-1-butyl acetate (CAS No 624-41-9))
Structural Formula	CH ₃ -CH ₂ -CH ₂ -CH ₂ -COO-CH ₃ (1-pentyl acetate) CH ₃ -CH ₂ -CH(CH ₃)-COO-CH ₃ (2-methyl-1-butyl acetate)

SUMMARY CONCLUSIONS OF THE SIAR

Data are presented for Primary Amyl Acetate, which is the reaction process derived mixture of two isomers (1-pentyl acetate, CAS No 628-63-7 and 2-methyl-1-butyl acetate, CAS No 624-41-9) as well as individually for 1-pentyl acetate, the major component of Primary Amyl Acetate. Based on structural similarity with 1-pentyl acetate, toxicity data for 1-propyl acetate (CAS109-60-4) and 1-butyl acetate (123-86-4) were used to support the assessment of acute fish toxicity of Primary Amyl Acetate.

Human Health

Primary Amyl Acetate has an acute oral LD₅₀ value of 12,306 mg/kg bw for female rats and >14,064 mg/kg bw for male rats. The dermal LD₅₀ in male rabbits was 8359 mg/kg bw, and >14,080 mg/kg bw in females. Rats exposed for 6 hours to substantially saturated Primary Amyl Acetate vapor exhibited difficulty breathing; mortality was 20% among males exposed to 3693 ppm (19,646 mg/m³) and 0% among females exposed to 3628 ppm (19,3000 mg/m³). Primary Amyl Acetate causes moderate skin and eye irritation. Signs of respiratory irritation were noted in rats exposed to 3620 ppm (19,284 mg/m³) Primary Amyl Acetate vapor. Human sensitization test data for Primary Amyl Acetate indicate that it does not induce dermal sensitization; negative results were also obtained in a human photoallergy test.

Information on repeated inhalation exposure is available in rats. Male and female rats were exposed by inhalation to 0, 100, 300, or 500 ppm (0, 532, 1596, 2660 mg/m³) for 14 weeks displayed no clinical signs of toxicity and no mortality. All exposed males exhibited a very slight decrease in body weight gain relative to control males. The NOAEC for males and females was 500 ppm (2660 mg/m³). In a 13-week inhalation neurotoxicity study, male and female rats were exposed to 0, 300, 600, or 1200 ppm (0, 1596, 3192, 6384 mg/m³) Primary Amyl Acetate vapor. No mortality and no signs of toxicity were observed in any group. There were no neurobehavioral effects observed using motor activity measurements, functional observation battery testing, or neuropathological examinations. The NOAEC for neurotoxicity was 1200 ppm (6384 mg/m³). There were no abnormalities observed in male and female rats fed Primary Amyl Acetate in their diet at concentrations of 0, 0.1, 0.5, or 1.0% for 90 days; doses in males were equivalent to 0, 68, 320, or 650 mg/kg bw/day; female doses were 0, 74, 350, and 720 mg/kg bw/day. The NOAEC for this study was 1% Primary Amyl Acetate in the diet, or based on the quantity of diet consumed, 650 and 720 mg/kg bw/day in males and females, respectively.

Primary Amyl Acetate has been tested *in vitro* in bacterial as well as animal cell cultures and is not genotoxic in these test systems both in the presence and absence of metabolic activation. Primary Amyl Acetate was negative when tested in a GLP chromosomal aberration assay in rat lymphocytes.

There were no significant effects observed on relative reproductive organ weights, and reproductive organs and tissues were normal in male and female rats exposed for 14 weeks to Primary Amyl Acetate vapor at concentrations up to 500 ppm (2660 mg/m³). There were no effects observed on male and female reproductive organs and tissues in rats fed up to 1% Primary Amyl Acetate in the diet for 90 days.

In two developmental toxicity studies, pregnant female rats and rabbits were exposed to Primary Amyl Acetate vapor at concentrations of 0, 500, 1000, and 1500 ppm (0, 2660, 5320, 7980 mg/m³) for 6 hours per day during organogenesis. Maternal toxicity was observed in rabbits at 1500 ppm (7980 mg/m³) and in rats at all dose levels

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as reduced food consumption and decreased maternal body weight gain. The decrease in corrected body weight gain during gestation in rats was significant at 1000 and 1500 ppm (5320 and 7980 mg/m³). The NOAEC for maternal toxicity in rabbits and rats was 1000 and 500 ppm (5320 and 2660 mg/m³), respectively. Among rabbits exposed between gestation day 6 and 18, no fetal malformations were observed and there was no evidence of developmental toxicity at any exposure level. Among rats exposed between gestation day 6 and 15, no fetal malformations were observed and overall incidence of variations was not increased. Female fetal body weights were reduced at 1000 and 1500 ppm. These fetal body weight decreases were accompanied by increases in one or three skeletal variations, at 1000 and 1500 ppm, respectively as well as two additional variations (one external and one visceral) at 1500 ppm. The NOAEC for developmental toxicity in rabbits and rats was 1500 and 500 ppm (5320 and 2660 mg/m³), respectively.

Environment

The available physicochemical data are adequate to describe the properties of Primary Amyl Acetate. Primary Amyl Acetate has a vapour pressure of 5.73 hPa at 25°C, and a water solubility of 1700 mg/L at 25 °C. It has a boiling point of 146 °C, a measured Log K_{ow} of 2.42, and an estimated melting point of -94°C. The vapor pressure of its major component, 1-pentyl acetate, is 4.67 hPa at 25°C and its aqueous solubility is 2,000 mg/L at 20°C. The vapor pressure and aqueous solubility of the second component, 2-methyl butyl acetate were calculated by EPIWIN to be 8.46 hPa and 1,070 mg/L, respectively. The preferred log K_{ow} values of 1-pentyl acetate and 2-methyl butyl acetate are 2.34 and 2.26, respectively.

The photochemical removal of 1-pentyl acetate, as mediated by hydroxyl radicals, occurs with a calculated half-life of 34 to 43 hours. Photochemical removal of 2-methyl butyl acetate was calculated to be 41 hours. Primary amyl acetate is biodegradable under aerobic conditions. Primary Amyl Acetate is anticipated to volatilise easily from moving rivers, but only moderately from quiescent lakes and other surface water bodies; the calculated volatilisation half-life for Primary Amyl Acetate is between 3.4 hours from a river and 5.5 days (132 hours) from a lake. Primary Amyl Acetate is not likely to bioaccumulate in food webs. Based on Level III distribution modelling for 1-pentyl acetate, it is estimated that the majority of Primary Amyl Acetate released to the environment will partition into water (26.7%) and soil (66.3%), with a smaller amount in air (6.8%). The stability of primary amyl acetate in water is pH dependent. The predicted half-lives of Primary Amyl Acetate at 25 °C at pH 4, 7, and 9 are 84.8, 138, and 21.9 days, respectively.

Primary Amyl Acetate exhibits low to moderate toxicity to fish, aquatic invertebrates and algae. Primary Amyl Acetate exhibited a 96-hr LC₅₀ in fish of 69 mg/L. In *Daphnia magna*, the 48-hr EC₅₀ was 40.9 mg/L. Finally, in green algae (*Pseudokirchneriella subcapitata*), Primary Amyl Acetate exhibited a 72-hr EC₅₀ of >466 mg/L (growth rate) and a 72-hr EC₅₀ (biomass) of 156 mg/L. Terrestrial data are not available for Primary Amyl Acetate or its components.

Exposure

Global production of Primary Amyl Acetate was estimated to be less than 10,000 tonnes in 2002. Consumption in 2002 was estimated to be 4,000 tonnes in the US, and 5,300 tonnes in Western Europe. In the United States, Primary Amyl Acetate is manufactured by one company in a continuous process in a closed system using engineering controls, which prevent the escape of liquid or vapors and minimizes release to the environment. Engineering controls are utilized during production, transfer, and loading operations to minimize exposure. The sole manufacturer of Primary Amyl Acetate in the U.S. does not isolate or market 1-pentyl acetate or 2-methyl-1-butyl acetate.

The predominant use of Primary Amyl Acetate is as a direct solvent component in the manufacture of OEM (original equipment manufacturers) factory-applied automotive paints and clearcoats. It is also used as a starting material and process solvent/extractant in the manufacture of pharmaceuticals. Primary Amyl Acetate may be present in cosmetics as a fragrance enhancer at ppm concentrations. The components of Primary Amyl Acetate have been identified in fruit and as naturally-occurring volatiles in cooked food.

Although its individual components may occur naturally in low concentrations in foods, Primary Amyl Acetate does not appear intentionally in food products, and is not approved as a direct or indirect food additive. It is a flammable liquid with a flammable range of 1.1 to 7.5 volume % in air (11,000 – 75,000 ppm) and a flash point of 37°C (99°F). The occupational exposure limit (ACGIH 8-hr TWA) for the components of Primary Amyl Acetate is 50 ppm.

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The general population may be exposed to Primary Amyl Acetate as a fugitive emission. The individual components of Primary Amyl Acetate may also be released from food products, landfills, and sewage.

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

The following recommendations are applicable only to Primary Amyl Acetate-Mixed Isomers (reaction process-derived product) and not to its individual components.

Human Health: The product is currently a low priority for further work. The product possesses properties indicating a hazard for human health (skin, eye and respiratory tract irritation, and potential developmental toxicity). Based on data provided by the sponsor country (relating to production by one producer in the United States which account for an unknown fraction of the global production and relating to the use pattern primarily in the United States), risk management measures are being applied (engineering controls, occupational standards, Material Safety Data Sheets) in occupational settings. Countries may desire to check their own risk management measures for this product to find out whether there is need for additional measures.

Environment: The chemical has properties indicating a hazard for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However the product is of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	_____
Chemical Name	Primary Amyl Alcohol-Mixed Isomers (commercial reaction process-derived mixture of approximately 65% 1-pentyl alcohol (CAS No 71-41-0) and 35% 2-methyl-1-butyl alcohol (CAS No 137-32-6))
Structural Formula	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -OH (1-pentyl alcohol) CH ₃ -CH ₂ -CH(CH ₃)-CH ₂ -OH (2-methyl-1-butyl alcohol)

SUMMARY CONCLUSIONS OF THE SIAR**Analog Justification**

Data are presented for Primary Amyl Alcohol, which is the reaction process derived mixture of two isomers (1-pentyl alcohol, CAS No 71-41-0 and 2-methyl-1-butyl alcohol, CAS No 137-32-6). Data from Primary Amyl Acetate toxicity studies have been included in the assessment of Primary Amyl Alcohol. Data from Primary Amyl Acetate are useful when assessing the hazards associated with the systemic toxicity of Primary Amyl Alcohol exposure due to the hydrolysis of Primary Amyl Acetate to Primary Amyl Alcohol *in vivo*. Exposure to Primary Amyl Acetate via inhalation exposure results in the appearance of Primary Amyl Alcohol in the systemic circulation. Since exposure to either Primary Amyl Acetate or Primary Amyl Alcohol results in systemic exposure to Primary Amyl Alcohol, systemic toxicity data from studies that administer Primary Amyl Acetate are useful in identifying hazards associated with Primary Amyl Alcohol exposure. Endpoints of Primary Amyl Alcohol toxicity that are associated with direct contact-mediated effects (e.g. eye, skin, and respiratory tract irritation) cannot be extrapolated from Primary Amyl Acetate data due to the difference in physical-chemical properties of the two materials. In addition, data from toxicity studies for 1-pentyl alcohol, the major component of Primary Amyl Alcohol, are included in the assessment for Primary Amyl Alcohol for human health endpoints.

Based on structural similarities and similar toxicities, data for 1-pentyl alcohol and 2-methyl butyl alcohol, the individual components of Primary Amyl Alcohol and for the 4-carbon structural analogs, 1-butyl alcohol (CAS No 71-36-6) and 2-methyl-1-propyl alcohol (CAS No 78-83-1) are also provided to address or augment environmental endpoints.

Human Health

A recent *in vivo* respiratory bioavailability study confirmed the hydrolysis of Primary Amyl Acetate to Primary Amyl Alcohol. Blood levels of the alcohol isomers exceeded those of the acetate ester isomers at every time point tested, demonstrating the hydrolysis of the ester to the corresponding alcohols (1-pentyl alcohol and 2-methyl-1-butyl alcohol). These alcohols were then metabolized to their respective acids, resulting in increased systemic levels of 1-pentanoic acid and 2-methyl butyric acid. Thus, organisms exposed to Primary Amyl Acetate can experience appreciable tissue concentrations of Primary Amyl Alcohol. In this way, the results of toxicity studies with Primary Amyl Acetate can be used as supplemental, surrogate data to provide information on the toxicity of Primary Amyl Alcohol.

The acute oral LD₅₀ value for Primary Amyl Alcohol was 2690 mg/kg bw for male rats and 4989 mg/kg bw for female rats. The dermal LD₅₀ in female rabbits was 4110 mg/kg bw; erythema, desquamation, eschar, and necrosis were observed at the application site. There was 20% mortality among rats exposed to a saturated concentration of Primary Amyl Alcohol vapor (approximately 14,000 mg/m³ or 3900 ppm) for 6 hours. Primary Amyl Alcohol is a corrosive liquid and causes severe skin and eye irritation. It should be considered a respiratory tract irritant. There are no animal or human sensitization test data for Primary Amyl Alcohol or its individual component isomers.

There are no repeated-dose studies available for Primary Amyl Alcohol. In a repeated inhalation exposure study, male and female rats were exposed by inhalation to Primary Amyl Acetate vapor at concentrations of 0, 100, 300, or 500 ppm (0, 532, 1596, or 2660 mg/m³) for 14 weeks; rats displayed no clinical signs of toxicity and no mortality; the NOAEL for males and females was 500 ppm or 2660 mg/m³. A 90-day repeated-dose oral toxicity

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study is available for 1-pentyl alcohol, the major component of Primary Amyl Alcohol. Male and female rats received daily doses of 1-pentyl alcohol in corn oil by oral intubation at doses of 0, 50, 150, 500, or 1000 mg/kg bw/day for 13 weeks. There were no clinical signs of mortality and no lesions or abnormalities were observed. The NOAEL for this study for male and female rats was 1000 mg/kg bw/day.

Primary Amyl Alcohol has been tested *in vitro* in bacterial as well as animal cell cultures. The mixture was negative for mutagenicity in the presence and absence of metabolic activation in both the Ames assay and an HGPRT assay. Primary Amyl Alcohol did not induce an increase in chromosomal aberrations or in sister chromatid exchanges in mammalian cell assays conducted in the presence and absence of metabolic activation.

There are no reproductive toxicity studies available for Primary Amyl Alcohol. Data are available for Primary Amyl Acetate and 1-pentyl alcohol. There were no significant effects observed on relative reproductive organ weights, and reproductive organs and tissues were normal in male and female rats exposed for 14 weeks to Primary Amyl Acetate vapor at concentrations up to 500 ppm or 2660 mg/m³. Similar results were obtained when male and female rats were exposed by oral gavage to 1-pentyl alcohol at doses up to 1000 mg/kg bw/day for 13 weeks.

In two developmental toxicity studies, pregnant female rats and rabbits were exposed to Primary Amyl Acetate vapor at concentrations of 0, 500, 1000, and 1500 ppm (0, 2660, 5320, or 7980 mg/m³) for 6 hours per day during organogenesis. Maternal toxicity was observed in rabbits at 1500 ppm and in rats at all dose levels as reduced food consumption and decreased maternal body weight gain; the decrease in rats was significant at 1000 and 1500 ppm. The NOAEL for maternal toxicity in rabbits and rats was 1000 and 500 ppm (5320 and 2660 mg/m³), respectively. Among rabbits exposed between gestation day 6 and 18, no fetal malformations were observed and there was no evidence of developmental toxicity at any exposure level. Among rats exposed between gestation day 6 and 15, no fetal malformations were observed and the overall incidence of variations was not increased. Female fetal body weights were reduced at 1000 and 1500 ppm. These fetal body weight decreases were accompanied by increases in one or three minor skeletal variations at 1000 and 1500 ppm, respectively, as well as external and visceral variations at 1500 ppm. The NOAEC for developmental toxicity in rabbits and rats was 1500 and 500 ppm (7980 and 2660 mg/m³), respectively. Inhalation of 3900 ppm (14,040 mg/m³) 1-pentyl alcohol vapor throughout gestation (day 1 through 19) produced maternal toxicity and a slight increase in the incidence of delayed ossification in rats, but no fetal malformations. These results suggest that Primary Amyl Alcohol may induce maternal and developmental toxicity at doses that induce maternal toxicity, but will not induce fetal malformations.

Environment

The available physicochemical data available for Primary Amyl Alcohol and its components are adequate to describe the properties of Primary Amyl Alcohol. Primary Amyl Alcohol has a vapor pressure of 3.3 hPa at 20°C and a relative density of 0.816 g/cm³; it has an estimated melting point of -110 °C, a boiling point of 134.46°C, and a log K_{ow} of 1.42. The water solubility of Primary Amyl Alcohol is 23,200 mg/L at 25 °C. Primary Amyl Alcohol is a flammable liquid with a flashpoint of 47°C and a flammable range of 1.2 to 10.0 volume percent.

The physicochemical data available for the components of Primary Amyl Alcohol, 1-pentyl alcohol and 2-methyl butyl alcohol are also adequate to describe the properties of Primary Amyl Alcohol. 1-Pentyl alcohol and 2-methyl butyl alcohol have vapour pressures of 2.93 at 20 °C and 3.4 hPa at 25°C, respectively; the water solubility of 1-pentyl alcohol is 22,000 mg/L at 25°C, the solubility of 2-methyl butyl alcohol is 30,000 mg/L at 25°C; log K_{ow} values for these two materials are 1.51 and 1.29, respectively.

The photochemical removal of 1-pentyl alcohol and 2-methyl butyl alcohol, as mediated by hydroxyl radicals, occurs with calculated half-lives of 30.9 and 29.93 hours, respectively. 1-Pentyl alcohol and 2-methyl butyl alcohol are readily biodegradable under aerobic conditions. Primary Amyl Alcohol volatilises moderately from moving rivers, but less so from quiescent lakes and other surface water bodies (calculated volatilisation half-lives of about 2 days from a river and 24 days from a lake). 1-Pentyl alcohol and 2-methyl butyl alcohol are not persistent in the environment and are not likely to bioaccumulate in food webs. Based on Level III distribution modelling, it is estimated that the majority of Primary Amyl Alcohol released to the environment will partition into water (36.8%) and soil (59.4%), with a smaller amount in air (3.7%).

Aquatic toxicity data are available for Primary Amyl Alcohol as well as its individual isomers, 1-pentyl alcohol and 2-methyl butyl alcohol. Static and flow through tests resulted in 96-hr LC₅₀s for fathead minnows between 472 and 606 mg/L. Since the duration of studies with *D. magna* (24 hours), green algae (8 days) and blue-green algae (8 days) with 1-pentyl alcohol is different than current OECD guidelines and because of uncertainties in study details, data for analogous compounds are presented. The analogous compounds used are 2-methyl-1-propyl alcohol and

1-butyl alcohol. For 2-methyl propyl alcohol, static tests were conducted using three water column-dwelling invertebrate species (*Daphnia magna*, *Daphnia pulex*, *Ceriodaphnia reticulata*) according to ASTM procedures. Forty-eight hour EC₅₀ values between 1100 and 1300 mg/L were reported for these species; for 1-butyl alcohol, a 48-hr EC₅₀ of 1328 mg/L was obtained for *Daphnia magna*. Using 1-butyl alcohol with the green algae *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capricornutum*), a 96-h EC₅₀ of 225 mg/L was reported. Terrestrial data are not available.

Exposure

Global production of Primary Amyl Alcohol was estimated to be approximately 35,000 tonnes in 1997. Consumption in 1997 was estimated to be 15,000 tonnes in the US, and 20,000 tonnes in Western Europe.

The predominant use of Primary Amyl Alcohol in the United States is as a chemical intermediate to provide the alkyl functionality in the lubricating oil additive, zinc diamyldithiophosphate (ZDDP or ZDDTP). Another major use is as an intermediate in the manufacture of Primary Amyl Acetate. Reported minor uses of Primary Amyl Alcohol are as a minor solvent in the manufacture of epoxy-based coatings, and nitrocellulose lacquers for factory-applied wood furniture finishes. It is also used in the manufacture of pharmaceuticals and xanthate ore floatation agents. A database search found no consumer products in the United States that contain Primary Amyl Alcohol. Both components of Primary Amyl Alcohol occur naturally in foods and may be released as plant volatiles. The major component of Primary Amyl Alcohol, 1-pentyl alcohol, is a direct food additive used as a synthetic flavoring agent. Although its individual components are present in very low concentrations in foods, Primary Amyl Alcohol is not approved for use as a direct or indirect food additive.

The occupational exposure limit for 1-pentyl alcohol, the major component of Primary Amyl Alcohol, is 100 ppm. Engineering controls are utilized during production, transfer, and loading operations to minimize flammability hazards and workplace exposure. Workplace exposure to Primary Amyl Alcohol during manufacture and use as industrial intermediate is anticipated to be limited in the US by an occupational exposure limit of 100 ppm.

Primary Amyl Alcohol may be released to the environment as a fugitive emission during production and use, or as naturally occurring emissions from food products, landfills, and sewage.

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

These recommendations are applicable only to Primary Amyl Alcohol-Mixed Isomers (reaction process-derived product) and not to its individual isomers.

Human Health: The product is currently of low priority for further work. The product possesses properties indicating a hazard for human health (skin, eye and respiratory tract irritation, and potential developmental toxicity based on a surrogate compound). Based on data provided by Sponsor country (relating to production by the sole manufacturer as well as two importers in the United States, which accounts for an unknown fraction of the global production, and relating to the use pattern primarily in the United States), risk management measures are being applied during manufacture (engineering controls, occupational standards, and Material Safety Data Sheets). Countries may desire to check their own risk management measures for this product to determine whether there is need for additional control measures.

Environment: The product is currently of low priority for further work due to its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	74499-35-7 [also covers 57427-55-1, 121158-58-5, 210555-94-5 & 27193-86-8]
Chemical Name	Phenol, (tetrapropenyl) derivatives Tetrapropenyl phenol
Structural Formula	HO-C ₆ H ₄ -(C ₁₀ H ₂₁ -C ₁₅ H ₃₁)

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

There are no specific toxicokinetic data for tetrapropenyl phenol. Due to the high lipophilicity and the effects in rat repeated-dose toxicity studies, intestinal absorption and distribution in the body is anticipated. Tetrapropenyl phenol is not acutely toxic, with LD50s of around 2000 and 15000 mg/kg by the oral and dermal routes of exposure, respectively. . Animal data indicate that this substance causes irritation to the eyes and skin, but it is not a skin sensitizer. The genotoxic potential of TPP has been well investigated , in vitro (bacterial gene mutation and MCGM) and in vivo (bone marrow cytogenetics), and gave negative results. Overall, TPP is not a genotoxicant. This substance causes adverse effects on organs and tissues in rats at dose levels that cause reductions in body weight gain. The NOAEL for repeated-dose toxicity in rodents is 5 mg/kg/day, as adrenal cortical hypertrophy was observed at doses of 20 mg/kg/day and above. It is noteworthy that similar changes were not observed in dogs administered up to 4000 ppm in the diet for 13 weeks.

In rats, tetrapropenyl phenol causes a reduction in the fertility of both sexes and a reduction in mean live litter size, in the presence of marked general toxicity, at a dose of 125 mg/kg/day, the highest dose tested. Effects on male and female reproductive organs were noted and some reduction in the growth rate of pups was observed during weaning at 25 mg/kg/day. This substance causes adverse developmental effects in rats (skeletal variations and malformations and external variations) at 300 mg/kg/day, the highest dose tested, but only in the presence of maternal toxicity.

Environment

Tetrapropenyl phenol is a complex mixture of components. It is a liquid with a low water solubility (2.1 mg/L for the bulk material, with a large contribution from lower molecular weight components) and vapour pressure of 9.2×10^{-3} Pa at room temperature. The octanol-water partition coefficient for the main component is high (log K_{ow} 7.14), which suggests a high bioaccumulation potential. An *in vivo* fish study is in progress to clarify this. It adsorbs strongly to laboratory glassware, and the Equilibrium Criterion (EQC Level 1) model indicates that this substance is likely to preferentially bind to the soil in the terrestrial environment and to sediment and suspended particles in the aquatic environment.

Tetrapropenyl phenol does not readily biodegrade, and is not inherently biodegradable. It does not undergo hydrolysis. An atmospheric half-life of 2.294 hours can be calculated based on hydroxyl radical interaction, but the low vapour pressure of this substance and its Henry's Law Constant indicate that partitioning into atmosphere will not be a significant pathway.

Tetrapropenyl phenol is very toxic to *Daphnia* (48-hr EC₅₀ = 0.037 mg/L (nominal)) and algae (72-hr growth rate EC₅₀ = 0.36 mg/L (nominal)). Although a reliable study on the acute toxicity of this substance to fish is lacking, it can be predicted that fish are not expected to be the most sensitive group of aquatic organisms using the ECOSAR Program in EPIWIN for the C12 homologue of tetrapropenyl phenol and bridging data from branched 4-nonylphenol. A 21-day reproduction NOEC of 0.0037 mg/L (nominal) was obtained for *Daphnia*. This substance is 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).

Exposure

Tetrapropenyl phenol is produced in a closed process in France, Germany, Poland, Singapore, the United Kingdom and United States of America. The total global production volume is estimated to be around 115,000 tonnes/year.

Tetrapropenyl phenol is used almost exclusively (>99.7%) as a raw material by the lubricant additives industry to manufacture more chemically complex detergent and inhibitor additives for the oil and lubricants industry. Typical examples of lubricant additives made from tetrapropenyl phenol include alkylphenate sulfide detergents and anti-wear and anti-rust additives. Typical finished gasoline engine oil may contain 390 ppm of residual tetrapropenyl phenol, and typical finished diesel engine oil may contain 1,520 ppm of residual tetrapropenyl phenol. During use of these engine oils, up to 95 % of the residual tetrapropenyl phenol is oxidized.

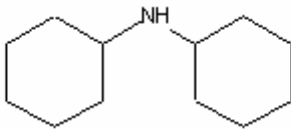
Occupational and consumer exposures to tetrapropenyl phenol are expected to be very low based on their physico-chemical properties, use and handling patterns. Potential releases of tetrapropenyl phenol to the environment may occur following production, use to make lubricant additives, blending lubricant additives into finished oils and use and disposal of used lubricants.

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 potential hazard for human health (effects on fertility and developmental toxicity at doses that also cause maternal toxicity). Member countries are invited to perform an exposure assessment, and if necessary a risk assessment.

Environment: The chemical is a candidate for further work for the environment. The chemical possesses properties indicating a hazard for the environment (high aquatic toxicity, persistence, bioaccumulation potential). Therefore, an exposure assessment and, if then indicated, an environmental risk assessment is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	101-83-7
Chemical Name	Dicyclohexylamine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

According to the available information from animal studies dicyclohexylamine is readily absorbed after oral application and following inhalation and dermal application and is excreted via urine.

The LD₅₀ following dermal application to rabbits ranges between 200 and 316 mg/kg bw and LD₅₀ (oral, rat) is 200 mg/kg bw.

Dicyclohexylamine is corrosive to the skin and has a strong eye irritant potential. There are no studies available to evaluate the possible activity to induce sensitization.

Repeated oral dose toxicity was assessed by a subacute toxicity study (28 days, Japanese Guideline) and in an OECD TG 421 assay in rats. Unspecific signs of intoxication in combination with changes in organ weights (adrenal glands, ovaries, testes) at the highest doses tested without histopathological correlates resulted in NOAELs (general toxicity) of 20 mg/kg bw/day (subacute study) or 40 mg/kg bw/day (OECD TG 421) for rats of both sexes, respectively.

Dicyclohexylamine showed no mutagenic activity in standard Ames test with and without metabolic activation system but induced chromosomal aberrations in Chinese hamster lung (CHL) cells at high concentrations and short exposure time (exposure time: 6 hours (a) with S9-mix: at 600 µg/ml; (b) without S9-mix: at 800 and 1000 µg/ml). Overall, dicyclohexylamine is not mutagenic but clastogenic *in vitro*. There are no valid data on genotoxicity *in vivo*.

There are no valid data on carcinogenicity studies *in vivo*. Using valid *in vitro* cell transformation assays with human cells and baby Syrian hamster cells, dicyclohexylamine yielded negative results.

In an OECD reproduction/developmental toxicity screening test (OECD TG 421) in rats dicyclohexylamine revealed effects on reproduction only in females at the highest oral dose tested (80 mg/kg bw/day) including slightly reduced gestation index, increase in stillborn pups and decrease in live born pups. Thus, the NOAEL (reproductive toxicity) is 80 mg/kg bw/day for males and 40 mg/kg bw/day for females. The NOAEL (offspring) is 40 mg/kg bw/day based on significant reduction in pup weights on day 0 and slight reduction in pup weights on day 4 in offspring of the parents dosed with 80 mg/kg bw/day. These adverse effects on the development of the F1-generation occur only in the presence of severe maternal toxicity (17 % mortality; 1 of 10 surviving dams without live pups; poor maternal behavior and nursing).

Environment

Dicyclohexylamine is a clear, colorless liquid with a melting point of – 0.1 °C, and a boiling point of 256 °C at 1013 hPa. The relative density of the liquid is 0.91 at 25 °C. The vapour pressure is 0.0442 hPa at 25 °C. The calculated log K_{ow} for the neutral and the protonated form are 4.37 and 1.26, respectively. The solubility in water is 0.8 g/l at 25 °C. The flash point is 105 °C, and the auto flammability (ignition temperature) 255 °C. A pK_a value of 10.39 indicates dicyclohexylamine to be a strong base which is mostly in its protonated form in the

natural aquatic environment.

In the atmosphere dicyclohexylamine is degraded by photochemically produced OH radicals. The half-life is calculated to be 2.9 hours. With regard to the chemical structure, dicyclohexylamine is not expected to hydrolyse under environmental conditions. An aerobic ready test was performed according to the national Japanese MITI test, comparable to the OECD TG 301C. After a period of 14 days 77 % biodegradation was observed. In a closed bottle test, comparable to OECD TG 301D performed with predominantly domestic sewage, more than 96 % of the test substance had been degraded after 20 days.

With a pK_a of 10.39 at 25°C, dicyclohexylamine will exist predominantly in its protonated form in the environment. According to the Mackay fugacity model level I, the favorite target compartment of the protonated form of dicyclohexylamine is water with 99.71 %. The Henry's Law constant for the neutral form of dicyclohexylamine, calculated with QSAR is 5.57 Pa m³/mol at 25 °C, prove a high potential for volatilization from surface waters. Regarding the Henry's Law constant for the protonated form of dicyclohexylamine of 4.26×10^{-7} Pa m³/mole, the substance is not expected to volatilize from water. The bioconcentration factor BCF = 459 for the neutral form of dicyclohexylamine calculated from the octanol-water partition coefficient indicates that there is a potential for bioaccumulation of dicyclohexylamine in aquatic organisms. The estimated BCF value of 3.2 for the protonated form indicates that there is no significant bioaccumulation potential of dicyclohexylamine in aquatic organisms. With an estimated K_{oc} value of 433 for the protonated form, dicyclohexylamine can be regarded as a substance with a moderate potential for accumulation in soil.

Concerning the toxicity of dicyclohexylamine to aquatic species reliable experimental results of acute tests with fish, *Daphnia*, and algae are available, and results from chronic tests with invertebrates and algae. The tests were performed according to standard procedures. The effect values from short-term tests are (n = nominal concentration; m = measured concentration):

<i>Danio rerio</i> :	96 h-LC ₅₀	= 62 mg/l (m)
<i>Oryzias latipes</i> :	96 h-LC ₅₀	= 12 mg/l (m)
<i>Daphnia magna</i> :	48 h-EC ₅₀	= 8 mg/l (m)
<i>Daphnia magna</i> :	48 h-EC ₅₀	= 70.1 mg/l (n)
<i>Daphnia magna</i> :	21 d-EC ₅₀	= 0.14 mg/l (m)
<i>Daphnia magna</i> :	21 d-NOEC	= 0.016 mg/l (m)
<i>Pseudokirchneriella subcapitata</i> :	72 h-EC ₅₀ growth rate	= 23 mg/l (m)
<i>Pseudokirchneriella subcapitata</i> :	72 h-NOEC _{growth rate}	= 2.0 mg/l (m)
<i>Desmodesmus subspicatus</i> :	72 h-EC ₅₀ growth rate	> 1 mg/l (n)
<i>Desmodesmus subspicatus</i> :	72 h-NOEC _{growth rate}	= 0.016 mg/l (n)

Since acute test results for dicyclohexylamine for three trophic levels and long-term results (NOEC) for *Daphnia* and *Pseudokirchneriella* are available, and there is convincing evidence that the chronic tests have been done on the most sensitive species, an assessment factor of 10 was applied for the derivation of the PNEC_{acqua} according to the EU Technical Guidance Document. The lowest chronic no effect concentration (NOEC of 0.016 mg/l) was found for the algae species *Desmodesmus subspicatus* and for *Daphnia magna* on reproduction resulting in a PNEC_{acqua} of 1.6 µg/l.

Exposure

The global production volume of dicyclohexylamine is estimated to be less than 10,000 tonnes by approximately 10 producers in 2003. In Germany, the only manufacturer of dicyclohexylamine has a manufacturing capacity of 1,000-5,000 tonnes/a. In Japan, there are 4 production sites with an estimated manufacturing volume of 1,000-5,000 tonnes/a in total.

Dicyclohexylamine is used mainly as an intermediate in chemical processes. It is used as an intermediate in the manufacturing of corrosion inhibitors, insecticides, paper and textile auxiliaries, emulsifiers, oil additives, vulcanization accelerators, plasticizers, and dyestuff precursors. Dicyclohexylamine is also used in the synthesis of pesticides, as a processing chemical for antibiotics, and as a fuel oil additive.

In Germany, the only producer manufactures dicyclohexylamine in closed systems. Virtually no dicyclohexylamine is emitted into the atmosphere or into the aquatic environment.

To protect workers from exposure, several precautionary and protective measures are taken, e.g. during sampling, repair and maintenance. Dicyclohexylamine is not processed in Germany. Traces of dicyclohexylamine were detected in machine cutting-fluid emulsion in Japan. Exposure of workers to

dicyclohexylamine is unlikely to occur. In the Sponsor country (Japan), similar measures are applied to protect the environment and the workers.

Dicyclohexylamine is listed in the Product Registers of Denmark, Finland, and Sweden in a total of 25 industrial preparations with a consumption of 9.1 tonnes in 2003 (last year of record). In Sweden, it is registered to occur in consumer preparations. For Norway there is a confidential listing. In Finland, dicyclohexylamine is used for the manufacture of chemicals, metal preparations, machinery and equipment. The main use category is "non-dispersive use".

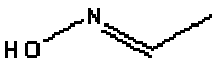
In the Swiss Product Register dicyclohexylamine is registered for 78 products, including 73 industrial products. Of the 5 consumer products listed in the Swiss Product Register, there are one fuel additive with a dicyclohexylamine content of 3 %, a brake fluid with 1 %, a coolant additive with 3 %, and two products in the category of propellants, lubricants and heat transfer media which contain less than 0.001 % dicyclohexylamine.

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 corrosivity, eye and respiratory tract irritation, chromosome aberration in vitro at high concentrations, developmental toxicity in the presence of severe maternal toxicity). Based on the data presented by companies in Japan and by the Sponsor company in Germany, exposure is controlled in occupational settings in the Sponsor country and in Germany, and exposure of consumers is low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical has properties indicating hazards for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However, the chemical is of low priority for further work because of its rapid biodegradability and its limited potential for bioaccumulation (protonated form).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-29-9
Chemical Name	Acetaldehyde Oxime
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Toxicokinetic data, with radiolabeled acetaldehyde oxime, show that the major route of elimination of the carbon derived from AAO is as CO₂ (~ 63-68%) and occurs rapidly after oral gavage administration to rats. Urinary excretion accounts for ~ 11-16% of the administered radioactivity, and fecal elimination is minimal (~1-3%). Elimination by the expired air and urine is essentially complete in the low and mid doses (7.5 and 75 mg AAO/kg bw) by 24 hours after administration. In the high dose, CO₂ elimination continues rapidly for 72 hours. The highest tissue concentrations were detected in liver and kidneys. Approximately 12-24% of the radioactivity remains in the tissues. Pretreatment of animals with Disulfiram significantly reduces the rate of excretion of labeled CO₂. The pattern of excretion of labeled CO₂ with increasing dose, and the reduction with Disulfiram treatment suggests that AAO is metabolized within the tricarboxylic acid cycle and its carbon may be utilized in cellular synthetic pathways. Toxicokinetic data also show that radiolabeled AAO is distributed rapidly throughout the body after oral and intratracheal administration to pregnant mice; highest concentrations detected in bone, nasal and bronchial epithelium, liver and pancreas. Secretion of AAO or its metabolites by the liver and kidney is also reported. In addition, increasing relative concentration with time is found in seromucous and salivary glands, liver, spleen, intestinal wall, thymus and fetuses (liver highest concentration). Urine and bile also contain considerable amounts of AAO.

The acute oral LD₅₀ in rats is 74 mg AAO/kg bw, acute dermal LD₅₀ in rats and rabbits is >1000 mg AAO/kg bw, and acute inhalation LC₅₀ in rats is 8.8 mg AAO/L (4-h exposure). AAO is mildly irritating to the skin and moderately to severely irritating to the eye. AAO is not a skin sensitizer.

In a 13-week repeated-dose study in rats, exposed to 12.5, 37.5 and 112.5 mg AAO/kg bw/day by gavage, the LOAEL was 12.5 mg AAO/kg bw/day (NOAEL < 12.5 mg AAO/kg bw/day) based on hematological findings (decreased hematocrit, hemoglobin, and erythrocyte counts), increased total bilirubin, blood urea nitrogen, and plasma and erythrocyte cholinesterase levels and increased spleen, thyroid, heart and liver weights. Microscopic examination revealed extramedullary hematopoiesis and increased pigment in the spleen and pigment in the liver. Systemic toxicity data from a reproduction study suggests a NOAEL for parental toxicity of <5 mg AAO/kg bw/day, based on the decrease in mean corpuscular hemoglobin concentration and histopathological changes in spleen of the males. In both studies, the spleen was the common target organ. The overall NOAEL from the one-generation reproduction study is considered the overall NOAEL for repeated dose toxicity, i.e. < 5 mg AAO/kg bw/day.

In vitro mutagenicity data were mixed; positive results were seen with and without metabolic activation only in one Ames and one mouse lymphoma test. All *in vivo* genotoxicity studies (sister chromatid exchange, UDS and mammalian cell transformation) were negative. Overall, AAO is not considered to be genotoxic as positive results *in vitro* were not confirmed *in vivo*.

No carcinogenicity data for AAO are available.

In a reproduction study the NOAEL for parental toxicity was < 5 mg AAO/kg bw/day based on the decrease in mean corpuscular hemoglobin concentration and histopathological changes in spleen of the males. No reproduction or developmental toxicity was reported for AAO in a one-generation study up to dose levels of 50 mg AAO/kg bw/day. The one-generation reproductive toxicity study showed no evidence for effects on fertility. In addition, no changes in testicular weight or microscopic pathology of the testes or ovaries of rats were observed in a sub-chronic study tested up to levels of 112.5 mg AAO/kg bw/day. The NOAEL for reproduction toxicity is considered to be > 50 mg AAO/kg bw/day. The NOAEL for developmental toxicity is considered to be > 50 mg AAO/kg bw/day.

Environment

The melting point of two crystalline forms of AAO is reported to be 47° C (α-form) and 12° C (β-form). The boiling point is 114.5° C and the vapour pressure is 8.7 hPa at 20° C. The density is 0.966 g/mL at 20° C. AAO is very soluble in water (> 10 g/L) at room temperature. In air, AAO is photochemically degraded (half life time is ca. 5 days). AAO is hydrolytically stable at pH 4, 7, and 9. In the aquatic environment, AAO is readily biodegradable. Volatilization from water is expected to be slow (half-lives expected to be between 3.2 and 37.8 days). The low log Kow of -0.13 of AAO indicates that bioaccumulation is not expected.

The estimated Mackay Level III fugacity model distribution predicts that, AAO released equally to all compartments, will most likely partition to water (51.7%) and soil (40.5%), with much smaller distributions to air (7.7 %) and sediment (0.1 %). When AAO is released to water, it will partition to water (99.4%), air (0.34%), soil (0.07%), and sediment (0.18%).

Acute LC₅₀/EC₅₀ values have been measured for rainbow trout (*Salmo gairdneri*) 28.5 mg AAO/L, bluegill sunfish (*Lepomis macrochirus*) 15.5 mg AAO/L, fathead minnow (*Pimephales promelas*) 76 mg AAO/L and the invertebrate, *Daphnia magna* 400 mg AAO/L. A study on fresh water green algae, using *Pseudokirchneriella subcapitata* resulted in the algal 72-h values of EbC₅₀ equal to 10.9 mg AAO/L and ErC₅₀ equal to 37 mg AAO/L.

Exposure

Acetaldehyde oxime (AAO) is produced as a pure liquid and sold industrially as an intermediate in the form of a 50% aqueous solution (50% AAO aqueous solution).

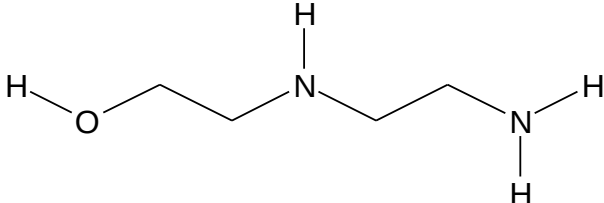
Annual production by the only producer is in the order of 1000 – 5000 metric tons. It is produced in closed systems for use as an intermediate in agricultural pesticide production and is consumed in the production. AAO is not sold to consumers. No information on exposure is available in the sponsor country (formulations only). Monitoring data indicate that occupational exposure during production is in the range of 0.45-2.4 mg a.s./m³ (8h TWA) aerosol. During loading of trucks, concentrations of 0.45 to 11.0 mg a.s./m³ were measured over an hour; stationary measurements during loading showed concentrations up to 260 mg a.s./m³. Exposure is minimised outside the production area by the use of personal protective equipment during, for example, tanker loading. Less than 0.01% of the production volume is emitted into the atmosphere during production at the DSM Special Products plant at Geleen, The Netherlands. Based on the amount of AAO discharged to the DSM WWTP, the biodegradability of AAO, the influent and effluent flow and the dilution of the effluent to the receiving water, the concentration in the receiving water is calculated to be < 1 µg active substance (AAO)/L. Therefore, environmental exposure is expected 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, eye irritation, and toxicity to spleen). Based on data presented by the sponsor country relating to use pattern in the sponsor country, exposure to humans is anticipated to be low (closed- system intermediate), 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: The chemical is currently of low priority for further work. The chemical has properties indicating a hazard for the environment (acute LC/EC50s for fish and algae between 1 and 100 mg/L), however, it is readily biodegradable and has limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-41-1
Chemical Name	2-(2-aminoethylamino)ethanol (AEEA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Unless otherwise stated, all studies were either in compliance with, or broadly consistent with, OECD Test Guidelines (TGs). 2-(2-aminoethylamino)ethanol (AEEA) is rapidly absorbed following oral administration to female Wistar rats ($t_{1/2}$ values 0.1-0.2 hours). Maximum blood levels were reached within 0.5 hours. Excretion was also rapid with most of the dose (85 - 98 %) recovered in the 0 - 48 hour urine, less in feces and only very low quantities in expired volatiles and as $^{14}\text{CO}_2$. The plasma elimination of orally administered ^{14}C -AEEA was biphasic, with alpha and beta elimination $t_{1/2}$ -values of 1.6 - 1.8 hours and 16.7 - 17.3 hours, respectively. Only the parent compound AEEA was found in plasma. Most of AEEA was excreted unchanged in the urine and 2 out of 4 metabolites are of unknown structure. The pregnancy status did not cause significant differences in absorption, elimination, excretion, and metabolic profile following the oral administration of AEEA.

After dermal application of a 10-fold higher dose, no quantifiable plasma levels were reached. Urinary excretion was quantifiable, and bioavailability was approx. 10 % compared to the oral route. The organ distribution was low and comparable in all experiments, and no significant difference occurred with respect to dose level, route of exposure, pregnancy status.

The acute oral LD_{50} -value was > 2000 mg/kg bw in rats (AEEA purity >99.5 %). Symptoms of toxicity were noted in animals receiving more than 2000 mg/kg bw including dyspnoea, apathy, and staggering, and the substance caused gastric irritation following single oral dosing. The acute toxicity of AEEA was largely influenced by caustic effects as neutralized solutions of AEEA showed no toxicity at otherwise fatal concentrations. Deaths occurred within one or two days post treatment. No inhalation hazard was noted in rats exposed to saturated atmospheres for 6 or 8 hours. The acute dermal LD_{50} -value was > 2000 mg/kg bw in rats and in rabbits. Skin irritation and necroses were noted at the treated sites. AEEA was corrosive to the rabbit's skin and the rabbit's eye.

AEEA was a skin sensitizer in the Guinea Pig Maximization Test and the mouse Local Lymph Node Assay (LLNA). Cross reactions were noted in Guinea pigs induced with AEEA and challenged with Di-, Triethyleamine, Ethylenediamine and Piperazine.

Clinical observations and positive human patch test results indicate a potential of an allergic contact dermatitis in humans. Inhalation of fumes of soldering flux and of AEEA caused delayed onset of severe allergic asthma that persisted for several hours or days in cable jointers who had been occupationally exposed to fumes of flux containing AEEA. No such reports were retrieved in the 30 years prior to 2006, which could be explained by increased industrial hygiene standards.

AEEA was tested in rats at 60, 250, and 1000 mg/kg bw/day in an oral gavage 28-day study. Blood chemistry

revealed statistically significantly increased glutamine-oxaloacetic transaminase activity only in males at the mid and high dose and decreased cholesterol in high dose females. In urine, protein was increased at 1000 mg/kg bw/day in both sexes. Urinary specific gravity was increased in mid- and high dose females, and volume was decreased in the high dose females. Increased absolute and relative kidney weights in males and increased relative kidney weight in females were observed at the high dose ($p < 0.01$). Histopathologically, deposition of amphophilic bodies and swelling in the renal proximal tubules were noted in all animals at the high dose and in males at 250 mg/kg bw/day. In the stomach, thickening of the mucosa at the limiting ridge was noted in all animals at 250 and 1000 mg/kg bw/day. All effects except those in kidneys and stomach were reversible in animals allowed to recover for 14 days. The NOAEL was 60 mg/kg bw/day in both sexes.

In a 28-day dermal study, rats were dosed with 0, 100, 300 or 1000 mg/kg bw/day. No evidence of systemic toxicity was observed in the animals. The only treatment related effects observed in the study were localized skin effects at the site of test material application consistent with the known dermal irritancy/corrosivity of AEEA. The NOEL for systemic toxicity was 1000 mg/kg bw/day.

In general it may be concluded that the systemic toxicity of AEEA is low, and that the primary effect is irritancy after oral and dermal exposure. While no systemic toxicity was observed after dermal exposure, slight changes in clinical chemistry, urinalysis, and kidneys were noted after oral exposure with a high NOAEL of 250 mg/kg bw per day if the local irritation of the stomach is discounted.

There are no indications that AEEA possesses genotoxic properties. No potential for genetic toxicity of AEEA was indicated in the Ames Test (Standard-plate or Preincubation method) using *S. typhimurium* (TA98, TA100, TA1535, TA1537) with and without metabolic activation including doses that were bacteriotoxic. In the mammalian cell forward mutation assay using Chinese hamster ovary cells (CHO/HGPRT) AEEA was not genotoxic even at cytotoxic concentrations both with and without metabolic activation. This also holds for Sister Chromatid Exchanges in the same cell line. No increase of structural chromosomal changes was noted in Chinese Hamster lung cells. A slight but statistically significant increased polyploidy was noted in one experiment (48h exposure) with AEEA without metabolic activation. However, this effect was not observed in the other experiments with or without metabolic activation, and no repeat experiment was conducted to verify the finding after 48h exposure. AEEA also tested negative for induction of Unscheduled DNA Synthesis (UDS) in isolated rat hepatocytes.

In a mouse bone marrow Micronucleus Test no increased frequency of micronuclei was noted in male and female mice after oral exposure. AEEA was tested in negative in male *Drosophila melanogaster* using the Sex-Linked Recessive Lethal assay in feeding and injection experiments.

No carcinogenicity study is known to exist. As a secondary amine, AEEA can form a nitrosamine under certain conditions. Some nitrosamines are suspected to be carcinogenic.

Developmental toxicity was observed with AEEA after oral (gavage) treatment with 0, 50, 250 or 1,000 mg/kg bw per day following the OECD TG 421 screening protocol. Effects were observed in the aorta and associated major arteries such as carotids and pulmonary arteries and consisted predominantly of aneurysms at 50 and 250 mg/kg bw per day, while no pups were delivered at 1,000 mg/kg bw per day due to a lack of implants in adult females. In a follow up developmental toxicity study (OECD 414) with 0, 0.5, 2, 10 and 50 mg/kg bw per day, no such findings were obtained at 50 mg/kg bw per day, a dose level, which caused a high incidence of those findings in the OECD TG 421 study. There was no indication of maternal toxicity, embryo-/fetotoxicity in this study. Histological investigations of pups in follow up mechanistic studies revealed dissecting aneurysms and/or focal necrosis in greater vessels such as aorta, pulmonary trunk, and arteria subclavia. Fragmented elastic fibers could be shown using special staining technique. It is assumed that the damage of vessel structure is occurring in utero; however the development of aneurysms is likely to occur during and shortly after birth when arterial blood pressure is significantly increased. Follow up studies indicate that these lesions in pups are visible shortly after birth, and that aneurysms undergo repair mechanisms with scars as residual findings in pups raised up to 60 days after birth. Physiological post birth maturation of vessels and effective repair mechanism explain why no mortality was seen in rats orally dosed with 1000 mg/kg bw in the 28-day study. In this study the animals were treated after maturation of the vessel system. A follow-up study similar to OECD TG 421 (0.2, 1, 5 and 50 mg/kg bw per day) indicated a LOAEL of 0.2 mg/kg bw per day based on aneurysms observed. From the original TG 421 screening study it is unclear if the lack of implants at the high dose level of 1000 mg/kg per day was due to embryotoxicity or fertility effects (fertility index 60% in the high dose group compared to 90-100% in the others). A NOAEL of 250 mg/kg bw was established for possible fertility effects.

Environment

2-(2-aminoethylamino)ethanol (aminoethylethanolamine, AEEA) is a colorless to yellowish liquid which is completely soluble in water (25 °C / 1013 hPa). The melting point, given as pour point, is -38 °C, the boiling point is 243.1 °C, and the density is 1.024 g/cm³ at 25 °C. Following SPARC estimations, at environmentally relevant pH values (pH 7-9) the substance exists predominantly (75 – 95 %) as a cation in aqueous solution. The vapor pressure of 0.018 hPa at 25 °C was computer-modeled (EASE for Windows, v2.0) using an experimentally derived value of 0.21 hPa at 63.5 °C as input data. The measured log Pow of -1.46 (25 °C) and the measured BCF of ≤ 3.7 do not indicate a significant potential for bioaccumulation.

According to Mackay Level I, AEEA will distribute almost completely into water (99.99 %). The calculated Koc of uncharged AEEA is 3.524 (log Koc = 0.547). Thus, the potential for adsorption to soil, sediment, and suspended solid may be low. However, binding of the substance to the matrix of soils (and sediments) with high capacities for cation exchange (e.g. clay) can not be excluded for the charged molecule. Data on the stability of AEEA in water are not available. In a recently performed manometric respirometry test (OECD TG 301 F), AEEA was shown to be readily biodegradable according to OECD criteria. In the atmosphere, it will be photodegraded by reactions with OH radicals (calculated half-life: 1.1 hours).

Results on acute aquatic toxicity are available for fish (*Pimephales promelas*; LC₅₀ (96 hours): 640 mg/l), invertebrates (*Daphnia magna*; EC₅₀ (48 hours): 22 mg/l), and algae (*Scenedesmus subspicatus*; EbC₅₀ (72 hours): 210 mg/l; ErC₅₀ (72 hours): 354 mg/l). In the three tests, high pH values as determined in the highest concentrations tested might have had contributory effects on the observed toxicity. Results of toxicity tests with microorganisms revealed EC₅₀ values of ≥ 135 mg/l. Based on the acute toxicity studies, AEEA is considered of moderate acute toxicity to aquatic organisms. A PNECaqua of 0.022 mg/l was obtained by applying an assessment factor of 1000 on the lowest endpoint, the result of the acute Daphnia test.

Exposure

The annual world production capacity in 2003 for ethyleneamines was estimated at 295,000 tons, subdivided into 138,000 tons/annum for Europe, 127,000 tons/annum for United States, and 30,000 tons/annum for Japan. Individual capacity data on AEEA are not available. AEEA is mostly used as an intermediate in the production of surfactants, for specialty personal care products, pharmaceuticals, and cleaning agents. Smaller volumes of AEEA are also used as chemical intermediates in the production of textile, polyurethane, lube oil, and fuel additives as well as in manufacturing of chelating agents and polyols. In Europe AEEA is also applied in production of hardeners for epoxy resins and as an additive in polyurethane (PU) production. PU and epoxy resins are often employed as building materials. In the Sponsor Country, AEEA is primarily used as a chemical intermediate for the synthesis of amphoteric surfactants (85 %) and an amide wax (15 %) for consumer uses. Minor use patterns are reported for varnishes and surface coating agents. In Switzerland the use of AEEA in soldering flux is reported for industrial products.

During processing and use of consumer products containing AEEA, exposure may occur via inhalation or skin contact. At the production sites, it is technically ensured that exposure of workers to AEEA is minimized. Significant exposure is normally not expected during production, transportation, and sampling, because these processes are largely enclosed. Occupational exposure is therefore limited to situations of maintenance and accidental spills. Concerning production and processing of AEEA, worker exposure via air is negligible. Exposure measurements resulted in concentrations that were below the limits of detection (<0.001 to 0.09 mg/m³). Consumers may be exposed through the use of waxes and surfactants (amphoteric tensides) which contain un-reacted AEEA at concentrations which are in the range of 5 ppm, or below 10 ppm in final cosmetic products.

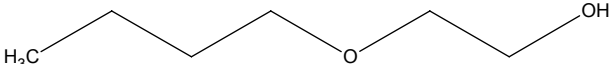
Releases of AEEA into the environment may occur during manufacturing and processing in the industry. Another source of environmental exposure may also be expected from the use of surfactants and waxes containing AEEA. AEEA is readily biodegradable and although no actual exposure information is available, only very small amounts of AEEA are to be expected in effluents of wastewater treatment plants at manufacturing and processing sites. During production and processing in 2004 at BASF AG (Ludwigshafen, Germany), AEEA was not emitted to air. Data regarding emission via waste water treatment effluent are not available from this site.

**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 and eye irritation, skin sensitizer, developmental toxicity on blood vessels). Further mechanistic studies to elucidate the detailed mode of action on developing blood vessels and the relevance of this finding for man are underway. Member countries are invited to perform an exposure assessment for consumers including residues in cosmetics and workers and if necessary a risk assessment.

Environment: The chemical is currently of low priority for further work. The chemical has properties indicating a hazard for the environment (acute toxicity to aquatic invertebrates: EC_{50} between 10 and 100 mg/l). However the chemical is of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS Number	111-76-2
Chemical Name	2-butoxyethanol Ethylene Glycol Butyl Ether (EGBE)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Nearly 100% of orally administered EGBE is absorbed. For dermal absorption studies of liquid EGBE a value of 30 % absorption (after at least 2 hours of exposure) represents a maximum. Depending on the experimental conditions, dermal penetration of vapour EGBE in humans is between 11 and 39 % of the total body burden. In human volunteers' inhalation studies, inhalation absorption of 55 % to 60 % has been measured.

EGBE reaches a maximum blood concentration rapidly after exposure independent of the route of exposure. EGBE is rapidly metabolised (with a plasma half life of about an hour).

Highest concentrations of EGBE were found in the liver, kidneys, thymus and stomach, in particular forestomach in the rat, independent of the route of administration (by oral or inhalation route).

The main metabolic pathway leads to the formation of Butoxy Acetic Acid (BAA) via Alcohol dehydrogenase and Aldehyde dehydrogenase in a saturable mechanism.

Elimination is rapid and mainly via the urinary route (80 to 90 % of the metabolites). The plasma half-life of metabolites is about 4 hours. A small amount is eliminated as CO₂ by respiration (10 to 20 %).

According to the available data and the physico-chemical properties of EGBE, excretion into the breast milk and exposure of the developing foetus is possible.

Acute inhalation toxicity studies showed that LC₅₀ in rats, mice and guinea pigs were about 500 ppm (2.45 mg/l). The effects seen in acute toxicity studies in animals were mainly acute haemolysis accompanied by non specific signs of toxicity (laboured breathing, lethargy, ataxia). Some hepatic and renal pathology was also seen in these studies. By dermal route, depending on the application (occlusive or not) the LD₅₀ varied mainly between 500 mg/kg and > 2000 mg/kg respectively in rabbits. In rats dermal LD₅₀ was greater than 2000 mg/kg whereas in guinea pigs LD₅₀ values varied between 200 and 6000 mg/kg. For this end point the most reliable studies were those in the rabbit. By the oral route, LD₅₀ values were greater than 1000 mg/kg in studies with mice and rats.

In humans following massive oral doses (0.4-4.5 g/kg bw.), the main toxic effect was metabolic acidosis sometimes with haematotoxicity (haematuria). For haematotoxicity, humans are much less sensitive than rodents via any route of administration (rodents are more sensitive than humans). Moreover according to human studies, it appears that there is not a great intraspecies sensitivity (no influence of age or haematological status). This end point was not the most sensitive end point for acute toxicity in human. Indeed, in cases of massive doses, haematotoxicity was not observed in all cases, but metabolic acidosis and CNS depression were invariably observed. The lowest dose leading to metabolic acidosis in human was 400 mg/kg (LOAEL). Mechanistic *in vitro* studies showed that BAA causes haemolysis at very low concentrations. It can be also estimated that BAA is responsible of hematotoxicity *in vivo*.

EGBE liquid is irritating to the skin and eyes. No sign of severe respiratory tract irritation was evidenced in human observations or chronic rodent exposures. Irritation of nose and throat was reported in a study with human volunteers exposed to 200 ppm of EGBE, whereas levels of 25 and 50 ppm were

without symptoms. No sensitisation properties (both skin and respiratory tract) linked directly to EGBE was seen from the available data on humans and animals.

For repeated dose toxicity, target organs identified in the different studies available (including the two-year toxicity studies in rats and mice) were red blood cells, liver, spleen, olfactory epithelium and forestomach. Haemolytic anaemia was observed in several studies. Rodents were more sensitive than human to the haemolytic effects of EGBE. Kupffer cell pigmentation was secondary to the haemolytic effects. Effects on spleen (including spleen fibrosis) were also related to haemolysis. Effects usually occur following administration of substances, which are able to cause iron accumulation in the splenic red pulp. Effects on the forestomach of rodents do not appear to be relevant for humans. The increased incidence of hyaline degeneration of the olfactory epithelium observed in rodents appears to be an adaptive response, the severity of the lesion remained unchanged with increasing exposure concentrations.

In species other than rodents, older studies were available. In dogs and monkeys, haemolysis was also described at relatively low doses. In guinea pigs, a species which is resistant to EGBE-induced haemolysis, mortality was seen at 375 ppm and higher.

The most reliable inhalation LOAEC was 31 ppm derived from a 6 month satellite group in a two-year study in rats. A NOAEC of 25 ppm was obtained in a 90-day rat inhalation study. For the oral route, a LOAEL of 69 mg/kg bw/d in male rats was derived from a 14 week oral study in rats. For dermal exposure, a NOAEL of 150mg/kg/day was established based on a rabbit study which showed no effects at the highest tested dose.

Most of the *in vitro* genotoxicity tests of EGBE in bacteria and in the mammalian cells were negative. Weak aneugenic effects were obtained in the only available study with EGBE and Butoxyaldehyde (BAL), but not with BAA. One of the main metabolites of EGBE, butoxy aldehyde (BAL) was positive in most *in vitro* genotoxicity tests. All the available *in vivo* genotoxicity tests were negative.

For reproductive toxicity, no specific effects were seen for fertility. In the continuous breeding study a NOAEL of 720 mg/kg in mice was set based on non specific effects observed at the higher doses tested (weight loss and mortality in dams and decreased number of litters, litter sizes, pup viability, and live pup weights in the presence of severe maternal toxicity. For developmental studies, embryonic and foetal effects seen in animals occurred at doses that also resulted in severe maternal toxicity (haemolysis). Overall based on the available animal data, EGBE was not considered to be a developmental toxicant. There are some epidemiological findings, which indicate that maternal work exposure to solvents or glycol ether and maternal occupations in health care or cleaning may be risk factors for cleft palate and neural tube defects in the studied population. However, it is not possible to distinguish clearly a unique source of glycol ether. Usually studies described co-exposure to various glycol ethers, including known developmental toxins such as EGME (Ethylene Glycol Methyl Ether) and other chemicals as well.

Two inhalation chronic-carcinogenicity studies have been conducted. Results obtained showed that EGBE was carcinogenic in male mice, where it caused a low incidence of haemangiosarcomas, and in female mice, where it caused an increased incidence of forestomach tumours. It was not carcinogenic in rats. In the case of forestomach tumours, these tumours do not appear to be relevant to human because of the specificity of this organ in rodents. In the case of the haemangiosarcomas, mice were more sensitive than rats and the proposed mechanism of action was related to haemolysis observed with EGBE. As humans are less sensitive than rodents to this toxicity, EGBE is not likely to represent a carcinogenic hazard under conditions of normal handling and use.

Environment

EGBE is a neutral, colourless liquid. Its melting point equals -74.8°C and its boiling point is 171°C . EGBE can be considered as volatile based on its vapour pressure of 1.41 hPa. However, due to its high solubility (more than 50 g/L), the volatilisation of EGBE from water will not be important. Indeed a $K_{\text{air-water}}$ of 3.23×10^{-5} indicates that volatilisation of EGBE from surface water and moist soil is expected to be very low. EGBE is not hydrophobic and has a log Kow of 0.8.

No experimental data were available on hydrolysis. However, alcohols and ethers like EGBE are generally resistant to hydrolysis.

EGBE released to the atmosphere is expected to degrade by reaction with hydroxyl radicals. An estimated atmospheric half-life value of ~13 hours has been calculated.

According to standard tests on ready biodegradation and further experimental data which confirmed high biodegradation rates, EGBE can be regarded as readily biodegradable. Therefore, the degradation rates can be estimated for surface water, soil and sediment corresponding to half lives of respectively 15, 30 and 300 days.

In view of the BCFs for fish and worm (0.97 and 1.6) calculated based on the log Kow, EGBE is expected to have a low bioaccumulation potential.

The results from a multimedia fugacity model (MacKay level I) and the physico-chemical properties of EGBE show that the hydrosphere is the preferential target of the substance in the environment (99.2% in water, 0.55% in soil).

For the assessment of the toxicity of EGBE toward aquatic organisms, the data presented in the following table were selected.

Species	Duration	Endpoint	Result (mg/L)	Lowest short term toxicity result for the same trophic level
Fish: <i>Brachydanio rerio</i>	21 days	NOEC	> 100	<i>Poecilia reticulata</i> LC ₅₀ after 7 days = 983 mg/L
Invertebrates: <i>Daphnia magna</i>	21 days	NOEC	100	<i>Hydra attenuata</i> EC ₅₀ after 72 hours = 540 mg/L <i>Daphnia magna</i> EC ₅₀ after 48 hours = 835 mg/L
Algae: <i>Pseudokirchneriella subcapitata</i>	72 hours	NOEC	286	<i>Pseudokirchneriella subcapitata</i> EC ₅₀ after 72 hours = 911 mg/L

An assessment factor of 10 has been applied to the lowest long-term result and a PNEC of 10 mg/L has been derived for freshwater.

Concerning the toxicity towards wastewater treatment plant micro-organisms, three tests were conducted with protozoa and one with an individual bacteria species. Studies testing ciliated protozoa can be used for the assessment of hazard for the sewage treatment plants. Consequently, the test conducted on *Uronema parduzci* has been chosen (EC₅ = 463 mg/L).

Exposure

EGBE belongs to the group of glycol ethers, which are mainly used as solvents. The annual production of EGBE in the European Union has been estimated to be 155,100 tons. The production in the European Union is located at five different sites.

EGBE has a wide range of uses as a solvent. Occupational exposure mainly occur during manufacture, formulation, coating/painting (industrial or decorative), printing (general printing or silk screening) and cleaning (wiping or spraying). Consumer exposures are mainly due to the use of cleaning products and paints. Minor uses have also been identified such as leather treatment operations, cosmetics and fire foams and the formulation of oilfield chemicals.

Emissions of EGBE in the environment principally occur to water and via direct releases in air. Highest exposure concentrations have been identified in water from the use of general industrial paints, automotive OEM coatings, the formulation of inks, use for leather finishing operations and for the formulation of oilfield chemicals. For the atmosphere, the highest calculated exposure concentrations can be attributed to the use of general industrial paints, can coatings and for metal cleaning operations.

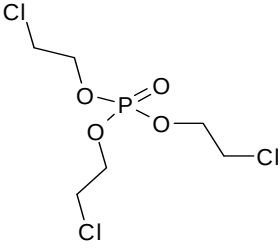
**RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND
NATURE OF FURTHER WORK RECOMMENDED**

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (irritation and haematotoxicity). The irritation hazard does not warrant further work as it is related to reversible effects which may become evident only at high exposure levels. It should nevertheless be noted by chemical safety professionals and users. Although haematotoxicity is noted in rodents exposed to high oral or dermal concentrations of 2-butoxyethanol, humans are significantly less sensitive to red blood cell toxicity caused by 2-butoxyethanol than rodents.”

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

Note : an EU risk assessment is in progress on this substance taking into account all the scenarios available in Europe.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	115-96-8
Chemical Name	Tris(2-chloroethyl)phosphate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Tris(2-chloroethyl)phosphate (TCEP) is well absorbed (> 90% of the dose) and distributed in rats after oral administration. High concentrations were found in liver and kidney 24 hours after administration and TCEP is thought to undergo enterohepatic circulation. The urinary metabolites were identical in rats and mice, and were mainly bis(2-chloroethyl) carboxymethylphosphate, bis(2-chloroethyl)hydrogen phosphate and bis(2-chloroethyl)-2-hydroxyethyl-phosphate glucuronide. Absorption data were not available for the dermal and inhalation route. Human data on toxicokinetics of TCEP were not available.

TCEP showed an oral LD₅₀ for rats in the range of 430-1230 mg/kg bw. In rabbits, a dermal LD₅₀ for 24-hours occlusive contact was in excess of 2150 mg/kg bw. In a limit inhalation test rats were exposed to a nominal concentration of 25.7 g/m³ for 1 hour. The animals revealed moderate lacrymation and salivation; no mortality resulted.

In Draize tests, neat TCEP produced mild irritant reactions when in 24 hour occlusive contact with the skin of rabbits (test according to OECD Test Guideline (TG) 404). The neat liquid instilled into the eyes of rabbits produced mild conjunctival irritation (test according to OECD TG 405). No skin sensitizing potential of TCEP was detected in guinea pigs whose skin was in repeated contact with the neat liquid (Buehler Test). Since negative results obtained with a Buehler test are considered to be insufficient for an appropriate assessment of skin sensitizing potential, a read across approach was performed using relevant data of two other structurally related chloroalkyl phosphates: Tris(2-chloro-1-methylethyl) phosphate (TCPP) and Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP). The results of valid skin sensitisation studies on TCPP and TDCP did not show a significant skin sensitizing potential. Taking into account all sensitisation studies, it is concluded that TCEP should be non-sensitizing to humans.

Kidney and brain were the main sites of the toxic effects in experimental animals after repeated oral administration of TCEP (dose ranges from 22 to 700 mg/kg bw/d in rats and from 12 to 1500 mg/kg bw/d in mice). Increased liver weight was also observed in rats and mice but no overt liver toxicity could be identified or could be related to TCEP treatment. Kidneys appear to be the most sensitive organs for repeated exposure of TCEP. Degenerative lesions in the brain were only manifested at higher doses in the rat. The incidence and severity of the adverse kidney pathology was dose- and time-related, and the nature of the lesions (mainly involving the kidney tubules and consisting of hyperplasia, hypertrophy and karyomegaly) was similar in two strains of rat (Sprague-Dawley and F344/N) and two strains of mouse (B6C3F1 and Scl:ddY). No NOAEL could be identified in long-term studies. Similar kidney lesions were observed at the lowest tested oral doses of 192 mg/kg bw/d administered in the diet to male Sprague-Dawley rats for three months, of 44 mg/kg bw/d given by gavage to male and female F344/N rats for 103 weeks, of 175 mg/kg bw/ given by gavage to B6C3F1 mice for 103 weeks, and of 12 mg/kg bw/d administered in the diet of Scl:ddY mice for 18 months. Therefore, the critical LOAEL for kidney lesions is 12 mg/kg bw/d.

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Orally administered TCEP induced a range of degenerative changes in the brain of rats: the incidence of these lesions was dose- and sex-related, and there was a clear time-response relationship in frequency and severity. Females were more susceptible than males. NOAELs for brain effects in rats from sub-chronic and chronic oral toxicity studies were in the range of 44 to 175 mg/kg bw/d. The NOAEL for the inhibition of serum cholinesterase activity that has only been reported in female rats was 88 mg/kg bw/d. In mice, oral doses of 350 mg/kg bw/d administered for 2 years produced no adverse brain pathology, and repeated oral doses up to 700 mg/kg bw/d had no effect on cholinesterase activity. Although several chlorinated alkyl phosphates have been shown to produce delayed neurotoxicity in hens (study according to OECD TG 418), an oral dose of 14200 mg TCEP /kg bw in hens did not cause behavioural effects or nerve damage suggestive of neurotoxicity.

No repeated dose studies on the dermal and the inhalation route were available.

In general, Ames tests in *S. typhimurium* (conducted according to OECD TG 471) provided no evidence of mutagenic potential. Gene mutations were not induced in mouse lymphoma and V79 cells in culture (OECD TG 476). There were no treatment-related increases either in chromosomal damage in CHO cells (OECD TG 473) or Unscheduled DNA Synthesis in human WI-38 cells (OECD TG 482). The small increases in Sister Chromatid Exchange seen at high TCEP concentrations in V79 cells in culture (OECD TG 479) were not considered to be a reliable indication of genotoxic potential. Two investigations (conducted according to OECD TG 474) of the induction of chromosome damage (micronuclei) in mice found no evidence of activity up to maximum tolerated doses. Overall, it is concluded that there is no convincing evidence that TCEP possesses genotoxic potential.

TCEP was carcinogenic in both sexes of rats and mice. It produced benign and malignant tumors in the kidney of rodents. These were seen in long-term studies in male and female F344/N rats at gavage doses ≥ 44 mg/kg bw/d, and in male B6C3F1 mice at 350 mg/kg bw/d; and in diet studies in male Scl:ddY mice at doses of 300 mg/kg bw/d and above. Dose-related increased incidences of hyperplasia and hypertrophy of the urinary tubule epithelium together with karyomegaly were also observed at doses of ≥ 44 mg/kg bw/d in male and female F344/N rats, at ≥ 175 mg/kg bw/d in male and female B6C3F1 mice, and at ≥ 12 mg/kg bw/d in male Scl:ddY mice. The value of 12 mg/kg bw/d is considered as the LOAEL for tumor formation. Since there was no evidence of a direct genotoxic mode of action, it can be assumed that the kidney tumours developed by a non-genotoxic (epigenetic) mechanism. If this is the case, the LOAEL for kidney toxicity would also be the LOAEL for kidney tumour formation. In addition to the kidney tumours, TCEP induced benign and malignant tumours in the liver of male Scl:ddY mice at 300 mg/kg bw/d and above, and in the Harderian gland of female B6C3F1 mice at ≥ 175 mg/kg bw/d. Again, since there was no evidence of a direct genotoxic mode of action, it could be assumed that these tumour types are mediated by non-genotoxic (epigenetic) mechanisms and as such the tumour incidence dose-responses would exhibit thresholds. These threshold doses would be higher than that derived for the kidney carcinogenic action.

Significant impairment of reproductive capacity and fertility was seen in a continuous breeding study in which CD-1 mice received 300 or 700 mg/kg bw/d by gavage. No similar fertility effects were seen at 175 mg/kg bw/d (NOAEL for fertility). Supplementary studies indicated male mice were more sensitive to TCEP treatment than were the females. Mice given high oral doses exhibited reduced testes weights and sperm counts. In a study which provided limited information there was no evidence of development toxicity in Wistar rats which were given oral doses of 50, 100, or 200 mg/kg bw/d on gestation days 7 to 15. Adverse effects (skeletal variations) were noted at maternally toxic doses.

Environment

Tris(2-chloroethylphosphate) (TCEP) is a liquid (melting point: < -70 °C) with a water solubility of 7820 mg/l at 20 °C and a log Kow of 1.78. A vapour pressure of 0.00114 Pa at 20 °C was extrapolated from a measured value of 43 Pa at 137°C.

According to the fugacity model of Mackay (level 1), the main target compartment is the hydrosphere (94.8 %). The calculated Henry's law constant of $4.155 \cdot 10^{-5}$ Pa.m³/mol at 20 °C indicates a low potential of volatilisation from water.

Hydrolysis does not contribute to the environmental degradation of TCEP ($t_{1/2} \approx 3980$ days). In the atmosphere, TCEP will react with photochemically produced hydroxyl radicals. Based upon atmospheric concentrations of $5 \cdot$

10^5 OH/cm^3 , the atmospheric half-life of TCEP has been estimated to be 17.5 hours. From the spectroscopic data available for TCEP, direct photolysis is not to be expected.

TCEP is non biodegradable (OECD 302 B: < 10 % after 27 d with industrial activated sludge as inoculum). The measured log Kow of 1.78 indicates a low potential for bioaccumulation. This was confirmed by experimentally determined BCF of 0.6 to 5 in various fish species (*Cyprinus carpio*, *Carassius auratus*, *Oryzias latipes*). The calculated Koc of 110 l/kg indicates a low potential for geoaccumulation.

Short-term tests are available for fish, invertebrates and algae. The lowest effect values from these tests were: *Carassius auratus*: 96h-LC₅₀ = 90 mg/l; *Daphnia magna*: 24h-EC₅₀ = 235 mg/l, *Scenedesmus subspicatus*: 72h-E_rC₅₀ = 3.6mg/l, 72h-E_bC₅₀ = 1.1mg/l (72h-E_rC₁₀ = 0.55mg/l, 72h-E_bC₁₀ = 0.2mg/l). In addition, a long-term test with *Daphnia magna* is available in which a 21d-NOEC of 13 mg/l was determined. Applying an assessment factor of 10 on the EC₁₀ for algae, provides a PNECaqua of 65 µg/l.

For the terrestrial compartment tests with plants and invertebrates are available. For *Avena sativa* a 14d-EC₅₀ of 64 mg/kg dw was determined. For the earthworm *Eisenia andrei* a 14d-LC₅₀ > 1000 mg/kg dw was determined. In a long-term test with springtail (*Folsomia candida*), a 28d-EC₁₀ of 19.3 mg/kg dw was determined for mortality. In a test on the inhibition of the dehydrogenase activity of soil microorganisms, both tested concentrations (5 and 50 mg/kg dw) caused effects in the sandy soil, but in the loamy soil only the higher concentration lead to an inhibition of the enzyme activity. A PNECsoil of 0.341 mg/kg dw was derived from the EC₁₀ for *Folsomia* using an assessment factor of 50.

Exposure

In 1998, TCEP was produced in the European Union (EU) in quantities of about 2000 tons/annum. However, the situation changed recently; at present there is no production of TCEP in the EU. A quantity of 1007 tons was imported into the EU in 2002. TCEP is mainly used as flame retardant. In an effort by industry to substitute TCEP by other flame retardants the EU tonnage has been in decline during the last decade (EU tonnage in 1991/1992: 10500 t). The substitution by analogs was based on the carcinogenic properties of TCEP.

Main field of application is the polymer industry (~ 90 %). The products are used in the manufacture of cars, railways, aircrafts; other branches to use TCEP containing products are furniture, textile and building industry. About 5 % of the total volume is used in paints and varnishes (flame retardant). A further 5 % serve as an intermediate in the chemical industry.

Releases of TCEP into the environment are to be expected during production, formulation and processing via waste water and, to less extent, exhaust gases. Further releases are to be expected during use and service life of TCEP containing products (polymers, paints). If these are disposed at landfill sites, significant leaching may occur due to high solubility of TCEP.

There are no indications for any direct application of TCEP by consumers. However, due to the use as flame retardant in various materials exposure of consumers is possible. It has been shown that TCEP will be released from a number of sources which have been treated with flame retardants, namely timber, foam rubber, carpets, plastic materials, glues, and lacquers. The release occurs primarily by abrasion thus leading TCEP to become a constituent of dust (house dust and airborne dust).

Inhalation exposure takes place by inhaling airborne particles. Dermal exposure can occur by direct contact (with e.g. upholstery and furniture coverings). Oral exposure of TCEP by dust uptake may represent a significant source of exposure for children. A significant source of oral exposure of babies could be sucking on toys containing TCEP.

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 (repeated dose toxicity, potential of neurotoxicity, carcinogenicity, impairment of fertility, and potential for developmental toxicity). Based on the available exposure information, member countries are invited to perform an exposure assessment, and if

necessary a risk assessment for human health.

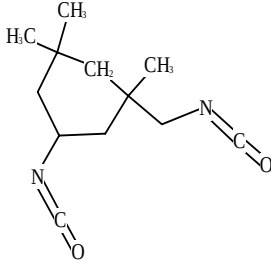
Note: A draft risk assessment performed in the context of the EU Existing Substances Regulation reveals concern for several toxicological endpoints, especially for carcinogenicity. For workers as well as consumers (including babies), risk reduction measures are recommended in the EU. For TCEP, three occupational exposure scenarios are evaluated: production, use for the production of formulations and use of TCEP-containing formulations including spray application and applications without formation of aerosols. The overall result of occupational risk assessment indicates that current exposure levels (inhalation and dermal contact) are too high for all three exposure scenarios.

Environment: The chemical is a candidate for further work.

The chemical possesses properties indicating a hazard for the environment (fish, aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment, and if necessary a risk assessment for the environment.

Note: A draft risk assessment for this chemical is currently under discussion in the EU in the context of the EU Regulation 793/93.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	4098-71-9
Chemical Name	3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

The only information available on the toxicokinetics of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate results from a test chamber exposure of three volunteers to concentrations of 0.0121, 0.0177 and 0.0507 mg/m³ for 2 hours at day 1, 3, and 5, respectively. After hydrolysis of blood and urine samples the corresponding amine, 3-aminomethyl-3,5,5-trimethylcyclohexylamine, was detected in urine but not in plasma. The average urinary excretion was 27 % and urinary elimination half-time was 2.8 hours. No 3-aminomethyl-3,5,5-trimethylcyclohexylamine was observed in samples without hydrolysis from exposed persons.

Assessment of the acute inhalation toxicity data indicates that effects caused by exposure to respirable aerosols of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate were confined predominantly to the respiratory tract. Clinical signs (serous nasal discharge, bradypnea, stridor) indicated respiratory distress. There are two studies according to OECD TG 403 with LC₅₀-values (4 h, rat) of approximately 40 mg/m³ and 31 mg/m³, respectively. Special investigations with male rats revealed airway rather than pulmonary irritation, which became evident after exposure of a concentration causing some lethality (25 mg/m³, 1 x 6 h). The dermal LD₅₀ determined in compliance with OECD TG 402 was > 7000 mg/kg bw for rats. Non-specific, transient signs of intoxication (sedation, ataxia) and obvious skin irritation at the application site were reported. The available studies revealed a low oral toxicity with LD₅₀-values (rat) of 4814 - 5490 mg/kg bw. Toxic symptoms after oral administration included decreased activity, piloerection, and diarrhea.

In two studies performed according to OECD TG 404, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was found to be corrosive to the rabbit skin. Strong irritation was observed in rabbit eyes when tested according to OECD TG 405. The toxicity studies indicate that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate vapor causes irritation of the upper respiratory tract. In a study with volunteers, a perception threshold for irritation of 0.64 mg/m³ was determined for short-term (1-5 minutes) exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was found to be skin sensitizing in the Buehler test according to or equivalent to the EU Directive, in the guinea pig maximization test comparable or according to OECD TG 406, in the mouse ear swelling test, and in the open epicutaneous test. Skin sensitization was also observed in humans. One case report describes respiratory hypersensitivity after occupational exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. No validated animal model is available to assess the potential for respiratory sensitization or asthma in humans, and one animal study did not show respiratory tract sensitization when exposed by inhalation (challenge) following intradermal induction. However, due to the well known reactivity of diisocyanates, respiratory sensitization is likely to occur.

No repeated-dose toxicity tests are available for the oral and dermal route of exposure. A subacute inhalation study (0.24, 1.05, and 4.1 mg/m³; 6 hours/day, 5 days/week, 4 weeks; OECD TG 412) with male and female Wistar rats indicates the respiratory tract to be the target organ. Clinical signs of respiratory tract irritation (nostrils: red encrustations, stridor, nasal discharge, breathing sounds, hypothermia) are restricted to the high concentration rats. The LOAEL is 1.05 mg/m³ (histopathological changes in nasal cavity and larynx). At 4.1 mg/m³ also the pharynx, trachea, and lungs are affected but the lesions are reversible within the four weeks of recovery with regard to the lung and trachea. However, lesions in the nasal cavity, the pharynx, and the larynx still occurred in some animals with minimal or slight degree. The most relevant systemic effects were a slight decrease in body weight gain in the high dose group and an increased leukocyte count in the peripheral blood in mid and high dose groups. The NOAEL is 0.24 mg/m³.

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was not genotoxic in bacterial systems *in vitro* (Ames test). Neither *Salmonella typhimurium* TA 102 nor *Escherichia coli* WP2 were tested in these Ames tests, however, this is an acceptable restriction because it can be assumed that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate has no oxidizing or cross-linking potential which may be detected by *S. typhimurium* TA 102 or *E. coli* WP2. In a chromosomal aberrations test performed on Chinese hamster ovary cells according to OECD TG 473, results were positive both with and without metabolic activation. *In vivo*, no mutagenic activity was detectable in a micronucleus assay on mice according to OECD TG 474 using the inhalation route of administration. However, as the micronucleus test only covers systemic genotoxic effects and given the well known high local reactivity of the substance local genotoxic effects cannot be excluded.

No studies have been performed to explicitly address the question of reproductive effects in animals caused by 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. Histopathological results of a subacute 28-day inhalation study in rats according to OECD TG 412 showed no effects regarding the reproductive organs in concentrations up to 4.1 mg/m³. Testes and ovary weights were also not affected. Taking into account the knowledge about the mode of action of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (local effects at sites of immediate contact clearly predominant), the lack of effect on the reproductive organs at 4.1 mg/m³, and as the NOAEL for repeated dose toxicity is set at 0.24 mg/m³ it seems quite unlikely that this substance might have critical effects on testis in this low dose range.

In a nose-only inhalation study performed in accordance with OECD TG 414, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate had no adverse effects on the development of rats up to and including a dose level of 0.929 mg/m³. A dose of 4.536 mg/m³ was maternally toxic as evidenced by effects on respiratory tract and fur as well as decreased feed intake and impaired body weight gain. All signs of developmental toxicity observed at the 4.536 mg/m³ exposure level, i.e. reduced fetal weights, delayed descensus testis, and slightly retarded ossification, were indicative of delayed fetal development and were only seen in the presence of maternal toxicity and thus considered secondary effects. There was no treatment related effect on incidence and type of fetal malformations up to and including 4.536 mg/m³. The NOAEL for both maternal toxicity and developmental toxicity was 0.929 mg/m³.

Environment

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is a colorless to yellowish, water sensitive liquid with a melting point of -60 °C, a boiling point (with decomposition) of approximately 310 °C at 1013 hPa, a water solubility of approximately 15 mg/l at 23 °C, a density of 1.058 g/cm³ at 20 °C, and a vapor pressure of 0.064 Pa at 20 °C. The calculated log K_{OW} is 4.75. The most important values for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (CAS No. 2855-13-2) concerning environmental behavior and ecotoxicity are a melting point of 10 °C, a vapor pressure of ca. 2 Pa at 20 °C, a measured log K_{OW} of 0.99 at 23 °C, and miscibility with water. This hydrolysis product was already evaluated in the OECD HPV Chemicals Program.

In the atmosphere, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is photodegraded by reaction with hydroxyl radicals with a calculated half-life of 1.8 days. For 3-aminomethyl-3,5,5-trimethylcyclohexylamine a half-life of 0.2 days is estimated. In water, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is expected to hydrolyze with a half-life of approximately 1 hour under environmental conditions, forming at high concentrations a white polymer, which is insoluble in water, or at low concentrations 3-aminomethyl-3,5,5-trimethylcyclohexylamine. Photolytic degradation in surface waters is expected to be of minor importance due to the absence of relevant chromophores in the chemical structure.

Biodegradation of the substance itself, which was not observed in a manometric respiratory test according to Directive 92/69 EEC, is irrelevant as a primary degradation step because hydrolysis is much faster. The hydrolysis

product 3-aminomethyl-3,5,5-trimethylcyclohexylamine is not readily biodegradable (OECD 301A: 8 % degradation after 28 days). However, in a simulation test with activated, non-adapted sludge, a degradation of 42 % (including a minor, though not negligible contribution by adsorption to sludge) was measured after a contact time of 6 hours.

Distribution modeling according to Mackay Level I indicates that the main target compartments will be soil and sediment with approximately 43 % each, followed by water with about 10 %. A calculated log K_{OC} of 4.562 indicates very high adsorption to the organic phase of soils and sediments. For the hydrolysis product a log K_{OC} of 2.532 corresponds to a moderate potential for geoaccumulation. An estimated Henry's law constant of $0.000446 \text{ Pa m}^3/\text{mol}$ for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine indicates also very low volatility. Due to the rapid hydrolysis of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, volatilization will not be an important fate process for the environment. The calculated Henry's law constant of $0.941 \text{ Pa m}^3/\text{mol}$ indicates low volatility from aqueous solution. Environmental distribution considerations for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate are of little relevance because the reaction with water is expected to eliminate the substance from the environment with a half-life of approximately 1 hour. The target compartment for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (CAS No. 2855-13-2) is water (99.8 %) as outlined in separate documentation on this compound (the chemical was already evaluated in the OECD HPV Chemicals Program).

A calculated bioconcentration factor of 910 is irrelevant because rapid hydrolysis inhibits bioconcentration. The hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine has a log K_{OW} of 0.99 which indicates a low bioaccumulation potential.

For bacteria (activated sludge of a predominantly domestic sewage) an EC_{50} (3 h) of 263 mg/l (nominal) 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was determined according to OECD TG 209. The aquatic effects of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate relevant in the environment will be those of its hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine. For this substance, the $PNEC_{\text{aquatic}}$ was derived in separate documentation (SIAM 18). For 3-aminomethyl-3,5,5-trimethylcyclohexylamine the lowest valid acute test results of aquatic testing determined for fish, daphnids, and algae were as follows:

<i>Leuciscus idus</i> (Directive 84/449/EEC, semistatic):	LC_{50} (96h) = 110 mg/l;
<i>Daphnia magna</i> (Directive 92/69/EEC, static):	EC_{50} (48 h) = 23 mg/l;
<i>Desmodesmus subspicatus</i> (Directive 88/302/EEC):	E_rC_{50} (72 h) > 50 mg/l; E_bC_{50} = 37 mg/l.

Long-term aquatic toxicity data for 3-aminomethyl-3,5,5-trimethylcyclohexylamine were available for two trophic levels:

<i>Daphnia magna</i> (OECD TG 202, semistatic):	NOEC (21 d) = 3.0 mg/l;
<i>Desmodesmus subspicatus</i> (Directive 88/302/EEC, static):	E_rC_{10} (72 h) = 11 mg/l; E_bC_{10} = 3.0 mg/l.

According to the EU Technical Guidance Document, an assessment factor of 50 was applied to the lower of two long-term results covering two trophic levels, i.e. NOEC for *Daphnia* = 3.0 mg/l. Thus a $PNEC_{\text{aquatic}}$ of 60 µg/l for aquatic organisms was calculated for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

Exposure

Commercial 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is manufactured from 3-aminomethyl-3,5,5-trimethylcyclohexylamine by reaction with either phosgene or urea, the urea route requiring additionally an aliphatic alcohol and a thermal cleavage step where the alcohol is eliminated again and recycled into the process. The global production volume is about 25 000 to 35 000 tons annually, approximately 2/3 thereof in Germany (one production site). Two other production sites are located in the U.S.A. and a fourth one in France.

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is exclusively used as an intermediate or monomer for polyurethanes or other polymers comprising urethane functions in various applications, particularly coatings, varnishes and impregnation for e.g. cars, floors, leather, cans and coils, and special (waterborne or hot melt) adhesives. 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is mainly not employed as such but used for the manufacture of polyurethane coating raw materials like pre-polymers and polyisocyanates.

By the formation of the polymer a high degree of conversion is required for an efficient cross-linking, which will

bind at least one of the two isocyanate functions to the polymer. So exposure to the aquatic environment is not likely to occur from these uses.

In European product registers numerous products containing 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate for such purposes can be found, some of which are consumer products. In the consumer products, the concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is mostly below 1 %, while in products for professional use it may exceed 50 %.

Releases into the environment may occur during production of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, during formulation and use of formulations as well as from its use as a monomer for the production of polymers or other downstream products. In the Sponsor country, the annual release to the atmosphere from production is below 25 kg and there is no release to other compartments of the environment. Direct releases to the hydrosphere can be excluded because the substance is produced and used in the absence of water.

The most probable human exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is through dermal contact or inhalation during manufacture or use. In the Sponsor country, exposure is controlled in occupational settings, and the substance could not be identified in the latest occupational exposure monitoring studies at a detection level of 0.001 mg/m³. In the French production plant ten occupational exposure analyses have been performed between 2002 and 2005 and all concentrations were below 0.01 mg/m³. In the U.S. production plant, the maximum concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate during the years 2003, 2004, and 2005 was 0.024 mg/m³.

In an extensive occupational exposure survey for the German paper industry, the concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was always below the detection limit of 20 µg/m³. In analyses in two car repair workshops, the maximum concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in air was 39 µg/m³.

Consumers may occasionally be exposed to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate when using paint, varnish, or lacquers products including this substance. The frequency and duration of such operations are expected to be low, and the generally low concentration of the substance in such products will keep the doses low. Consumer use is expected to decrease as a consequence of recommendations of the producers since the producers have agreed to recommend in their safety data sheets that handling the substance “requires appropriate protective measures. These products may therefore be used only in industrial or trade applications. They are not suitable for use in homemaker (DIY) applications.”

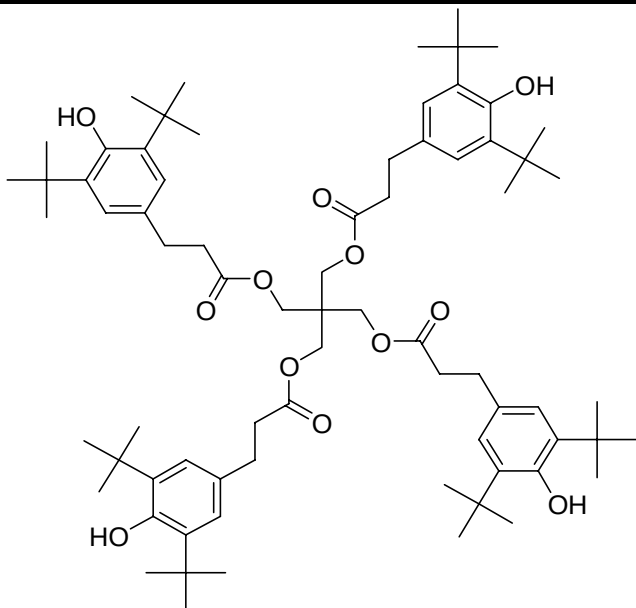
Because of the reactions of the chemical aquatic exposure to the environment will be very limited from these uses.

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 inhalation toxicity [target: respiratory tract], skin corrosion and serious eye damage, skin sensitization and predicted to be a respiratory tract sensitizer because it is a diisocyanate, genotoxicity in vitro). Based on data presented by the Sponsor country (relating to production by one producer which accounts for more than 50 % of global production and relating to the use pattern in several OECD countries), occupational and consumer exposure is anticipated to be low. Adequate risk management decisions are in place regarding the workplace. 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: The chemical is currently of low priority for further work. The chemical (including its hydrolysis product) possesses properties indicating a hazard for the environment (acute aquatic toxicity to invertebrates). Based on the data presented by the Sponsor country (relating to production of one producer which accounts for more than 50 % of the global production and relating to the use pattern in several OECD countries), exposure to the environment 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6683-19-8
Chemical Names	Pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate)
Structural Formula	
SUMMARY CONCLUSIONS OF THE SIAR Human Health No ADME data are available for this compound. The acute oral LD₅₀ of pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) in rats and mice is >5000 mg/kg bw. No clinical signs were reported. For acute dermal toxicity the LD₅₀ in rats is >3160 mg/kg bw. Slight erythema and desquamation were noted. The LC₅₀ for inhalation toxicity in rats is >1951 mg/m³. Ruffled fur and exophthalmus were reported until day 5 after exposure. No human data on acute toxicity are available. Based on tests with rabbits pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) is not considered to be a skin or eye irritant. No human data are available. No sensitization potential is found in the guinea-pig in a Maurer optimisation test. Repeated oral exposure to pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) (0, 1000, 3000 and 10000 ppm) induced decreases of body weight gain, food consumption and thyroid weight in a two year study with rats at 10000 ppm. The NOAEL is set at 3000 ppm (135-166 mg/kg bw/day). No effects were observed in a 90-day study in dogs, leading to a NOAEL of 10000 ppm (302-343 mg/kg bw/day). Pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) was negative in an Ames test and in an <i>in vivo</i> micronucleus test. There are no indications that pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) possesses genotoxic properties.	

In a 2-year dietary carcinogenicity assay in mice (0, 100, 300 and 1000 ppm) and a chronic toxicity study in rats (0, 1000, 3000 and 10000 ppm) no increased tumour incidence was found at any of the dose levels tested.

In a two generation study in rats pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) (0, 1000, 3000 and 10000 ppm) did not have any adverse effects on reproduction based on absence of effects on mating performance, pregnancy rate and gestation duration at the highest dose tested 688 mg/kg bw/day (males) and 823 mg/kg bw/day (females). The NOAEL for developmental toxicity is 688-823 mg/kg bw/day (10000 ppm) based on the absence of effects at the highest dose tested.

In teratogenicity studies in rats and mice (0, 150, 500 and 1000 mg/kg bw/day) performed mainly according to OECD TG 414 the NOAEL for maternal toxicity and teratogenicity is 1000 mg/kg bw/day. The NOAEL for developmental effects is set at 500 mg/kg bw based on an increased incidence of delayed ossification in mice at 1000 mg/kg bw. No teratogenic effects were observed.

Environment

Pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) is a white to off-white powder with a melting point of 116.5°C, a calculated boiling point of 1130°C and a negligible vapour pressure (1.55E-31 Pa at 25 °C). The substance has a very low solubility in water (<0.1 mg/L) and a high log Kow (≥ 5). The substance has four phenolic hydroxyl groups that can undergo protolysis. Dissociation constants (pK_{a1} to pK_{a4}) are calculated to be 10.90, 11.54, 12.11, and 12.75 at 25 °C. Therefore the substance is a very weak acid and is expected to occur almost entirely as non-dissociated (neutral) species in natural aquatic environment.

Pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) is not readily biodegradable under experimental test conditions (4-5% in OECD TG 301B). The substance contains ester bonds that are not expected to hydrolyse rapidly under environmental conditions. Hydrolysis is not considered to be an important abiotic degradation process (EPIWIN, calculated $T_{1/2}$ for hydrolysis in water is 75 days at pH 8 and 2 years at pH 7).

The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) in air is 1.2 hours. Level III fugacity modelling showed that after release to the environment 99-100% of pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) will partition to sediment and soil, while <1% ends up in water.

Despite its high log Kow (19.6) the large diameter of the molecule (17.9 Å) indicates that the chemical is not considered to be bioaccumulative. An experimental determination of the BCF is available indicating a low potential for bioaccumulation of the substance in fish (BCF <2.3). Although the reliability of the test is not assignable the measured BCF is confirmed by calculations with QSAR models (EPIWIN) and EUSES.

For pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) no effects at the water solubility level (<0.1 mg/L) were observed in acute fish, daphnia and algae tests. A static study in zebra fish performed according to OECD TG 203 showed no treatment related mortality at the highest concentration tested (96-h LC_{50} >83 mg/L). *Daphnia magna* were exposed to the substance (dispersant used) during 24 hours in a static test (OECD TG 202). No effects on mobility were found at any of the concentrations tested (24-h EC_{50} is >100 mg/L). A 72h study with the algae *Scenedesmus subspicatus* showed no effect at the highest concentration tested (72-h EC_{50} >141 mg/L measured; growth rate and inhibition of biomass).

Exposure

For the year 2005 the global market for pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) was estimated to be 34,600 tonnes. The primary use of pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) is as a sterically hindered phenolic primary antioxidant for processing and long-term thermal stabilization. The substance is used as a non-discolouring stabilizer for organic substrates like polyolefins and other plastics, synthetic fibres, elastomers, adhesives, waxes, oils and fats. It protects against thermo-oxidative degradation. Concentration levels in the polymers will range from 0.05-0.5% depending on the substrate and processing conditions (e. g. temperature of the processed polymer).

Limited consumer exposure is expected from the primary use of pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) as phenolic antioxidant bound in a polymeric matrix (e.g. packaging materials). Other uses of pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate) are preparations and articles

such as adhesives, lubricants, construction and insulating materials, fillers, screeding compounds and joint sealants, paints, lacquers and varnishes (Products Register of Nordic Countries and Swiss Register of Chemical Products).

There is potential environmental exposure during production and processing of pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) and due to losses of the antioxidant from preparations/products during service time or waste treatment. The migration rate from the polymer matrix in landfills is expected to be very low.

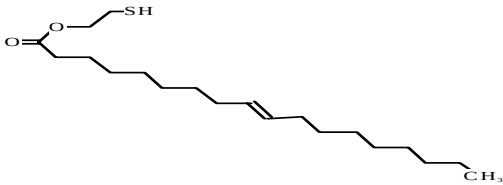
The use of low-dust granules and pellets will limit occupational exposure during packaging and handling of the additive (e.g. opening of bags, blending or filling operations).

RECOMMENDATION, 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 profile.

Environment: The substance is a candidate for further work. Short-term aquatic toxicity tests at 3 trophic levels are available which show no effects at the water solubility level in any of the tests. Although apparent emissions at manufacturing and processing sites in the sponsor country and emissions from the substances use in chemical preparations and articles are expected to be low, an exposure assessment and if then indicated a risk assessment is recommended. As pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) is not readily biodegradable and might end up in the sediment and soil, further testing on sediment dwelling organisms and degradation in sediment and soil may be necessary.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	68440-24-4
Chemical Name	Fatty acids, tall-oil, 2-mercaptoethyl esters (2-MET)
Structural Formula (and Chemical Identity Information)	2-Mercaptoethyl oleate (representative structure for 2-MET)  Reaction product of tall oil fatty acid with 2-mercaptoethanol (variable) $\text{HSCH}_2\text{CH}_2\text{OCOC}_n\text{H}_{2n+1}$ where $n=13$ to 17
SUMMARY CONCLUSIONS OF THE SIAR Human Health There were no available data on the toxicokinetic, metabolism or distribution of 2-MET. The oral (gavage) LD₅₀ in female rats (1/dose group) of 2-MET is > 800 mg/kg bw but < 2500 mg/kg bw. The LD₅₀ in male rats (1/dose group) of 2-MET is > 1700 mg/kg bw but < 2500 mg/kg bw. Instances of nasal discharge, fecal and urinary staining, and/or reduced food consumption; respiration and activity were noted, primarily in the females during the first 24 to 48 hours after dosing. The dermal LD₅₀ in rabbits of 2-MET is > 2000 mg/kg bw. Mild to moderate erythema and edema and desquamation were observed. 2-MET is moderately irritating to skin and mildly irritating to the eyes. Sensitisation data are not available for 2-MET. In a repeated-dose and reproductive/developmental screening study, groups of male and female rats received 2-MET by gavage at doses of 0, 40, 125 and 400 mg/kg bw/d for 14 days prior to mating and during the mating period. Daily dosing of the females was continued throughout pregnancy and up to day 4 of lactation. Males were dosed for at least 46 days and until the day prior to scheduled necropsy. Test item related effects indicative of systemic toxicity were observed in the mid and high dose group. The NOAEL for male animals was 40 mg/kg bw/d based on inflammatory edema of the forestomach; for females the NOAEL was 125 mg/kg bw/d. Repeated-dose inhalation or dermal studies are not available for 2-MET.	

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An *in vitro* bacterial mutation assay has not revealed any evidence of genotoxic potential of 2-MET. However, an *in vitro* study in mammalian cells (V-79 cells of the Chinese Hamster) with 2-MET was negative for chromosome aberrations in the absence of metabolic activation and equivocal for chromosome aberrations in the presence of metabolic activation. 2-MET was negative in an *in vivo* mouse micronucleus assay. 2-MET showed evidence for clastogenic potential when tested *in vitro*.

In the above-mentioned repeated-dose and reproductive/developmental screening study, two high-dose females were found dead on days 20 and 22 of the gestation period, respectively. The cause of death of one female was considered to be test substance-related. The cause of death of the second female could not be established. Beginning near the end of the pre-mating period and until the day before scheduled necropsy, all females in the 400 mg/kg bw/d dose group showed signs of discomfort after administration of the test substance. At 400 mg/kg bw/d, changes in food consumption (males: -5.7%; females: -17.0% pre-pairing, -31.9% lactation) and body weight (-5.7%) were observed in both sexes and mean liver and kidney weights were significantly increased in both sexes. In males, prostate and seminal vesicle weights were significantly decreased. The NOAEL for fertility was 125 mg/kg bw/d based on an increased pre-coital time, a reduced gestation index and an increase in post-implantation loss at the highest dose tested. The NOAEL for maternal toxicity was 125 mg/kg bw/d based on the above effects at the highest dose. The NOAEL for developmental effects was 40 mg/kg bw/d based on increased liver weight in pups at 125 and 400 mg/kg bw/d. The NOAEL for teratogenicity is 400 mg/kg bw/d (the highest dose tested).

Environment

2-Mercaptoethyl tallate [2-MET] is a mixture produced by a reaction of 2-mercaptoethanol [$\text{SCH}_3\text{CH}_2\text{OH}$; 2-ME] with tall oil fatty acid [TOFA]. TOFA is a complex mixture of saturated aliphatic straight chain fatty acids made principally of C_{16} but ranging from C_{14} to C_{18} .

The freezing point of 2-MET is 16.9°C and the mean boiling point is 298 °C at 1023.9 hPa. The vapor pressure is 0.00161 hPa at 20 °C. The water solubility of 2-MET is 0.083 mg/L. 2-Mercaptoethyl oleate was used as a representative structure for estimation of partition coefficient and Henry's Law Constant since this oleic acid ester is the predominant component in 2-MET. The estimated log Kow of 2-mercaptoethyl oleate is 8.45 and the Henry's Law Constant is $8.217 \times 10^{-4} \text{ atm}\cdot\text{m}^3/\text{mole}$. 2-Mercaptoethyl oleate was used as a representative structure for estimation of photodegradation and transport of 2-MET in the environment. The overall OH rate constant for 2-mercaptoethyl oleate ranges from $117.8 \times 10^{-12} \text{ cm}^3/\text{molecule}\cdot\text{sec}$ [cis] to $125.4 \times 10^{-12} \text{ cm}^3/\text{molecule}\cdot\text{sec}$ [trans] with a half-life range in hrs of 1.090 [cis] to 1.024 [trans]. These results apply for photodegradation in air.

The hydrolysis of 2-MET in water without solvent could not be measured due to its very low water solubility (which prevents analysis at extremely low concentrations) and because it is a mixture of fatty acid esters (which makes analyzing the parent compounds and hydrolysis products difficult). However, the hydrolysis of 2-MET was experimentally determined in the presence of co-solvent (50% acetonitrile). Estimated half-lives for 2-MET under these conditions at pH 4, 7 and 9 were indefinite, four days and less than one day, respectively. The anticipated hydrolysis products are 2-ME and TOFA. The hydrolysis observed could be more rapid in the presence of acetonitrile than would be observed in the absence of a co-solvent. Therefore, reliably determining the "rate" is problematic because of the limited water solubility.

Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 1000 kg/h for each media, shows the following percent distribution for 2-mercaptoethyl oleate: Air = 0.08%; Soil = 28%; Water = 7.3%; Sediment = 64.6%. In a ready biodegradability test (Modified Sturm Test (CO₂ evolution) test), at the end of the 28-day exposure period, the mean biodegradation of the test substance was 71.2%, showing that 2-MET is readily biodegradable. Bioaccumulation is anticipated to be low since the calculated bioconcentration factor of 2-mercaptoethyl oleate is 21.

Aquatic toxicity testing has not been conducted with 2-MET. The aquatic toxicity endpoints have been addressed using surrogate data from the breakdown/hydrolysis products of 2-MET. These breakdown products include 2-mercaptoethanol (2-ME; CAS No. 60-24-2), which was assessed within the OECD HPV Programme and Tall Oil

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Fatty Acid (TOFA; CAS No. 61790-12-3), which was assessed in the USEPA HPV Challenge Program.

The following values are available from the short-term tests on aquatic species with 2-ME: fish: LC_{50} (96 h) = 37 mg/l; invertebrates: EC_{50} (48 h) = 0.4 mg/l; algae: E_rC_{50} (72 h) = 18.6 mg/l (E_bC_{50} : 7.0 mg/l). The following values for TOFA are available from the short-term tests on aquatic species with fish, invertebrates and algae: *Pimephales promelas* 96 hr LC_{50} >1000 mg/L; *Daphnia magna* 48 hr EC_{50} >1000 mg/L; and *Pseudokirchneriella subcapitata* 72 hr ErC_{50} >1000 mg/L (72 hr EbC_{50} = 854.9 mg/L h). Although a chronic daphnia study with 2-MET was proposed, 2-MET has low water solubility, as such a high concentration (50%) of co-solvent is needed to keep 2-MET solubilized, and this level is incompatible with life for any of the aquatic test species. Further, development of a methodology to analyze 2-MET in freshwater to support ecotoxicological studies proved unsuccessful. It appears that several factors potentially including irreversible adsorption to glassware, loss on rotary evaporation and hydrolysis of the ester functionality to the corresponding acid and alcohol precluded the successful development of this methodology.

Exposure

Approximately 12,250 tonnes were produced in the sponsor country (USA) in 2002. Purity of the commercial product ranges from 75 to 95%. Impurities include 0-15 % 2-mercaptoethanol (2-ME; CAS 60-24-2) and 0-15 % tall oil fatty acid (TOFA; CAS 61790-12-3).

In production plants, 2-MET is handled in closed systems (closed piping). Air streams and waste water are treated prior to release to the environment. Air emissions from the manufacturing process are treated using a caustic scrubber and then a thermal oxidizer with a demonstrated removal efficiency > 99.9% for volatile organic compounds (VOCs). Wastewater from the process area is treated on site in a biological wastewater treatment system (primary and secondary treatment). Equipment is not washed with water but instead with solvent or polyvinyl chloride (PVC), which is reprocessed; this method should limit emissions and potential for exposure. Personal protective equipment is used during production to minimize exposure. Worker exposure during manufacture due to non-accidental releases includes exposure during stabilizer sampling and possibly during maintenance. Potential routes of exposure during manufacture include dermal, ingestion and inhalation. 2-MET is stored at ambient temperature in bulk storage tanks with atmospheric vents. This material is transported from the manufacturer by road, marine and air in several container types and sizes.

The predominant uses for 2-MET are as a reactant used in the production of organotin PVC stabilizers and as a diluent in organotin PVC stabilizers. 2-MET's presence within PVC is approved for use as an indirect food additive. Studies showed that 2-MET and other stabilizers did not leach out of the matrix of PVC products.

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

Human Health: This chemical is a candidate for further work. The chemicals possess properties indicating a hazard for human health (acute and repeated-dose toxicity, *in vitro* mammalian genotoxicity, and reproductive/developmental toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: This chemical is of low priority for further work. The chemical has properties indicating a hazard for the environment (acute toxicity to fish, aquatic invertebrates, and algae (2-ME)). However the chemical is of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7632-00-0
Chemical Name	Sodium nitrite
Structural Formula	$\text{O}=\text{N}-\text{O}^- \quad \text{Na}^+ \quad \text{NaNO}_2$

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Sodium nitrite has been reviewed by a number of international organizations: JECFA (Joint FAO/WHO Expert Committee on Food Additives); National Academy of Sciences (NAS); US National Institute of Environmental Health Sciences (NIEHS); National Institute of Public Health and the Environmental Hygiene, Netherlands; US National Toxicology Program (NTP); and California EPA (CAL/EPA).

Nitrite in blood is highly reactive with haemoglobin and causes methaemoglobinaemia. Ferrous iron associated with haemoglobin is oxidized by nitrite to ferric iron, leading to the formation of methaemoglobin. Humans are considered to be more sensitive than rats in this respect.

The primary acute effect of sodium nitrite in rats and mice is methaemoglobinaemia. Methaemoglobin concentrations in SD rats increased from 45% to 80% over 1 hour after an oral dose of sodium nitrite at 150 mg/kg bw and they returned to normal levels within 24 hours in surviving rats.

LD₅₀ values by gavage are 214 mg/kg bw (males) and 216 mg/kg bw (females) in mice. In an acute inhalation study (which could not be validated) methaemoglobin levels in female rats were significantly increased after 4 hours exposure to 10 mg/m³ sodium nitrite. The increase was judged not to be haematologically significant. No significant increase was observed in exposed males. There were no toxicologically significant effects on animals maintained for 14 days post exposure. No information on acute dermal toxicity is available.

Based on the available information, sodium nitrite is a moderate eye irritant, but is non-irritant to skin in rabbits. No studies are available investigating the sensitising potential of sodium nitrite in animals. No cases of sensitisation have been reported in humans.

In a repeated dose toxicity study [NTP] male and female F344/N rats were exposed to 0, 375, 750, 1500, 3000 or 5000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 30, 55, 115, 200, or 310 mg/kg bw/day in males and 0, 40, 80, 130, 225, or 345 mg/kg bw/day in females) in drinking water for 14 weeks. Methaemoglobin levels were significantly elevated in all treated groups compared to the controls by the end of the treatment period. For males, mean methaemoglobin levels after 14 weeks were 0.03±0.01, 0.08±0.01, 0.12±0.02, 0.25±0.07, 0.71±0.20 and 3.38±0.80 g/dL at doses of 0, 30, 55, 115, 200, and 310 mg/kg bw/day. For females, mean methaemoglobin levels after 14 weeks were 0.06±0.02, 0.14±0.02, 0.16±0.02, 0.48±0.05, 0.99±0.20 and 2.27±0.54 g/dL at doses of 0, 40, 80, 130, 225 and 345 mg/kg bw/day. The NOAELs were not determined (increased methaemoglobinaemia). The LOAELs for other endpoints were 115 mg/kg bw/day (decreased sperm motility) in males and 225 mg/kg bw/day (increased relative weight of the kidney and spleen) in females.

In a second 14-week repeated dose toxicity study [NTP] male and female B6C3F1 mice were exposed to 0, 375, 750, 1500, 3000 or 5000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 90, 190, 345, 750, or 990 mg/kg bw/day in males and 0, 120, 240, 445, 840, or 1230 mg/kg bw/day in females) in drinking water. Methaemoglobin levels were not reported however there were no clinical signs of toxicity. The LOAELs

were 750 mg/kg bw/day (extramedullary haematopoiesis in the spleen, degeneration of the testis) in males and 445 mg/kg bw/day (extramedullary haematopoiesis in the spleen) in females.

In a two-year chronic toxicity/carcinogenicity study [NTP] male and female F344/N rats were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 35, 70 or 130 mg/kg bw/day in males and 0, 40, 80 or 150 mg/kg bw/day in females) in drinking water. There were no clinical findings related to exposure. Methaemoglobin levels were measured at two weeks and three months. At both 2 weeks and three months, methaemoglobin levels were high at night when the rats were actively feeding and drinking and low during the day when the rats were less active. Methaemoglobin levels tended to increase with increasing dosage.

In a second two-year study [NTP] male and female B6C3F1 mice were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 60, 120 or 220 mg/kg bw/day for males and 0, 45, 90 or 165 mg/kg bw/day for females) in drinking water. There were no clinical findings related to exposure. At 12 months, no significant increase in methaemoglobin level was observed in either sex at any dose.

Based on the two-year studies, the NOAELs for rats were 130 mg/kg bw/day in males and 150 mg/kg bw/day in females. For mice the NOAELs were 220 mg/kg bw/day in males and 165 mg/kg bw/day in females

Sodium nitrite is a direct-acting, base-pair substitution mutagen in organisms ranging from bacteria to mammalian cells *in vitro*. This substance induced chromosomal aberrations in mammalian cells *in vitro*. There is evidence of potential *in vivo* genotoxicity. The substance tested positive in a micronucleus test (peripheral blood) when mice were dosed by gavage at 10 – 20 mg/kg bw (4 times at 24 hrs intervals) but was negative in a second study where mice were dosed via drinking water at dosed up to 900 mg/kg bw/day (females) for 14 weeks. In a chromosomal aberration test, pregnant rats were dosed with 210 mg/kg bw/day for 13 days. Positive results for the induction of chromosomal aberrations in bone marrow of the parents and liver cells of embryos were reported.

In a two-year chronic toxicity/carcinogenicity study [NTP] male and female F344/N rats were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 35, 70 or 130 mg/kg bw/day for males and 0, 40, 80 or 150 mg/kg bw/day for females) in drinking water. The incidences of hyperplasia of the forestomach epithelium in high dose males (44/50) and females (40/50) were significantly greater than those in the control groups (12/50 males, 8/50 females). The incidence of fibroadenoma of the mammary gland was significantly increased in 80 mg/kg bw/day females, and the incidences of multiple fibroadenoma were increased in 40 and 80 mg/kg bw/day females; however these neoplasms occur with a high background incidence and no increase was seen in the high dose group. The incidences of mononuclear cell leukemia were significantly decreased in 70 and 130 mg/kg bw/day males (7/50 and 3/50, respectively) and 80 and 150 mg/kg bw/day females (1/50 and 1/50, respectively) compared with controls (17/50 males, 15/50 females). Under the conditions of this study there is no evidence of carcinogenic activity of sodium nitrite in F344/N rats at approximate doses of up to 130 mg/kg bw/day in males and 150 mg/kg bw/day in females over a two year period.

In another NTP study male and female B6C3F1 mice were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 60, 120 or 220 mg/kg bw/day for males and 0, 45, 90 or 165 mg/kg bw/day for females) in drinking water for two years. The incidences of squamous cell papilloma or carcinoma (combined) in the forestomach of female mice occurred with a positive trend (1/50, 0/50, 1/50 and 5/50 at doses of 0, 45, 90 or 165 mg/kg bw/day, respectively). The incidence of hyperplasia of the glandular stomach epithelium was significantly greater in 220 mg/kg bw/day males (10/50) than in the controls (0/50). Under the conditions of this study there is no evidence of carcinogenic activity of sodium nitrite in male B6C3F1 mice at doses up to approximately 220 mg/kg bw/day over a two year period. There is equivocal evidence of carcinogenic activity in female mice, based on the positive trend of squamous cell papilloma or carcinoma (combined) in the forestomach.

Various other carcinogenicity studies in rats were negative. Moreover, some even showed a reduction in tumor risk (e.g. lymphoma or leukemia). WHO concluded that there was no evidence of carcinogenic activity of sodium nitrite in rats and mice based on the findings of NTP carcinogenicity studies.

There is evidence for transfer of sodium nitrite to fetuses in rats and mice. Reproductive success in the F1 generation was not affected. Increase in mortality of pre- and postnatal offspring and decrease in body weight of preweaning pups were observed in rat dams given a diet containing sodium nitrite at 0.0125% (10.75 mg/kg bw/day), 0.025% (21.5 mg/kg bw/day) and 0.05% (43 mg/kg bw/day), and the NOAEL is considered to be 10.75 mg/kg bw/day. Reproductive toxicity by continuous breeding in the mice was conducted with drinking water at doses of 125, 260 and 425 mg/kg bw/day, and no adverse effect on reproductive performance or necropsy endpoint were observed. The NOAEL is estimated to be 425 mg/kg bw/day. Sodium nitrite caused maternal anemia and the incidence of abortion and fetal mortality increased when administered to pregnant guinea pigs in drinking water and LOAEL is considered to be at 60 mg/kg bw/day.

From the weight of evidence, sodium nitrite appears to affect erythropoiesis, haematological parameters and brain development resulting in mortality and poor growth of offspring.

In humans, sodium nitrite causes smooth muscle relaxation, methaemoglobinaemia, and cyanosis. Infants are particularly sensitive. A large proportion of haemoglobin in infants is in the foetal haemoglobin form, which is more readily oxidised to methaemoglobin than adult haemoglobin. Further, reduced nicotinamide-adenine dinucleotide (NADH)-dependent methaemoglobin reductase, the enzyme responsible for reduction of methaemoglobin back to normal haemoglobin, has only about half the activity present in adults.

Environment

Sodium nitrite is white or slightly yellow hygroscopic granules, rod or powder, which is very soluble in water (820 g/L at 20 °C). Melting point, boiling point, vapour pressure and partition coefficient are 271 °C, >320 °C (decomposes), 9.9E-17 hPa (25°C) and log Kow = -3.7, respectively. Fugacity model Mackay level III calculations suggest that the substance will distribute mainly to soil if released to the air or soil compartments separately or to all three compartments simultaneously and almost exclusively to water if released to the water compartment. Estimated value of Henry's constant is 2.06E-07 atm-m³/mole. This substance dissociates immediately into sodium and nitrite ions in water. The nitrite ion is a component of the nitrogen cycle. In the environment, bacteria of the genus *Nitrobacter* oxidise nitrites to nitrates. Nitrates are reduced to nitrogen by anaerobic bacteria present in soil and sediment. The estimated BCF is 3.162 and hence bioaccumulation is not significant. Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 82.3 days.

The LC₅₀ values for the acute toxicity of sodium nitrite to fish reported in the literature vary widely between the species tested; LC₅₀ (96h) = 0.54 mg NaNO₂/L for *Oncorhynchus mykiss*; LC₅₀ (96h) = 35 mg NaNO₂/L for *Ictalurus punctatus*; LC₅₀ (96h) = 691.0 mg NaNO₂/L for *Micropterus salmoides*; and LC₅₀ (96h) = 1010.4 mg NaNO₂/L for *Anguilla japonica*, for example. This difference has been attributed to the ability of certain species, such as eels, bass and sunfish to prevent nitrite from crossing the gill membrane and entering the blood, whilst other species such as rainbow trout concentrate nitrite in their blood. The range of toxicity values reported for some species of fish varies widely and is believed to be dependant on the quality of the water used in the test with pH, chloride and calcium ion concentration all having an influence. In particular, chloride ion concentration has been shown to be important, with increasing concentrations leading to a decrease in the toxicity of nitrite. As with fish, there is variation in toxicity between invertebrate species. Sodium nitrite is toxic to invertebrates such as *Cherax quadricarinatus* (LC₅₀ (96h) = 4.93 mg NaNO₂/L and *Thamnocephalus platyurus* (LC₅₀ (24h) = 3.9 mg NaNO₂/L), whereas other species, such as *Procambarus clarkii* (LC₅₀ (96h) = 18.7 mg NaNO₂/L) and *Penaeus paulensis* are much less sensitive (LC₅₀ (96h) = 539.2 mg NaNO₂/L). The presence of chloride ions has been found to mitigate nitrite toxicity in some species. Acute toxicity to green alga (*Desmodesmus subspicatus*) is > 100 mg/L (72-h E_rC₅₀ and E_bC₅₀) [OECD TG 201].

No data is available for chronic toxicity of sodium nitrite in fish. In invertebrates, an 80-day NOEC of 9.86 mg NaNO₂/L for *Penaeus monodon* has been reported. The NOEC value in green alga (*Desmodesmus subspicatus*) is 100 mg/L (72-h for growth rate and biomass) [OECD TG 201].

For other aquatic organisms, the EC₅₀ (48h, deformation) and LC₅₀ (48h) for the protozoa *Spirostomum ambiguum* were 421 and 533 mg NaNO₂/L, respectively; for the microalgae *Tetraselmis chuii* the EC₅₀ (96h, mobility) and NOEC (96h, mobility) were 7886 and 3740 mg NaNO₂/L, respectively.

Exposure

Total production of sodium nitrite in Japan was 10,000 - 50,000 t/year in 2001. Worldwide production of sodium nitrite is not available.

This substance is used in closed system, for non dispersive use, and also for wide dispersive use. Workers are recommended to wear protective gear such as a mask, rubber gloves and goggles to prevent exposure. There are no available official recommendations or regulations for occupational exposure limits to this substance. This substance is widely used in various industries in the category including agricultural, basic chemicals, chemical industry, and others. The use in synthesis includes as raw material for caprolactam and others. This substance is used widely as food/foodstuff additives, corrosion inhibitor, and so forth.

The nitrite ion is ubiquitous in the environment, where it forms part of the nitrogen cycle. The source of nitrogen is natural or anthropogenic. Fertilizers are considered to be the main anthropogenic source of nitrogen, although anthropogenic nitrogen oxide and dioxide present in the atmosphere from combustion processes are also sources of nitrite and nitrate in soils and surface waters, delivered via acid rain. Naturally occurring nitrogen oxide and dioxide in the atmosphere are also possible sources of nitrite. It should be noted that although the nitrite ion (NO_2^-) may cause a concern when assessing the potential eutrophication hazard including drinking water quality in certain regions, the use of this substance (NaNO_2) as a fertilizer has not been reported. Therefore this substance has a potential of eutrophication, but its influence is lower than that of the fertilizers.

The most common source of exposure of anthropogenic sodium nitrite to consumers is from its use in cured meat products. Exposure to nitrite also occurs from vegetables and drinking water. Nitrite can be formed in the body through reduction of nitrate by enteric bacteria and mammalian nitrate reductase. The Joint FAO/WHO Expert Committee on Food Additives established an acceptable daily nitrite intake of 0 to 0.07 mg/kg bw/day. Various countries have set limits for nitrite through water quality regulations.

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

Human Health: The chemical is a candidate for further work.

Environment: The chemical is a candidate for further work.

The chemical possesses properties indicating a hazard to human health (acute toxicity, irritation, repeated toxicity, mutagenicity, and reproductive toxicity) and the environment (acute toxicity). Given the wide dispersive use of this substance, member countries are invited to perform an exposure assessment, and if necessary a risk assessment for these uses. It is acknowledged that some uses (e.g. as a food additive) as well as the presence in drinking water are already regulated in many member countries. It is recommended that the information on possible total exposure from regulated and non-regulated use be shared between regulatory agencies.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7758-11-4
Chemical Name	Dipotassium hydrogenphosphate (DKP)
Structural Formula	$ \begin{array}{c} \text{O}^- \\ \\ \text{HO}-\text{P}-\text{O}^- \\ \\ \text{O} \\ \text{K}^+ \quad \text{K}^+ \end{array} $ K_2HPO_4

SUMMARY CONCLUSIONS OF THE SIAR

Note: The current assessment focuses exclusively on dipotassium hydrogenphosphate and the results of tests performed with dipotassium hydrogenphosphate. This assessment should be considered as a contribution to an overall assessment of phosphoric acid and its salts. The conclusions reached in this assessment only apply to dipotassium hydrogenphosphate, acknowledging that other test results with other phosphates could lead to revisions of these conclusions.

Human Health

There is no information on toxicokinetics, metabolism and distribution of DKP. The acute oral toxicity study (OECD TG 423) of DKP in rats showed that this chemical did not cause any significant changes at 2,000 mg/kg bw. Therefore, the oral LD₅₀ value in female rats was greater than 2,000 mg/kg bw.

No valid skin/eye irritation studies were available for DKP.

No sensitization studies have been identified for DKP.

In the repeated oral dose toxicity study (following partly OECD TG 422) rats were administered with DKP at doses of 0 and 1,000 mg/kg bw/day for 42 days for males and for 42 to 54 days for females. Although there was significant decreases in the liver and heart weights to body weight ratio, there were no gross or histopathologic alterations. The significant increases in haematological parameters (RBC, hemoglobin, hematocrit in female) and clinical chemistry findings (aspartate aminotransferase and potassium in male and chloride, creatinine, total protein, albumin, phosphorus and calcium in female) were found. These changes were reversible after 14 days and therefore were not considered adverse. Consequently, the LOEL was considered to be 1,000 mg/kg bw/day in male and female rats. In another dietary study, the NOAEL for rats is 5.1 % (equivalent to 2,623 mg/kg bw/day) the highest doses tested, based on significantly increased kidney weights without histopathological lesions.

An *in vitro* bacterial reverse mutation test with *Salmonella typhimurium* (TA 97 and 102) has not revealed any evidence of genotoxic potential of DKP. This substance has negative result in an *in vitro* chromosome aberration test (OECD TG 473).

DKP did not show reproductive/developmental toxicity because any changes in histopathological, weight of reproductive organs, and the mating parameters were not observed in rats. In addition and, no effect on growth and development in pups exposed through parent animals (for 42 days in males and for 42 to 54 days in females) (following partly OECD TG 422). The NOAELs for the fertility and developmental toxicities were 1,000 mg/kg bw/day. No carcinogenicity study is available.

Environment

DKP exists as a white crystalline powder or as hygroscopic granules. It is very soluble in water (1,493 g/L of cold water). DKP decomposes at high temperature and does not have a melting point. It is estimated vapour pressure of 1.78×10^{-10} mmHg. Due to its inorganic properties, no data were applicable for partition coefficient in n-octanol/water. This chemical dissociates in water releasing potassium and phosphate ions. The predominant species in alkaline phosphate solutions is KHPO_4^- . In the acidic phosphate solution, H_3PO_4 is the predominant species. Photodegradation, environmental fate modelling and biodegradation cannot be performed with the available data and bioaccumulation is not expected.

The following studies for aquatic organisms are available:

Fish (*Oryzias latipes*): LC_{50} (96 h) > 100 mg/L

Invertebrates (*Daphnia magna*): EC_{50} (48 h) = 118.9 mg/L

Green algae (*Pseudokirchneriella subcapitata*): E_rC_{50} (72 h) > 100 mg/L (growth rate),
 E_bC_{50} (72 h) = 60mg/L (biomass)

Exposure

In Korea, the estimated amount of production for DKP was 2,767, 3,107, and 2,406 tonnes in 2003, 2004, and 2005, respectively. In Nordic countries, the total use volume of DKP was 43 and 130 tonnes in 2003 and 2004. This chemical is the High Production Volume (HPV) chemical in EU.

The substance has widespread uses as food/foodstuff additives, a nutrition agent in powdered milk, a coffee cream stabilizer, a sub-material of ferment, a stabilizer of lubricant oil, a washing agent, an anticorrosive, a pH buffering and fertilizer in Korea.

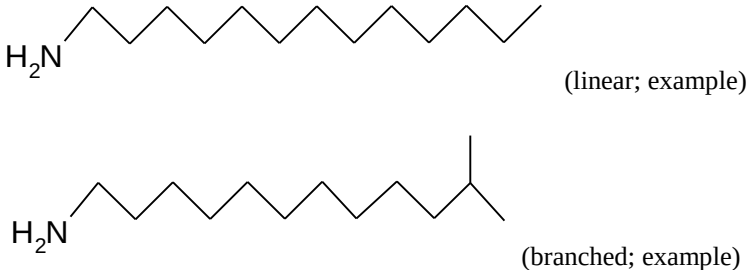
Industrial hygiene monitoring data shows that exposure values have been under acceptable limits. The 8hr-TWA (Time Weighted Average) concentrations of phosphoric acid were N.D. ~ 0.0012 mg/m³ in the workplaces, which are below the occupational exposure limit of 1 mg/m³. The dust containing DKP is controlled by ventilation systems and PPE (person protective equipment) in all facilities of Korea. Therefore, it is inferred that exposure possibility is low for workers.

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 low hazard for human health.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a low hazard profile although Phosphate has indirect and long-term effects to the ecosystems based on eutrophication. This is an inorganic chemical that readily dissociates in water and bioaccumulation is not expected.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	86089-17-0
Chemical Name	Tridecylamine, branched and linear (TDA)
Structural Formula	 (linear; example) (branched; example)

SUMMARY CONCLUSIONS OF THE SIAR**Analogue rationale**

Tridecylamine, branched and linear (TDA; CAS 86089-17-0) is a mixture of isomers with C13-amines as the dominating group of isomers (ca. 68 %). Approximately 16 % refer to C12-amines and ca. 12 % to C11-amines; the remaining percentage belongs to C10- and C14-amines. Data from the linear C13-amine n-tridecylamine (n-TDA; CAS 2869-34-3), which is a component of the isomeric mixture were used to bridge existing data gaps in environmental chemistry (log K_{OW} , log K_{OC} , Henry's law constant, photo degradation) and ecotoxicity for TDA (tests for all three endpoints are available for TDA, but no tests with measured concentrations are available for TDA.). n-TDA was selected as a worst case situation (based on QSAR-calculations [EPIWIN] branched TDA have lower log K_{OW} and ecotoxicity than n-TDA.).

Human Health

TDA, like other monoalkylamines, undergoes oxidative deamination by monoamine oxidase and is further metabolized to CO_2 after i.p. injection.

TDA induced acute oral toxicity in rats with an oral LD_{50} of 820 mg/kg bw. Clinical signs included dyspnea, encrusted eyes and noses, diarrhea, restlessness, salivation, piloerection, and hunched posture.

There are no acute dermal toxicity data available. In mice, exposed head-nose only via inhalation to 23 or 90 mg/m^3 of TDA for 45 minutes, clinical signs included piloerection, poor general condition, and - at 90 mg/m^3 only - labored breathing.

TDA was corrosive to the rabbit skin and eye. Upon contact with the human skin or eye, it may cause burns and serious damage to the eye. A depression of the respiratory rate indicative of pulmonary irritation was found in mice exposed to 3.8 - 90 mg/m^3 of TDA vapors via head-nose inhalation for 45 minutes.

There were no studies on the sensitization potential of TDA available.

The repeated dose toxicity of TDA was tested under GLP conditions in a 90 day oral gavage study according to OECD TG 408 (including a Functional Observation Battery) in male and female Wistar rats at dose levels of 5, 15, and 45 mg/kg bw/day. No changes were seen in animals at 5 mg/kg bw/day. In the groups at 15 mg/kg bw/day, signs of toxicity included statistically significantly reduced body weights in males and reduced food efficiency in males during the first 14 days of treatment, and respiration sounds and labored respiration in 4/10 male and in 4/10 females starting from day 32 until the end of the study. Similar findings, but in higher frequency and severity were seen in the groups at 45 mg/kg bw/day. This dose also led to increased relative liver weights in females and was lethal for one male and one female animal. Sensimotor tests and reflexes were not affected by the treatment in any group except for the landing foot-splay test in high-dose males, probably due to the generally

poor condition of these animals. Histopathological examinations revealed no changes beyond the normal. The NOAEL was at 5 mg/kg bw/day.

TDA was not mutagenic in an Ames test that was conducted under GLP according to the old OECD TG 471(1983) using the *S. typhimurium* test strains TA1535, TA100, TA1537, and TA98, both with and without metabolic activation. Both the standard plate and the preincubation test were performed. *In vivo*, TDA did not induce clastogenic or aneugenic effects in a micronucleus study performed under GLP conditions on mice according to the OECD TG 474. Clinical signs of toxicity were seen at the oral doses of 400 and 600 mg/kg bw, and erythropoiesis was slightly inhibited at 600 mg/kg bw showing that the target organ was reached. TDA is therefore considered as non-genotoxic.

There is no fertility study with TDA available. No histopathological changes and no relevant effects on reproductive organ weights or on reproductive function parameters (sperm parameters, estrous cycle) were found in a 90-day oral study on rats according to OECD TG 408 with additional investigations of reproductive toxicity up to and including the highest tested dose level of 45 mg/kg bw/day (NOAEL).

At a maternally toxic dose level of 80 mg/kg bw/day (based on significantly decreased corrected body weight), slight indications of TDA-induced effects on skeletal maturation, but no effects on fetal weights and no malformations were found in a developmental toxicity study with rats according to OECD TG 414. Gestational parameters were unaffected at 5, 20, and 80 mg/kg bw/day. The NOAELs for maternal toxicity and for developmental toxicity were 20 mg/kg bw/day in this study.

Environment

Tridecylamine, branched and linear (TDA; CAS 86089-17-0) is a slightly water-soluble (0.04 g/l at 20 °C) yellowish liquid and has a vapor pressure of 0.07-0.19 hPa at 20° C (extrapolated, based on measured vapor pressure data at higher temperature), a melting point of < - 70 °C, a boiling point of 243.8-247 °C at 1013 hPa, and a density of 0.816 g/cm³.

In the atmosphere, the uncharged n-TDA (CAS 2869-34-3) would be rapidly photodegraded by reactions with OH radicals (calculated half-life ($t_{1/2}$) for a 24-h day 0.34 days).

In water at environmental pH conditions hydrolysis of TDA (CAS 86089-17-0) is not expected to be a relevant degradation process due to the absence of hydrolysable groups.

Two biodegradability tests following OECD TG 301B and 301D respectively, have shown that TDA (CAS 86089-17-0) is not readily biodegradable.

The HLC of uncharged n-TDA (CAS 2869-34-3) of 11.15 Pa·m³/mol indicates moderate potential for evaporation. According to Mackay Level I, and depending on the assumed vapor pressure, uncharged n-TDA (CAS 2869-34-3) would distribute into the compartments air (29 % / 53 %), soil (34 % / 23 %), and sediment (34 % / 23 %), and with only a small amount to water (2 %). From the pKa-value of 10.35 it can be assumed that under environmental conditions the substance is available as cation. Therefore, binding of the substance to the matrix of soils (and sediments) with high capacities for cation exchange (e.g. clay) can be expected.

The log K_{OW} and the BCF for the uncharged n-TDA were calculated to be 5.25 and 222, respectively. However, for ionic compounds with log K_{OW} values of 5.0 - 6.0 the BCF is likely to be lower. As no experimental data with TDA are available, the maximum BCF value of 158, as found experimentally for ionic substances with long alkyl chains (≥ 11 carbons), can provisionally be used.

Because of the expected adsorptive behavior of the substance, nominal concentrations provided below may underestimate the true toxicity. Acute toxicity values for aquatic species are as follows:

TDA, (CAS 86089-17-0)

<i>Leuciscus idus</i> (fish)	96-h LC ₅₀ = 1.26 mg/l (nominal; TDA)
<i>Daphnia magna</i> (invertebrates)	48-h EC ₅₀ = 0.7 mg/l (nominal; TDA)
<i>Desmodesmus subspicatus</i> (algae)	72-h E _r C ₅₀ = 0.015 mg/l (nominal; geometric mean of several tests; TDA)
	72-h E _b C ₅₀ = 0.012 mg/l (nominal; geometric mean of several tests; TDA)

As supporting information n-TDA (CAS 2869-34-3)

<i>Pimephales promelas</i> (fish)	96-h LC ₅₀ = 0.0654 mg/l (measured; n-TDA)
<i>Daphnia magna</i> (invertebrates)	48-h EC ₅₀ = 0.015 mg/l (measured; n-TDA)

Based on the acute toxicity studies, TDA (CAS 86089-17-0) is considered of very high acute toxicity to aquatic organisms. For bacteria (activated sludge) the lowest, reliable toxicity value determined was a 30-min EC₅₀ of approx. 40 mg/l (nominal). Tests on terrestrial species are not available.

Since acute test results for three trophic levels are available, according to the EU risk assessment procedure a PNEC_{aquatic} of 0.000015 mg/l (= 0.015 µg/l) was obtained by applying an assessment factor of 1000 on the lowest reliable endpoint, the measured EC₅₀ value from the acute *Daphnia* study.

Exposure

At BASF AG, Ludwigshafen, Germany the annual production of TDA is in the range of 1000 – 5000 t as closed system intermediate (precursor; non dispersive use, > 95 %) for corrosion inhibitors (additive for lubricants), agricultural products (fungicides), dyestuffs for mineral oils, and as a co-catalyst in the production of vitamin E. The distribution of the product via traders accounts for < 5 %. In the Sponsor country, TDA is not known to occur in consumer products. According to the SPIN database, all registered products containing TDA are listed in industrial use categories (i.e. lubricants, base oils, machinery and equipment).

In the Sponsor country, only a few workers handle TDA in a very limited number of work processes. TDA is manufactured in campaigns in closed systems, and transportation of the chemical is controlled. Due to its physico-chemical properties, including a low volatility, and the control measures in place during manufacture, processing and transport, exposure may only occur in case of accidental spills with inhalation and dermal routes being the only relevant routes of exposure. Regular workplace monitoring minimizes the risk of any unforeseen repeated exposures.

At the production and processing sites, personal protective equipment, including gloves, face shields, and safety goggles, has to be used by the workers.

According to the data reported to the German Emission Register 2004, during production and processing in 2004 at BASF AG emissions of TDA to air accounted for less than 5 kg/a. Data regarding emission via waste water treatment effluent are not available from BASF AG production and processing sites.

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 (corrosivity, repeated dose toxicity). Based on data presented by the Sponsor country, relating to production by one producer in one country which accounts for an unknown fraction of global production, and relating to the use pattern in one OECD country, exposure of workers is controlled and exposure of the general public is negligible. Countries may wish to investigate any exposure scenario that was 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 aquatic toxicity to fish, *Daphnia*, and algae). Based on data presented by the Sponsor country, relating to production by one producer in one country which accounts for an unknown fraction of global production, and relating to the use pattern in one OECD country, exposure to the environment is anticipated to be low. Member countries may decide to perform further exposure assessment and if indicated a risk assessment.

Note: The bioaccumulation potential of these chemicals is currently being investigated within the framework of the EU. The evaluation of this issue is still in progress. In case of considerable bioaccumulation potential, TDA may be considered to be a chemical possessing persistent, bioaccumulative, and toxic properties (PBT substance).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-09-5
Chemical Name	2-Ethylbutyric acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

The acid is primarily excreted unchanged in the urine as the glucuronic acid conjugate after oral and subcutaneous administration of 2-ethylbutyric acid in rabbits and rats. In dogs, 2-ethylbutyric acid undergoes β -oxidation and decarboxylation to yield 2-pentanone.

In an acute toxicity study of 2-ethylbutyric acid with rats, the oral LD₅₀ was more than 2,000 mg/kg bw in both sexes. No acute inhalation or dermal studies are available for 2-ethylbutyric acid.

There are no experimental data on irritation and sensitisation.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), rats were given 2-ethylbutyric acid by gavage at 0, 10, 50, or 250 mg/kg bw/day. Males were dosed for a total of 42 days beginning 14 days before mating and females were dosed beginning 14 days before mating to day 4 of lactation throughout the mating and pregnancy period. There were no deaths related to this chemical. Transient salivation was observed in one male and one female at 250 mg/kg bw/day. There were no effects on body weight gain and food consumption in both sexes. In hematological examination, decreases in white blood cell count at 50 mg/kg bw/day and higher, and in platelet count were observed at 250 mg/kg bw/day in males, but no effects were found in females. There were no effects in blood chemistry and necropsy findings in both sexes. Increases in relative weight of the kidney in males and in absolute and relative weights of the kidney in females were noted at 250 mg/kg bw/day. In histopathological examinations, no toxicological changes were found in both sexes. Based on these findings, the NOAELs for repeated dose toxicity are considered to be 10 mg/kg bw/day in males and 50 mg/kg bw/day in females. There are no inhalation and dermal repeat dose studies available for 2-ethylbutyric acid.

This chemical was not mutagenic in an Ames test with and without exogenous metabolic activation, but this chemical was mutagenic in a chromosomal aberration test using CHL/IU cells without metabolic activation. In an *in vivo* mammalian erythrocyte micronucleus assay, no evidence of genotoxicity was noted. These data indicate that this chemical is not mutagenic *in vivo*.

There is no information available on carcinogenicity.

In the above mentioned combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), histopathological examinations of the testes, epididymides and ovaries revealed no toxicological changes. No adverse effects were observed on reproductive parameters, such as estrous cycle, copulation index, fertility index, precoital interval, gestation length, numbers of corpora lutea and implantations, gestation index, implantation index and delivery index. Although poor maternal behavior or nursing was observed in three dams at 50 mg/kg bw/day and one dam at 250 mg/kg bw/day, no dose dependency was found. The number of live pups on days 0 and 4 of lactation, birth index and live birth index decreased at 250 mg/kg bw/day. There were no treatment-related changes in body weight, external appearance or necropsy findings in rat pups.

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Based on these findings, the NOAEL for reproductive toxicity is considered to be 250 mg/kg bw/day (highest dose tested) and the NOAEL for developmental toxicity is considered to be 50 mg/kg bw/day.

Environment

2-Ethylbutyric acid is a colourless liquid with melting point of -31.8 °C, boiling point of 194 °C and vapour pressure of 0.08 mmHg at 20 °C (measured), 0.486 mmHg at 25 °C (calculated). As 2-ethylbutyric acid is a weak acid with pKa of 4.69, this substance is expected to be dissociated in water in environmental conditions. This substance has a high water solubility of 17 g/L at 25 °C. The measured log Kow is 1.68 and the calculated log Koc is 0.850. This substance is readily biodegradable under aerobic conditions. A calculated BCF value of 3.162 indicates that bioaccumulation in aquatic organisms is not expected. In the atmosphere, this substance is indirectly photodegraded by reaction with OH radicals with a half-life of 2.0 days. Environmental distribution using the Mackay level III model suggests that when 2-ethylbutyric acid is released into the environment, it distributes mainly into soil and water compartments (64.7 % in soil, 30.6 % in water, 4.55 % in air and 0.096 % in sediment).

Ecotoxicity data are available in aquatic species from three trophic levels. The GLP tests using a freshwater fish (OECD TG 203, *Oryzias latipes*), a daphnid (OECD TG 202, *Daphnia magna*) and green alga (OECD TG 201, *Pseudokirchneriella subcapitata*) were conducted. All toxicity tests were conducted without adjustment of pH although the test substance is acidic. Therefore organisms were subjected to both low pH effects and true toxic effects, if present, of the chemical.

The reliable acute aquatic toxicity results are:

Oryzias latipes; 96 h LC₅₀ > 50 mg/L (<100 mg/L)

Daphnia magna; 48 h LC₅₀ = 70 mg/L

Pseudokirchneriella subcapitata; 72 h EC₅₀ > 63 mg/L (rate method)

Chronic toxicity results with daphnids (OECD TG 211, *Daphnia magna*) and algae (OECD TG 201, *Pseudokirchneriella subcapitata*) were available according to GLP tests. The reliable toxicity results are:

Daphnia magna; 21 d NOEC = 49 mg/L

Pseudokirchneriella subcapitata; 72 h NOEC = 39 mg/L (rate and biomass method).

Exposure

The total production volume of 2-ethylbutyric acid was less than 500 tons/year in 2005 in the sponsor country. Information on the worldwide production volume is not available. In the sponsor country, 2-ethylbutyric acid is produced in a closed system for the main use as an intermediate. This substance is also used as a flavouring agent.

At production and processing sites, small amounts of 2-ethylbutyric acid might be released into waste-water stream. However, in the sponsor country, exposure of this substance into the environment should not be significant as the waste-water stream is treated with waste-water treatment plant and this substance is readily biodegradable.

2-Ethylbutyric acid is a semi-volatile liquid at normal temperature, and its log P_{ow} is 1.68, major occupational exposure routes are expected to be inhalation and dermal. Since the maximum vapour concentration is 247 ppm, exposure can be controlled by personal protective equipments even if workers are in direct contact with this chemical. Since this chemical is produced in a closed system and major use is as intermediates, direct contact is expected to be minimal. Workplace measurements data or occupational exposure limit values are not available. Even if consumer are exposed to this chemical, the level of exposure is expected to be very low, because this chemical is permitted only as a flavouring agent by Food Sanitation Law in the Sponsor country. This chemical can be used as a fragrance in cosmetics in other OECD countries.

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 developmental toxicity). Based on the data presented by the sponsor country (related to production by one producer in one OECD country which accounts

for an unknown fraction of the 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: This chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute aquatic toxicity; LC_{50} values between 10 and 100 mg/l for algae, fish and daphnia). However, these hazards do not warrant further work because of the rapid biodegradation and limited potential for bioaccumulation of the chemical.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category Name	Alkylamidopropyl betaines		
CATEGORY MEMBERS: Chemical Names	1-Propanaminium, N-(carboxy-methyl)-N,N-dimethyl-3-[(1-oxododecyl) amino]-, inner salts (A) Lauramidopropyl betaine	1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivatives, inner salts (B) Cocamidopropyl betaine inner salts	Amides, coco, N-[3-(dimethyl-amino)propyl], alkylation products with chloroacetic acid, sodium salt (C) Cocamidopropyl betaine sodium salts
CAS Registry Numbers	4292-10-8	61789-40-0	70851-07-9
STRUCTURAL FORMULAS	A C B		

SUMMARY CONCLUSION OF THE SIAR**Category Justification**

The members of the alkylamidopropyl betaines category are amphoteric surfactants containing a quarternary ammonium ion, a carboxylic structure, and an amide bond. The alkylamidopropyl betaines are referred to as inner salts due to their zwitterionic character. They are all manufactured from oils, usually coconut oil, containing mixtures of C₈ to C₁₈ fatty acids and marketed as aqueous solutions (20 - 40 %).

Because of the structural and functional similarities and comparable physico-chemical properties of cocamidopropyl betaine inner salts and sodium salts, a similar ecotoxicological and toxicological profile can be expected. Values for physico-chemical endpoints for lauramidopropyl betaine are similar or within the range of values for cocamidopropyl betaines, supported by accepted (Q)SARs even though there may be limitations for surface active substances. Therefore similar ecotoxicological properties were assumed. All available physico-chemical and environmental fate data are similar for lauramidopropyl betaine and cocamidopropyl betaine and hence support this category approach.

Only the alkyl chain length differs for the chemicals in the mixture, therefore they should have the same mode of action for aquatic toxicity.

The main component of the category, **lauramidopropyl betaine** (C₁₂; ca. 50-60%) is in the middle of the alkyl-chain distribution of the mixture. The distribution ranges from C₈ (ca. 5%) to C₁₈ (ca. 10%) in steps of two.

Based on (Q)SAR the aquatic toxicity is expected to increase with increasing chain length. The aquatic toxicity of C₁₂ should be in the order of the toxicity of the mixture. So data from the mixture can also be used to address the toxicity of lauramidopropyl betaine.

However, the lack of (eco-) toxicity data for lauramidopropyl betaine must be noted.

Human Health

No reliable toxicokinetic or metabolism studies were available for the category members. As amphoteric surfactants are easily absorbed by the oral route and are excreted partly unchanged via the feces or are metabolized to short-chained fatty acids and carbon dioxide, this can also be expected for the alkylamidopropyl betaines.

The acute toxicity of cocamidopropyl betaine (30 – 35.5 % aqueous solutions) in rats is low, with a dermal LD₅₀ value greater than 2000 mg/kg bw (i.e., greater than 600 mg active substance/kg bw), and oral LD₅₀ values generally greater than 5000 mg/kg bw (i.e., greater than 1500 mg active substance/kg bw). Other than irritation, there were no clinical signs reported after acute dermal exposure; after oral exposure to high doses, decreased motor activity, diarrhea, and ataxia were found. The acute toxicity of lauramidopropyl betaine is expected to be in the same range. No studies were available for the respiratory route of exposure.

In studies according to OECD TG 404, cocamidopropyl betaine (as ca. 30 % aqueous solution) was only very slightly irritating to the skin of rabbits. When tested as moistened, spray-dried powder, it was not irritating. Clear signs of irritation were seen in rabbits after occlusive treatment with concentrations of about 30 %. Aqueous 30 % solutions and the spray-dried cocamidopropyl betaine powder induced corneal and/or iris damage in rabbits which was still present in some animals at the end of the observation period of 21 d. 5 to 10 % solutions caused mild to moderate effects, which were all reversible within the observation period. The skin and eye irritation potential of lauramidopropyl betaine is expected to be similar.

Three out of four animal studies gave no indication of a sensitizing potential of cocamidopropyl betaine; the lack of concurrent positive control data weakens, however, their reliability. Ambiguous results in the fourth study, a Guinea pig maximization test, may have been caused by impurities. In humans, the sensitizing potential of cocamidopropyl betaine is low. Commercial cocamidopropyl betaine may, however, contain impurities identified as sensitizers (amidoamine and/or 3-dimethylaminopropylamine) which may explain positive results in human patch tests. There is no evidence for a photosensitizing potential. Overall, the sensitizing potential of the alkylamidopropyl betaines category is considered to be low.

The repeated dose toxicity with 250, 500, and 1000 mg/kg bw/day of a 30 % aqueous solution of cocamidopropyl betaine (corresponding to about 75, 150, and 300 mg active substance/kg bw/day, resp.) was tested in 28- and 90-day oral studies with rats in accordance with OECD TG 407 and 408, respectively. The only substance related findings were forestomach lesions, probably as a result of the irritant effect at dose levels of 500 mg/kg bw/day (after 90 days) and 1000 mg/kg bw/day (after 28 days). The NOAELs were 250 mg/kg bw/day after 90 days and 500 mg/kg bw/day after 28 days (corresponding to about 75 and 150 mg active substance/kg bw/day). A similar repeated dose toxicity pattern is expected for lauramidopropyl betaine. No repeat dose dermal or inhalation studies were available for this category.

In vitro tests in bacteria (Ames) and mammalian cells (Mouse lymphoma test; no information on cytotoxicity) showed no genotoxicity of the 30 % aqueous solution of cocamidopropyl betaine. A limited i.p. mouse micronucleus test with 27 % active cocamidopropyl betaine showed no evidence of clastogenicity *in vivo* at non-toxic dose-levels of 200 mg/kg bw/day (highest tested dose, corresponding to 54 mg active substance/kg bw). There is no evidence for a genotoxic potential of the alkylamidopropyl betaines category.

There are no valid carcinogenicity studies available.

There were no fertility studies with alkylamidopropyl betaines available. From a 90-day oral study there is no evidence, that 30 % aqueous cocamidopropyl betaine has an adverse effect on reproductive organs up to the highest dose tested (1000 mg/kg bw/day, corresponding to 300 mg active substance/kg bw/day).

In a developmental toxicity study according to OECD TG 414, 330, 990, and 3300 mg/kg bw/day of a 28.9 % aqueous solution of cocamidopropyl betaine (corresponding to 95, 286, and 950 mg/kg bw/day, resp.) showed dose-related maternal toxic effects (reduced body weights and stomach ulcers) at 990 mg/kg bw/day and above. Embryotoxic effects (increased numbers of resorptions, decreased number of viable fetuses, decreased fetal body weight) were found only at the maternal toxic dose level of 3300 mg/kg bw/day. The NOAEL for maternal toxicity was 330 mg/kg bw/day (corresponding to 95 mg active substance/kg bw/day) and the NOAEL for developmental toxicity was 990 mg/kg bw (corresponding to 286 mg active substance/kg bw). Similar results would be expected for lauramidopropyl betaine.

Environment

Alkylamidopropyl betaines are usually not available as a 100 % pure substance; they are mainly marketed in about 30% aqueous solutions. Therefore experimentally determined physico-chemical properties of the pure substances are only available for selected endpoints. Often measured physico-chemical properties exist only for the aqueous solutions. The following physico-chemical properties have been calculated for the alkylamidopropyl betaines with $C_8 - C_{18}$ fatty acids, i.e. for the shortest and longest chain length in the mixtures. The alkylamidopropyl betaines are solid substances with melting point ranges from 260 to 320°C while measured values for purified fractions range between 55 to 208°C. For purified fractions calculated values for boiling points range from 600 to 730°C, for vapor pressure they are less than 2×10^{-13} hPa, for the log K_{OW} they range from -1.28 to 3.63 and for water solubility they range from 1.62 to 8769 mg/l. For these kinds of chemicals there is uncertainty associated with the calculated water solubility. For example the calculated water solubility for lauramidopropyl betaine is 1755 mg/l the measured value is > 100 g/l at 20°C. Whereas melting and boiling points as well as log K_{OW} increase with an increase in alkyl chain length, the water solubility decreases. The particular behavior of these amphoteric is related to their zwitterionic character, so they are completely dissociated in aqueous systems. At very low pH values they are present in a protonated form.

According to the Mackay Level I model calculation, the main target compartment for lauramidopropyl betaine is the hydrosphere (> 99 %). Based on the calculation for caprylamidopropyl betaine (C_8 fatty acid derivate) and stearamidopropyl betaine (C_{18} fatty acid derivate), cocamidopropyl betaine will be mainly distributed to the hydrosphere (59 - 100 %), and to a lesser extent to soil and sediment (0 - 20 % each). The Henry's law constants for alkylamidopropyl betaines calculated for every single fatty acid chain length indicate a very low potential for volatilization from surface waters under environmentally relevant conditions. The soil sorption coefficients (K_{OC}) calculated for the alkylamidopropyl betaines indicate a low to very high potential for sorption to organic matter of soils and sediments. The low sorption potential is confirmed by experimentally obtained values for laurylamidopropyl betaine (C_{12} derivative) and tetradecylamidopropyl betaine (C_{14} derivative) from the screening HPLC-method according to OECD TG 121. A high potential for sorption applies only for the alkylamidopropyl betaines with the C_{16} and C_{18} fatty acid chain length.

Based on the calculated half lives ranging from 6 - 9 h, photodegradation in air by the reaction with OH radicals is expected to be very rapid. However, due to the very low vapor pressure of the alkylamidopropyl betaines this degradation pathway is assumed to be of low environmental significance. No information on direct photolysis is available. With regard to their chemical structure, alkylamidopropyl betaines are not expected to hydrolyze under environmental conditions; a hydrolysis half life of $t_{1/2} > 1$ year has been calculated.

According to the results obtained in guideline studies, the alkylamidopropyl betaines can be considered as being readily biodegradable under aerobic conditions. In guideline tests biodegradation rates of 86 – 100 % after 28 days (OECD TG 301A/B/D/E), 90 – 93 % after 35 days (OECD TG 301B) and 100 % after 20 days (Directive 84/449/EEC, C.5) were determined with cocamidopropyl betaine. Lauramidopropyl betaine was degraded by 95 % based on COD after 28 days in the Modified MITI Test (Directive 92/69/EEC). In a "Coupled Unit Test" (OECD TG 303A) a DOC removal of 97 % (+/-4 %, 95 % probability level) after 35 days and in a "Porous Pot activated sludge simulation test" a removal of 96.8 – 105.2 % (95 % confidence limits) after 161 days were observed indicating that cocamidopropyl betaine is easily removable in sewage treatment plants. Under anaerobic conditions, 80 – 90 % mineralization after 60 days or 56 % after 56 days were observed for cocamidopropyl betaine.

Based on the calculated BCFs between 3 (with C_8 fatty acid) and 71 (with $C_{10} - C_{18}$ fatty acids), a low potential for bioaccumulation is to be expected for alkylamidopropyl betaines. However, it should be noted that results of BCF calculations for surfactants should be used with care.

For the acute toxicity of cocamidopropyl betaine to aquatic species reliable results from tests with fish, daphnia, algae, and microorganisms are available. The lowest acute LC/EC₅₀ values for the three trophic levels fish, *Daphnia*, and algae are in each case in the range of 1.3 – 2 mg active substance/l. Furthermore, one long-term test with fish (according to OECD TG 215), and several chronic tests with *Daphnia* and algae were conducted. The lowest NOECs are 0.16 mg active substance/l for fish (*Oncorhynchus mykiss*), 0.03 mg active substance/l for *Daphnia magna*, and 0.09 mg active substance/l for green algae (*Desmodesmus subspicatus*). These values were derived with analytical monitoring (photometric) except for the algae test. However, the effect values within the same species (e.g., *Desmodesmus subspicatus*, *Daphnia magna*) have shown a high variability. Recent guideline studies performed in accordance with OECD TG 211 and 201 using state-of-the-art analytical monitoring and a quality of cocamidopropyl betaine currently commercialized, resulted in a lower aquatic toxicity. In these studies the lowest NOEC for daphnids was determined to be 0.932 mg active substance/l. the lowest NOEC (72 h, based

on growth rate) for algae was determined to be 3.55 mg active substance/l (72 h- E_rC_{50} = 9.86 mg active substance/l). This latter NOEC for algae is further supported by the similar NOEC of 3.53 mg active substance/l calculated using the geometric mean of all valid tests with this algae species. Furthermore, for algae a potential for recovery from the effect up to a concentration of 96 mg active substance/l has been observed.

Because of a proportion of approx. 50 % lauramidopropyl betaine in a mixture of cocamidopropyl betaines it could be assumed, as a worst case, that if lauramidopropyl betaine was the only component responsible for toxic effects of this mixture, the respective toxicity value would decrease by 50 % for lauramidopropyl betaine as single substance.

Two studies (without analytical monitoring) of effects on terrestrial organisms (earthworm and higher plants) showed low toxicity. Taking additionally into account that the adsorption potential of the main components of cocamidopropyl betaine (the C_8 to C_{14} derivatives) is low, a risk for the terrestrial compartment is not expected.

Exposure

In Western Europe 59 000 tons alkylamidopropyl betaines (as 100 % active matter) were produced in the year 2002. Among the 59 000 tons alkylamidopropyl betaines produced in 2002, < 5 % account for lauramidopropyl betaine. The values for sales and captive use in the year 2002 for the alkylamidopropyl betaines are 57 000 tons. About 18 000 tons were produced in USA and 10 000 tons in Asia in the year 2003. European producers are located in Germany, Spain, France, Italy, and UK. Cocamidopropyl betaine and lauramidopropyl betaine are predominately used as cosmetic ingredients, mainly in shampoos and shower gels (50% of the produced volume), and as detergents, mainly in cleaning agents (50 % of the produced volume).

Occupational exposure may occur during manufacture, processing, transport, and use of alkylamidopropyl betaine containing products, mainly through the dermal route. In the Sponsor country appropriate safety measures are in place and controlled regularly by safety inspections. Workers wear protective clothing, gloves, and safety glasses or face shields. They are trained regularly with regard to the safety instructions.

Consumers are mainly exposed through the dermal route by using personal cleansing products and detergents. The betaine concentrations in these products which are between 0.03 and 15% (for cocamidopropyl betaine), and up to 4 % (for lauramidopropyl betaine), do not cause skin irritation. Accidental eye contact is another possible route of exposure. Exposure of the general public via the environment or via the food chain is not expected.

During production, manufacturing, storage, transport, and transfer processes no intended release of the alkylamidopropyl betaines into the environment will occur. Only in case of accidents the product may be released into the environment. Incidental environmental releases may occur during formulation processes such as decanting or transfer processes (e.g., transfer between tanks), and during cleaning processes, mainly into waste water treatment.

As cocamidopropyl betaine and lauramidopropyl betaine are used in personal care products (e.g., shampoos, shower gels), or hand washing agents, it is to be expected that the product will almost entirely be discharged mainly into the waste water treatment.

Data on emissions of the alkylamidopropyl betaines into the environment from production and processing processes are lacking. Also, there is no data available from wastewater treatment plants and surface waters.

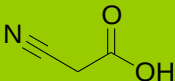
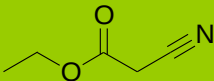
RECOMMENDATION, RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED**Human Health:**

The chemicals in this category are currently of low priority for further work. Alkylamidopropyl betaines possess properties indicating a hazard for human health (aqueous solutions with ≥ 30 % active ingredient caused corneal and/or iris damage in rabbits which was still present in some animals at study end, fetotoxicity at maternal toxic doses). This hazard does not warrant further work as it is related to an effect which may only become evident at high exposure levels. It should nevertheless be noted by chemical safety professionals and users. In the Sponsor country, occupational exposure is controlled and adequate risk reduction measures are in place for consumers (classification and labelling). Member countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment:

The chemicals in this category are candidates for further work. Alkylamidopropyl betaines possess properties indicating a hazard for the environment (lowest acute aquatic toxicity values around 2 mg/l, high chronic toxicity to aquatic organisms). Therefore, an exposure assessment and, if then indicated, an environmental risk assessment is recommended.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category Name	Cyanoacetates	
CATEGORY MEMBERS:		
Chemical Names and CAS Registry Numbers	Cyanoacetic acid 372-09-8	Ethyl cyanoacetate 105-56-6
Structural Formulas		

SUMMARY CONCLUSIONS OF THE SIAR**Category Justification**

Ethyl cyanoacetate is the ethyl ester of cyanoacetic acid. Ethyl cyanoacetate hydrolyzes rapidly under neutral and alkaline conditions to cyanoacetic acid and ethanol (and so it does under most physiological and environmental conditions), while in acid pH the half life is considerably longer. It also is likely that unspecific esterases in the body catalyze the hydrolysis to cyanoacetic acid and ethanol, as it has been shown for the structurally related ethyl acetate, which is rapidly hydrolyzed *in vitro and in vivo* by various esterases to yield ethanol and acetic acid. Ethanol is a physiological substance that is metabolized via physiological pathways. Ethanol (CAS. 64-17-5) was evaluated within the OECD HPV Chemicals Program. It can be assumed that for most endpoints cyanoacetic acid will be the common metabolite that determines the toxicity of both substances. Furthermore the production and use pattern of both, ester and acid, are comparable. As the acid and the ester have different physical chemical properties due to their chemical nature, effects that are related to the acidity of the acid (e.g. ecotoxicity data, local irritating effects) have to be assessed separately. The environmental and toxicokinetic distribution can however be expected to range in a similar order of magnitude due to the similar polarity, vapor pressure and log Kow. The biodegradation behavior is also expected to be comparable as the ester is probably cleaved and the metabolites further degraded.

Human Health

From the physical chemical properties of both cyanoacetic acid and ethyl cyanoacetate it can be expected that both substances will be moderately absorbed by all exposure routes. A relatively even distribution between tissues and also to embryonic tissues of pregnant rats was observed after oral administration of cyanoacetic acid. A similar behavior can be expected for ethyl cyanoacetate. Ethyl cyanoacetate is likely to be metabolized by unspecific esterases of different tissues, in particular in the liver to cyanoacetic acid and ethanol.

While no mortality and no signs of toxicity were observed in a 7-hour vapor inhalation study in rats with saturated vapors of cyanoacetic acid, the 4-hour LC₅₀ in rats for an aerosol of 50 % cyanoacetic acid in water was 1900 mg/m³. The most prominent symptoms were signs of severe irritation of eyes, mouth and respiratory tract. In a 1-hour inhalation study (according to US EPA DOT, 49 CFR, GLP) with ethyl cyanoacetate at the maximum attainable aerosol concentration of 7380 mg/m³ the only substance related findings were reversible signs of irritation of the eyes and the upper respiratory tract. For cyanoacetic acid a dermal LD₅₀ > 2000 mg/kg bw in rabbits was reported. In this study with limited documentation local irritant effects on the skin and some systemic effects (dyspnea, behavioral changes) were reported, indicating a possible systemic toxicity after dermal exposure. For ethyl cyanoacetate a dermal LD₅₀ > 1000 and > 2000 mg/kg bw was reported in rabbits and rats, respectively, in studies in accordance with OECD TG 402 or 92/69/EEC B.3. No treatment related findings except for slight local skin irritation in the study in rabbits were observed. An acute oral LD₅₀ value in rats of 1010 mg/kg bw has been reported for cyanoacetic acid. Symptoms including dyspnea, labored breathing, apathy and staggered gait were observed from doses of 1000 mg/kg bw and necropsy revealed local effects in the stomach. Only systemic effects similar to those reported for cyanoacetic acid were observed with ethyl

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cyanoacetate at a limit dose of 2000 mg/kg bw in rats (studies in accordance with OECD TG 401 or EC 92/69/EEC B.1 and GLP).

Cyanoacetic acid was corrosive to rabbit skin (study according to Dir. 92/69/EEC, B.4. and GLP) and eyes (sufficiently documented study) while ethyl cyanoacetate was not irritating to rabbit skin (studies in accordance with OECD TG 404, GLP) and moderately irritating to rabbit eyes (study according to OECD TG 405, GLP). Based on the results of the inhalation toxicity studies, cyanoacetic acid can be regarded as highly irritating to the mucous membranes of the respiratory tract while ethyl cyanoacetate only had a slight irritant effect on the respiratory tract.

Both substances were not skin sensitizing in a Buehler test in guinea pigs according to US EPA OTS 798.4100 and GLP.

One 90-day oral (gavage) study in rats according to OECD TG 408 and GLP has been conducted with ethyl cyanoacetate at doses of 0, 100, 300 and 1000 mg/kg bw/day. The NOAEL in this study was 100 mg/kg bw/day for female rats and 300 mg/kg bw/day for male rats. A significant dose related reduction in hemoglobin values was observed at dose levels of 300 and 1000 mg/kg bw/day in female animals. In males of the 1000 mg/kg bw/day dose group increased urine volume and reversible pathological changes in liver (chronic peribiliary inflammation) and adrenals (vacuolization in the zona fasciculata of the adrenals) were observed. An additional examination of sperm counts and sperm motility in high dosed males revealed an apparently treatment related decrease in the percentage of motile sperms and sperm counts in the epididymis (changes within 2 standard deviations of the historical control data, no significant changes in organ weights or pathological findings in testes or epididymis). No effects were observed on female sex organs and estrous cycle.

Both cyanoacetic acid and ethyl cyanoacetate were not mutagenic in the standard Ames assay in bacteria with and without metabolic activation. Neither *Salmonella typhimurium* TA102 nor *E. coli* WP2 were tested in these Ames tests, however, this is an acceptable restriction, because it can be assumed that neither cyanoacetic acid nor ethyl cyanoacetate has oxidizing or cross-linking potential, which may be detected by TA102 or *E. coli* WP2. Ethyl cyanoacetate did not show any clastogenic activity in the *in vitro* cytogenetic assay with V79 Chinese Hamster lung cells in the presence and absence of a metabolic activation system. All tests with ethyl cyanoacetate were conducted according to OECD or EC guidelines and GLP. For both substances, there is no structural alert for genotoxicity. In conclusion, from the available information, there is no indication of a genotoxic potential of the substances, both for gene mutations and chromosomal aberrations.

No data are available on carcinogenicity.

No specific studies on fertility are available for cyanoacetic acid or ethyl cyanoacetate. In a 90-day oral gavage study (according to OECD TG 408 and GLP) with ethyl cyanoacetate that included a histopathological evaluation of the gonads as well as additional investigations on sperm motility and sperm counts a NOAEL for these fertility related endpoints of 300 mg/kg bw/day was derived. A decrease of sperm motility and epididymal sperm counts observed in this study at 1000 mg/m³ (LOAEL) were not accompanied by significant reductions in testicular, epididymal, ovary or uterus weights, or any histopathological findings in these organs. Moreover, these effects are observed together with systemic toxicity.

In a developmental toxicity study with ethyl cyanoacetate according to OECD TG 414 and GLP the NOAEL for embryotoxic or fetotoxic effects was 100 mg/kg bw/day based on an increase in minor skeletal anomalies in litters of the 300 and 1000 mg/kg bw/day dose groups and a reduced mean fetal weight at 1000 mg/kg bw/day. The NOAEL for maternal toxicity in this study was 300 mg/kg bw/day. Maternal toxicity in this study was however, only defined based on clinical signs, body weight development and macroscopic organ changes. Therefore it can not be excluded that the observed developmental effects are due to maternal toxicity.

Studies on repeated dose toxicity and developmental toxicity conducted with ethyl cyanoacetate are considered relevant for cyanoacetic acid as well, as the ester will be rapidly metabolized to cyanoacetic acid and ethanol and its toxicity is likely to be mediated predominantly by cyanoacetic acid. Furthermore the study of the ester represents a "worst case" assumption for the acid as it can be assumed that the slightly more lipophilic ethyl ester is more readily absorbed than the corresponding acid and the maximum applicable dose of the ester is not limited by local irritation to mucous membranes. Therefore the ester can be administered at higher dose levels and is assumed to have a better bioavailability than the acid.

Environment

Cyanoacetic acid is a white crystalline solid; ethyl cyanoacetate is a colorless liquid. Cyanoacetic acid has a water

solubility of about 890 - 1000 g/l at 20 °C, a vapor pressure of 0.047 hPa at 25 °C and a measured log K_{OW} of -0.76. Ethyl cyanoacetate has a water solubility of 20 g/l at 25 °C, a vapor pressure of 0.05 hPa at 25 °C and a calculated log K_{OW} of 0.02. Ethyl cyanoacetate is readily biodegradable (95 to 100 % in a DOC-die away test, criteria of 10 day-window fulfilled) and undergoes hydrolytic degradation to cyanoacetic acid and ethanol. The half-life was ≤ 2.4 h (50 °C) at pH 9 and 7, and increased to 191 hours at pH 4 and 50 °C corresponding to 72 days at 25 °C. A photodegradation via oxidation by OH-radicals with half lives of about 25 days for cyanoacetic acid and 9 days for ethyl cyanoacetate in air was estimated. The generic fugacity model I indicates that both substances are preferably distributed in the water phase (> 99 % for both substances). The measured octanol-water partition coefficient (log K_{OW} -0.76 for cyanoacetic acid and 0.02 for ethyl cyanoacetate) and the calculated soil sorption coefficient (K_{OC} 1.0 for cyanoacetic acid and 4.1 for ethyl cyanoacetate) indicate a low potential for bio- or geoaccumulation.

Acute toxicity data for 3 trophic levels of the aquatic environment are available for ethyl cyanoacetate, and for 2 trophic levels for cyanoacetic acid. The 96 h LC_{50} for fish (*Leuciscus idus*) was 68 mg/l for cyanoacetic acid. This test was conducted without pH adjustment. A test with pH adjusted cyanoacetic acid solution with a satellite group of *Leuciscus idus* revealed only 10 % mortality after 96 h at a concentration of 215 mg/l. For ethyl cyanoacetate a 96 h LC_{50} of 59 mg/l was derived (*Danio rerio*). This test was conducted under flow-through conditions to ensure stability of the test concentration. The 48 h EC_{50} for *Daphnia magna* was 59 mg/l for cyanoacetic acid and 471 mg/l for ethyl cyanoacetate (nominal concentration). The 72 h E_rC_{50} for algae (*Scenedesmus subspicatus*) was 142 mg/l (72 h E_bC_{50} 72.4 mg/l) and the NOEC based on growth rate was 17 mg/l for ethyl cyanoacetate. It can reasonably be assumed that hydrolysis of the ester occurred in this study and the acid and the lowered pH have contributed considerably to the toxicity. Therefore the data of the ester are relevant for cyanoacetic acid as well. Acute toxicity tests for three trophic levels are available for ethyl cyanoacetate. According to the EU technical guidance document a $PNEC_{aqua}$ of 59 µg/l based on the lowest LC_{50} of 59 mg/l for fish can be derived for ethyl cyanoacetate using an assessment factor of 1000. Only two acute toxicity tests for fish and invertebrates are available for cyanoacetic acid. Therefore no $PNEC_{aqua}$ can be calculated. However, as ethyl cyanoacetate hydrolyzes quickly under environmental conditions the value for ethyl cyanoacetate may be relevant for cyanoacetic acid as well.

No growth inhibition of ethyl cyanoacetate to terrestrial plants in soil was observed up to concentrations of > 100 mg/kg soil (dry weight) and no toxicity to *Eisenia fetida* was observed at concentrations of 1000 mg ethyl cyanoacetate /kg soil (dry weight) after 14 days of exposure.

Exposure

In 2001 the estimated worldwide annual production capacity for cyanoacetates was more than 15 000 metric tons. The estimated annual production capacities were approximately 8000 metric tons in the US, 3500 metric tons in Europe, 3000 metric tons in Japan, 4000 metric tons in China and 1000 metric tons in India. Recent estimates of production capacities by the Sponsor Company for 2005 were 5000 metric tons in Europe, 12 000 metric tons in US, 800 metric tons in Japan, 1000 metric tons in India and 56 000 metric tons in China for cyanoacetic acid and for ethylcyanoacetate 6400 metric tons in US and 30 000 metric tons in China. The Sponsor Company imports ethyl cyanoacetate and cyanoacetic acid from its production site in USA to Germany where they are used as intermediates. Cyanoacetic acid and ethyl cyanoacetate are used as internal and external intermediates in the chemical industry; cyanoacetic acid for the production of photochemicals and flavor & fragrances ethyl cyanoacetate for the production of cyanoacrylate adhesives, pharmaceuticals, agrochemicals, dyes, photochemicals and UV-adsorbers. In the SPIN database there are no hints on other uses as the aforementioned.

From production at the Sponsor Company only limited exposure can be expected as both substances cyanoacetic acid and ethyl cyanoacetate are produced in a continuous closed system at Degussa AG. Waste water is sent at the sponsor's site to a biological waste water treatment plant, where it is completely degraded.

Short-term occupational exposure cannot be excluded during filling and sampling operations. Whenever a possible exposure is anticipated personal protective equipment consisting of goggles, face shield, gloves and chemical resistant suits is used. At the production site of Degussa AG and processing sites regular workplace measurements are not conducted

There are no data available on other production or processing sites in the Sponsor Country. There exist no occupational exposure limit values for cyanoacetic acid and ethyl cyanoacetate. No consumer products are listed to contain ethyl cyanoacetate in the Danish, Finnish, Norwegian and Swedish Product Registers. There are no data given on cyanoacetic acid in the Nordic Product Registers.

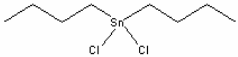
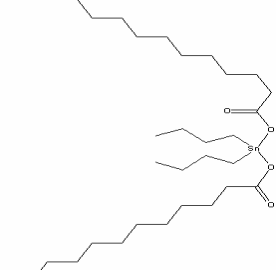
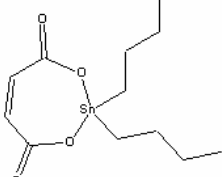
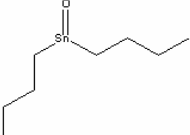
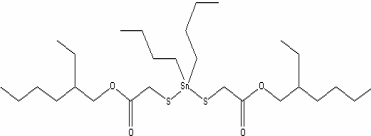
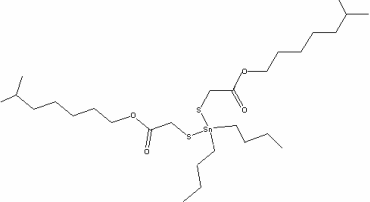
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED**Human Health**

The chemicals are candidates for further work. The chemicals possess properties indicating a hazard for human health (skin and eye corrosivity and respiratory irritation for cyanoacetic acid, at high doses effects on hematology, liver, adrenals and sperms after repeated dosing, embryotoxic or fetotoxic effects). Based on data presented by the Sponsor Company, exposure of workers during manufacturing in the Sponsor Company is anticipated to be low. The substances are not expected to be present in consumer products. As no worker exposure data is available on other production and processing sites in the Sponsor Country, it is recommended to conduct an exposure and if indicated a risk assessment at the workplace apart from the production site of the Sponsor Company.

Environment

The chemicals are currently of low priority for further work. The chemicals possess properties indicating a hazard for the environment (acute toxicity to fish [both substances] and invertebrates [cyanoacetic acid]). However, the chemicals are of low priority for further work because of their rapid biodegradation and limited potential for bioaccumulation. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	Dibutyltin dichloride and selected thioglycolate esters	
Structural Formula, Chemical Names and CAS Registry Numbers		Dibutyltin dichloride DBTC, CASRN 683-18-1
		Dibutyltin dilaurate DBTL, CASRN 77-58-7
		Dibutyltin maleate DBTM, CASRN 78-04-6
		Dibutyltin oxide DBTO, CASRN 818-08-6
		Dibutyltin bis(2-ethylhexylthioglycolate) DBT(EHTG), CASRN 10584-98-2
		Dibutyltin bis(isooctylthioglycolate) DBT(IOTG), CASRN 25168-24-5

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

DBTC, DBTL, DBTM, DBTO, and DBT(EHTG) are considered one category of compounds for mammalian toxicology studies via the oral route. The justification for this category is based on structural similarities and the simulated gastric hydrolysis studies of DBTL, DBTM, DBTO, and DBT(EHTG) demonstrated that these dibutyltin compounds readily converted (> 80% to 100%) to DBTC within < 0.5 to 3.5 hours under physiological conditions (pH 1 to 2). Thus, DBTC is an appropriate anchor compound and a valid surrogate for the mammalian toxicology endpoints of repeated dose, reproduction, developmental, and *in vivo* genetic toxicity, when they are assessed using oral administration.

Sensitization, irritation and *in vitro* genotoxicity are not covered under the category approach and the results of the mammalian *in vivo* tests via the oral route with the representative chloride cannot be extrapolated to the dermal or inhalation routes. However, the esters have much higher molecular weight and lower volatility than the chlorides, reducing the possibility of toxicity via inhalation and dermal routes.

The category approach was not used for the ecotoxicity and environmental fate endpoints. The considerable differences in the structures of the labile ligands cause differences in water solubility between the alkyltin chloride and the thioesters and carboxylates affecting their respective bioavailabilities and distribution in the environment. Furthermore, DBT thioesters or carboxylates will degrade in aqueous solution such that organisms will be exposed to the parent material and their different degradation products. DBTC is not an appropriate surrogate for the thioesters and carboxylates for the ecotoxicity and environmental fate endpoints.

Analogue Rationale

Data for DBT(EHTG) and DBT(IOTG) are used interchangeably because they are isomers, differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand. In addition, the breakdown products of DBT(EHTG) and DBT(IOTG) are the thioglycolate esters (EHTG and IOTG), which have the common degradates, thioglycolic acid and C-8 alcohols (either 2-ethylhexanol or isooctanol). EHTG and IOTG also have similar physicochemical and toxicological properties.

EHTG (CAS No. 7659-86-1) and IOTG (CAS No. 25103-09-7) form the Thioglycolic Acid Esters B Category, assessed at the OECD HPV Chemicals Program.

Human Health

The majority of toxicology studies were conducted with commercial mixtures having high dialkyltin to monoalkyltin ratios. Toxicokinetic data were not available for these substances. For DBTC, DBTL, DBTM, DBTO, and DBT(EHTG)/(IOTG), acute rat oral LD₅₀ values ranged from 58 (DBTC) to > 5000 (DBT[EHTG]) mg/kg bw, rat acute inhalation LC₅₀ values ranged from 59 (DBTC) to > 22,000 (DBT[IOTG]) mg/m³, and acute rat dermal LD₅₀ values ranged from 777 (DBT[EHTG]) to ≥ 2000 (DBTO) mg/kg bw.

The dibutyltin compounds tested ranged from slightly irritating (DBTO) to highly irritating/corrosive [DBT(EHTG), DBT(IOTG), and DBTC] to the skin of rabbits and slightly [DBTO, DBT(EHTG), and DBT(IOTG)] to severely DBTC irritating to the eyes of rabbits. DBT(EHTG)/(IOTG) blends are skin sensitizers in guinea pigs. Absorption through human epidermis was slow (0.210 to 0.002 µg/cm²/h) at non-irritating, environmentally relevant concentrations [500 µg/cm² DBTC and 21,120 µg tin/cm² as DBT(EHTG)].

Multiple repeated dose studies have been conducted with DBTC and its related esters. The critical study for hazard assessment was the 90-day dietary study in rats using DBTC (99.7% purity). In this study, the concentrations were 10, 20, 40, or 80 ppm in the diet. The NOAEL was 40 ppm (~2 mg/kg bw-day) and the LOAEL was 80 ppm (~7.5 mg/kg bw-day) based on reduced body weight and food consumption, hematological effects (significant decrease in hemoglobin concentrations in males and females), and decreased absolute kidney weight (males). In the repeated dose screening study to assess reproductive/developmental effects, immunotoxicity with thymus atrophy and severe lymphoid depletion were noted in the parental animals. The

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NOAEL was 0.3-0.4 mg DBTC /kg bw/day

DBTC, DBTL, DBTM, DBTO, and DBT(EHTG)/(IOTG) were not mutagenic in standard Ames assays with multiple strains of *Salmonella typhimurium*, conducted both with and without metabolic activation. However, DBTC produced evidence of mutagenic or clastogenic effects in 5/7 *in vitro* studies reviewed, including an SOS chromotest, Rec-assay, HGPRT assay, and a chromosomal aberration test conducted with and without activation. In mouse micronucleus assays, DBTC was not clastogenic in one study and was clastogenic in the other at a dose that also caused some lethality. DBTC showed a potential to cause clastogenic effects. Overall, this category is considered to be genotoxic.

In a rat reproduction/developmental toxicity screening test of DBTC (OECD Test Guideline (TG) 421) dietary concentrations were 5, 30, or 200 ppm (ca. 0.4, 2, or 12 mg/kg bw/day). Absolute and relative thymus weights of the mid and high dose dams were decreased and accompanied by moderate to severe lymphoid depletion. Treatment-related post implantation losses, increased number of stillborn pups and decreased pup weights and increased number of runts, and pup mortality were confined to the high dose group. The maternal NOAEL was 5 ppm (0.3–0.4 mg/kg bw/day). The NOAEL for reproduction/ developmental effects was 30 ppm (ca. 2 mg/kg bw/day).

Multiple developmental toxicity studies also have been done with DBTC and its related esters. In one study [with DBTC(?)] in rats, craniofacial malformations, ankyloglossia and cleft jaw, were observed. The DBT moiety produced developmental toxicity in several additional rat studies using an oral route of administration. In these studies, a classical developmental response pattern was observed and gestation day 8 was determined to be the most sensitive day, with other periods refractory to the teratogenic effects of DBT. In rat developmental toxicity studies of DBTC, NOAELs for maternal toxicity were established at 1 and 5 mg/kg bw/day, and NOAELs for developmental toxicity and teratogenicity were 2.5 and 5 mg/kg bw/day, respectively.

There were no carcinogenicity studies for this category of compounds.

Environment

The EPIWIN suite developed by Syracuse Research Corporation has not been validated for chemicals that contain metals 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.

At room temperature, DBTC, DBTO and DBTM are solids or powders, and DBT(EHTG)/(IOTG) are oily liquids. DBTL can be produced as either an oily liquid or as a solid material. DBTC, DBTL, DBTM, DBTO, and DBT(EHTG) have melting points ranging from -80°C [DBT(EHTG)] to 110°C (DBTM), and boiling points ranging from 113.6°C (DBTC) to $\geq 260^\circ\text{C}$ [decomposition of DBT(EHTG)]. Measured and calculated vapour pressures range from $5.4\text{e-}11$ hPa (DBT(EHTG)) to 0.0016 hPa at 25°C (DBTC). Measured vapor pressure values for the organotin compounds are difficult to obtain. Similar problems exist for measuring vapor pressure as for water solubility and partition coefficient. The lower molecular weight impurities in the named substance will volatilize more readily and, therefore, influence the measured vapor pressure. In order to confirm that the vapor pressure is completely attributable to the named substance, a derivitization method to analyze the organotin compounds would have to be used. This method involves ligand exchange and currently there is no analytical method available to quantify the entire organotin compound with its associated ligands. Therefore, only calculated vapor pressure values are provided. The water solubilities of the dibutyltin compounds range from relatively insoluble (0.07 mg/L for DBTL) to moderately soluble (320 mg/L for DBTC). Log Kow values range from 0.97 (DBTC) to 11.43 [DBT(EHTG)]. Log BCFs of -0.9 to 2.13 for DBTC, 1.5 to 2.0 for DBTL, 2.0 for DBTM, and 2.0 for DBT(EHTG) indicate a low potential for bioaccumulation; however, a log BCF of 4.80 indicates that DBTO may bioaccumulate in the tissues of aquatic organisms.

None of the dibutyltin compounds are readily biodegradable. However, they are atmospherically degraded by photochemically-induced hydroxyl radicals; half-lives range from 4.7 hours [DBTL, DBT(EHTG), DBT(IOTG)] to 9.0 hours (DBTC and DBTO). DBTM may also be degraded by atmospheric ozone ($t_{1/2} = 6.6$ days).

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In water, DBTC undergoes rapid degradation by hydrolysis and is expected to hydrolyze within minutes. It is expected that the chlorines in DBTC will be displaced to form dibutyltin hydroxide which eventually precipitates as the oxide (DBTO) which will precipitate.

In water, DBT(EHTG)/(IOTG), DBTL, undergo rapid degradation by hydrolysis ($t_{1/2}$ = 10 - 12 hrs and < 38 minutes, respectively.) Although there is no stability data for DBTM, data for DBTL and DBT(EHTG)) indicate that DBTM is expected to hydrolyze within minutes to hours. Maleic acid and lauric acid are the hydrolysis products of DBTM and DBTL, respectively. Similarly, the thioester ligands on DBT(EHTG)/(IOTG) will be rapidly displaced. It is also possible that the labile ligands can be displaced by other anions in the medium. The displaced thioester ligands, EHTG/IOTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid and either ethylhexanol or isooctanol, respectively.

DBTL, DBTM, DBTO, and DBT(EHTG)/(IOTG) are sparingly soluble in water, from estimated values of 0.07 mg/L at 20°C (DBTL) to 8 mg/L (DBTM). The low solubility and occurrence of hydrolysis reactions present significant challenges to testing and analyzing organotin compounds in aqueous solution. The named substance contains a certain percentage of impurities and the lower molecular weight impurities will hydrolyze more readily in solution. These organotin impurities, including hydrolysis reaction products, will be present in solution along with the named substance. At least some of these impurities are often more soluble in water than the named substance and, therefore, confound the reported solubilities.

Based on the results of the Level III distribution modelling, DBTC and DBTM are expected to partition primarily to water (43–44%) and soil (55–56%), and DBTO, DBT(EHTG) and DBT(IOTG) are expected to partition primarily to soil (25–57%) and sediment (30–73%). For DBTL, the results of the distribution modelling (using a measured log Pow of 3.12) indicated that DBTL would partition primarily to water (79.4%). However, DBTL is relatively insoluble in water (ca. 0.07 mg/L). The results of distribution modelling using the calculated log Pow of 10.64 indicate that DBTL is expected to partition primarily to the soil (30.4%) and sediment compartments (65.9%).

DBTC contains technical impurities, including tributyltin chloride (TBTC). Because of its high toxicity, the level of this impurity should be taken into account when assessing the ecotoxicological profile of commercial products. Typically, the DBTC commercially produced contains less than 1% TBTC by weight. Also, in the ecotoxicity tests, the organisms were most likely exposed to parent substance as well as hydrolysis/degradation products.

The acute 96 hr LC_{50} toxicity values to zebra fish (*Brachydanio rerio*) ranged from >3 mg/L (DBTC, DBTL, DBTO) to ≥ 11 mg/L [DBT(EHTG)] based on measured concentrations. The acute 48-h toxicity values to *Daphnia magna* ranged from 0.21 mg/L (DBTM) to 2.52 mg/L (DBTL) based on measured concentrations. For freshwater algae, 72-h EC_{50} values ranged from 0.56 mg/L [DBT(EHTG)] to 8.0 mg/L (DBTC), and the 72 h EC_{50} values ranged from 2.5 mg/L (DBT(EHTG)) to 5.9 mg/L (DBTM). NOECs ranged from 0.19 to 2.8 mg/L. Other studies with lower toxicity values but not considered to be key studies are also mentioned in the SIAR.

DBTC (containing 0.12% (w/w) TBTC) reduced parental growth in chronic *D. magna* studies. The 21-d EC_{50} was > 0.08 mg/L (as DBTC), and the NOEC and LOEC were 0.015 and 0.03 mg DBTC/L, respectively. The NOEC and LOEC in a 110-d survival and growth test with rainbow trout (*O. mykiss*) fry were 0.04 and 0.2 mg/L, respectively, based on nominal concentrations of DBTC. The overall NOEC and LOEC were 0.098 and 0.574 mg/L, respectively, in a chronic *D. magna* toxicity study of DBT(EHTG).

Exposure

In 2000, worldwide production was 10,000 to 15,000 tonnes of DBTC, 1000 to 5000 tonnes each of DBTL and DBTO, 500 to 1000 tonnes of DBTM, and 7500 to 12,500 tonnes of DBT(EHTG). DBTC, DBTL, DBTM, and DBTO are used as industrial intermediates and/or reaction catalysts in the production of organotin chemicals or are sold to chemical and coating/coating formulation manufacturers. DBT(EHTG) and DBT(IOTG) are used commercially as heat stabilizers and are added to polyvinyl chloride (PVC) and chlorinated polyvinyl chloride (CPVC) as heat stabilizers intended to preserve the polymeric structure and properties of the resins during the

final stages of fabrication into finished articles. However, over the past several years, the IOTG product has been gradually replaced by the EHTG version due to raw material availability, cost, and customer preference. After being blended into the PVC and CPVC resin, the stabilizers remain there throughout the subsequent processing steps. All systems are designed and maintained to ensure that moisture is kept away from the resin compound, because the presence of water creates significant problems during processing. Therefore, losses to water during blending and melt processing are low, as these are designed to be “dry” processes.

Over a period of approximately ten years, use of DBT(IOTG) has gradually decreased, and DBT(EHTG) is being used instead.

Dibutyltin chemicals either leach out of PVC and CPVC articles or are released into the atmosphere during processing. The dibutyltin compounds that leach out of PVC articles into the environment will be hydrolyzed to the dibutyltin cations and associated anions. When tested, PVC water pipes showed an initial release of dibutyltins, which is followed by decreased releases until lower levels of release are reached. Other articles that have dibutyltin stabilizers, such as window profiles and building siding, will show the same type of leaching behavior, i.e., initial level falling to lower levels.

DBT concentrations in drinking water passed through new CPVC pipe at two temperatures initially ranged from 1.9–5.9 ng Sn/g and 31.2–100.4 ng Sn/g at 24 and 65°C, respectively, and declined to 0.5–0.8 ng Sn/g and 1.3–3.7 ng Sn/g, respectively, over a period of 20 repetitive extractions. DBT concentrations measured in potable water in Canada range from non-detected (< 0.5 ng Sn/L) to 52 ng Sn/L. In the U.S., organotins are on the contaminant candidate list (published in February 2005) because they are known or anticipated to occur in public drinking water systems and are of sufficient concern to warrant further investigation.

Consumers may also be exposed to DBT compounds in fish/fishery products, and DBT levels in cultured fish products were higher than levels found in marine products (maximum values: 65.5 ng/g vs. 6.12 ng/g). Whole-body DBT levels in freshwater fish range from non-detected (0.00097 µg/g detection limit) to a maximum of 0.221 µg/g. DBT levels reported in mussels and other bivalves ranged from not detected to 2.6 µg Sn/g wet weight. DBT also has been reported in a small number (4 of 95 items) of household items in Japan; the maximum concentration measured was 33.7 µg/g. Average concentrations of DBT found in household dust in two studies were 0.25 µg/g (United States) and 0.56 µg/g (United Kingdom).

Exposure in the workplace is controlled through equipment design and administrative controls such as the use of personal protective equipment. Based on an air monitoring survey in 2003, workers in PVC processing facilities that manually handled the stabilizer had exposures ranging from 50 percent of the threshold limit value (TLV) to equal to the TLV.

Most PVC and CPVC articles will either be recycled or landfilled at end of life. A portion of the PVC products entering the total solid waste stream will be incinerated, which destroys organotins and converts them to inorganic tin oxides. Landfill leachate may directly enter the environment; tests have shown that organotin leaches out from PVC at µg/L levels. If landfill leachate should directly enter the environment, the leachate would likely be more dilute, resulting in lowered environmental concentrations.

Organotins detected in untreated wastewater were primarily associated with suspended solids and 80-98% was removed from wastewater primarily by sedimentation and adsorption into sewage sludge. In soil, dibutyltins have a half-life of approximately 5 months.

A multi-year (1992–1998) national monitoring program that measured butyltins in water, sediment, and bivalve tissue collected in and around US commercial harbors, shipyards/dry docks, marinas, and ecologically significant areas (ESAs) found that butyltin concentrations have been generally steadily declining over time. In 1999, mean DBT concentrations ranged from ≤ 3.2–7.8 ng/L in surface waters regardless of depth, 9.6–16 ng/g in surface sediments, 9.1–19 ng/g in deep sediments, and 38–145 ng/g in bivalve tissue.

Several monitoring studies were conducted in areas where antifouling paints have been used. In U.S. freshwaters, a concentration of 160 ng/L was found in North Carolina. Other data on sediments showed similar results, although some have shown higher maximum levels. For instance, a maximum dibutyltin concentration of 0.71 mg Sn/kg tissue was found in a survey of freshwater estuaries in Spain. Also, in the St. Lawrence River in Canada, a

maximum dibutyltin sediment concentration of 1.00 mg Sn/kg tissue was found. A maximum dibutyltin concentration of 345 ng Sn/g mussel tissue was found off the coast of Portugal in a recent study.

Tin is not listed as a hazardous waste constituent by the EPA; therefore, its disposal is not restricted by federal land disposal restrictions. The recommended method of disposal is incineration in an approved hazardous waste incinerator. This method converts the organotin to inorganic tin. Most PVC and CPVC articles will either be recycled or landfilled at end of their use.

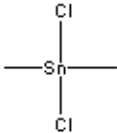
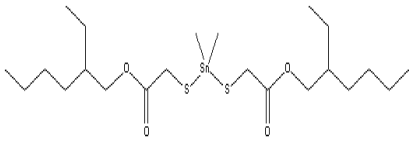
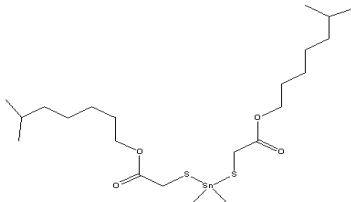
Exposure and risk assessments specific to several countries are available. These assessments were performed in countries that produce dibutyltins for use in PVC.

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

Human Health: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for human health (acute, repeated-dose, corrosivity, immunotoxicity, genotoxicity and reproduction/developmental toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for the environment (toxicity to fish, aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	Dimethyltin chloride and selected thioglycolate esters	
Structural Formula Chemical Names and CAS Registry Numbers		Dimethyltin dichloride (DMTC), CASRN 753-73-1
		Dimethyltin bis[2-ethylhexyl thioglycolate] [DMT(EHTG)], CASRN 57583-35-4
		Dimethyltin bis[isooctyl thioglycolate] [DMT(IOTG)], CASRN 26636-01-1

SUMMARY CONCLUSIONS OF THE SIAR**Category Rationale**

DMTC, DMT(EHTG), and DMT(IOTG) are considered one category of compounds for mammalian studies via the oral route. The justification for this category is based on structural similarities and the demonstrated rapid conversion of all of the esters to the DMTC when placed in simulated mammalian gastric contents [0.07M HCl] under physiological conditions. The data from the simulated gastric reaction study of DMT(EHTG) shows that essentially all DMT(-EHTG) is converted to DMTC at pH 1.5 within 0.5 hours. Thus, DMTC is the appropriate surrogate for mammalian toxicology studies via the oral route.

Acute toxicity, sensitization, irritation and *in vitro* genotoxicity are not covered under the category approach and the results of the mammalian *in vivo* tests via the oral route with the representative chloride cannot be extrapolated to the dermal or inhalation routes. However, the esters have much higher molecular weight and lower volatility than the chlorides, reducing the possibility of toxicity via inhalation and dermal routes.

The category approach was not used for the ecotoxicity and environmental fate endpoints. The considerable difference in the structures of the labile ligands causes differences in water solubility between the alkyltin chloride and thioesters affecting their respective bioavailabilities and distribution in the environment. Furthermore, DMT(EHTG) and DMT(IOTG) will degrade in aqueous solution such that organisms will be exposed to the parent material and their different degradation products. DMTC is not an appropriate surrogate for the thioesters for the ecotoxicity and environmental fate endpoints.

Analogue Rationale

Data for DMT(EHTG) and DMT(IOTG) are used interchangeably because they are isomers differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand. In addition, the breakdown products of DMT(EHTG) and DMT(IOTG) are the thioglycolate esters (EHTG and IOTG), which have the common degradates, thioglycolic acid and C-8 alcohols (either 2-ethylhexanol or isooctanol). EHTG and IOTG also have similar physicochemical and toxicological properties.

EHTG (CAS No. 7659-86-1) and IOTG (CAS No. 25103-09-7) form the Thioglycolic Acid Esters B Category, assessed in the OECD HPV Chemicals Program.

Human Health

The majority of toxicology studies were conducted with commercial mixtures having high dialkyltin to monoalkyltin ratios.

No toxicokinetic data are available for DMTC, however studies were conducted with DMT(EHTG) in which simulated gastric fluid (0.07M HCl under physiological conditions) converted this substances to dimethyltin chloride and the respective organic acid. *In vitro* data for DMTC and DMT esters indicate the dermal penetration of these compounds is low. Published data indicate that dimethyltin can cross the placenta.

Acute oral LD50s for the dimethyltin compounds have a wide range, but the most reliable data place the LD50 at approximately 400 mg/kg for DMTC and approximately 1200 mg/kg for the thioglycolates. The most reliable inhalation LC50 values range from 115 (4-h aerosol exposure) for DMTC to 132,000 mg/m³ for DMT(IOTG) and comparisons are complicated by inadequate descriptions of the aerosol in some studies. Dermal LD50 values in rabbits ranged from 380 to >2000 mg/kg for DMTC and >1050 to >3100 mg/kg for the thioglycolates. Again, study comparisons are complicated by inadequate descriptions of the tested compounds.

DMTC is corrosive to skin and eyes. DMT(EHTG)/(IOTG) are slightly to moderately irritating to skin and minimally to not irritating to eyes. DMTC is not a sensitizer. Data on DMT(2-EHTG) and DMT(IOTG) suggest that the DMT thioesters are weak sensitizers and the hydrolysis products, EHTG or IOTG, are sensitizers.

There are two repeated-dose oral studies of DMTC (90-day drinking water and 90-day feeding). The results are consistent and they are considered in tandem. DMTC had a NOAEL of 15 ppm in feed (~1.0 mg/kg/d). The critical toxic effect in both studies was neurotoxicity; tremors and convulsions were observed in a dose-related manner. Histopathology (feed study) confirmed neuronal death in the cerebellum and lesions in the hippocampal region, the piriform, entorhinal, and perirhinal cortices, the amygdala, the olfactory nuclei and the tenia tecta. The NOAEL was 15 ppm (feed) and the LOAEL was 25 ppm (water; ~2.2 mg/kg bw day).

DMTC was negative in two Ames tests, with and without metabolic activation, but was positive in *Salmonella typhimurium* strain TA100 without metabolic activation in another test. DMT(EHTG) was negative in a standard Ames assay. Although DMTC was positive in an *in vitro* chromosomal aberrations assay with metabolic activation, it was negative in an *in vivo* mouse micronucleus test. Based on these observations the overall conclusion is that DMTC does not have genotoxic potential.

Data from DMTC repeated dose studies with rats indicated no gross or histopathological effects on the reproductive organs of either sex. In separate studies, DMTC was administered to rats from days 7 to 17 of gestation at doses of 5, 10, 15, and 20 mg/kg bw/day. The NOAEL for developmental toxicity was 10 mg/kg-bw/day, with reduced fetal weight observed at 15 mg/kg-bw/day, and fetal death, cleft palate and other effects observed at 20 mg/kg bw/day, which also resulted in severe maternal toxicity (20% deaths, vaginal bleeding, tremors and other effects). In the same study, DMTC was also administered at 20 and 40 mg/kg bw/day at 4 different time periods during gestation (all 3-day intervals). Effects included increased numbers of fetuses with skeletal variations, cervical ribs, and/or splitting of first cervical vertebral arch at 40 mg/kg bw/day in the protocols where DMTC was administered on days 7-9 or 13-15 of gestation. At 40 mg/kg bw/day and days 16-17 of gestation, the number of fetuses with kinked ureters were statistically increased. Maternal toxicity in this portion of the study was limited to the gestation day 10-12 protocol at both 20 and 40 mg/kg bw/day. DMTC was fetotoxic at maternally toxic doses.

Environment

The EPIWIN suite developed by Syracuse Research Corporation has not been validated for chemicals that contain metals 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.

DMTC is a solid at room temperature and melts at 90°C, boils at 188-190°C, has a calculated vapor pressure of 0.25 hPa at 25°C, and is soluble in water (823 g/L). The log Kow is -2.18, and is not likely to bioaccumulate (log BCF=0.5). DMTC is not readily biodegradable, but atmospheric degradation occurs by photochemical induced hydroxyl radicals, with a half-life of 7.9 days. If released to the environment, DMTC is expected to partition primarily into water (51.6%) and soil (47.3%).

In water, DMTC undergoes rapid degradation by hydrolysis and is expected to hydrolyze within minutes. It is expected that the chlorines in DMTC will be displaced to form di-methyltin hydroxide which eventually precipitates as the oxide. (The alkyltin moiety (DMT) was hydrolytically stable at pH 4, 7, and 9 ($t_{1/2} > 1$ year at 25°C)).

DMTC has sufficient water solubility that it can be studied in water using analytical methods that involve derivitization. This analysis method only measures the amount of the alkyltin moiety, and can determine if the alkyltin itself is degrading. This method does not identify the other ligands attached to the tin, and thus hydrolysis of the chloride on tin to the hydroxide is NOT detected using this method. DMT(EHTG) is a liquid at room temperature, has a freezing point of -75 to -65°C, decomposes at $\geq 290^\circ\text{C}$, and a calculated vapor pressure of 0.004 hPa at 25°C. DMT(EHTG) is slightly soluble in water (0.1–4.9 mg/L), hydrophobic (log Kow = 8.48), and has a moderate potential to bioaccumulate (log BCF = 2.7). DMT(EHTG) is not readily biodegradable, but is atmospherically degraded by hydroxyl radicals and UV radiation. If released to the environment, DMT(EHTG) is predicted to partition to sediment (68%) and soil (28%), with smaller amounts in water (3.8%) and air (0.3%). DMT(IOTG) is predicted to partition into sediment (70.4%) and soil (27.5%), with smaller amounts in water (1.9%) and air (0.13%).

DMT(IOTG) and DMT(EHTG) are sparingly soluble in water as shown by the data for DMT(EHTG) that estimates solubility as 0.1-4.9 mg/L. In water, DMT(EHTG)/IOTG undergo rapid degradation by hydrolysis. Although there is no stability data for DMT(EHTG)/(IOTG), data for other organotins [DOTC, DBTL, and DBT(EHTG)] indicate that the dimethyltin compounds are expected to hydrolyze within minutes to hours in water. The thioester ligands on DMT(EHTG)/(IOTG) will be rapidly displaced to form dimethyltin hydroxide which eventually

precipitates as the oxide. It is also possible that the labile ligands can be displaced by other anions in the medium. The displaced thioester ligands, EHTG/IOTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid and either ethylhexanol or isooctanol, respectively.

In the ecotoxicity tests the organisms were most likely exposed to parent substance as well as hydrolysis/degradation products.

DMTC was not acutely toxic to *B. rerio* at 100 mg/L. The 96-h LC₅₀ for *P. promelas* was reported to be 320 mg/L. The 48-h EC₅₀ to *D. magna* was 17 (12–24) mg/L. The 72-h EC₅₀ (growth rate) for *S. subspicatus* was reported as 37 mg/L.

Acute aquatic toxicity data for DMT(EHTG) are available for fish, daphnia, and algae; and chronic aquatic toxicity data are available for daphnia. A 96-h LC₅₀ for *P. promelas* was reported to be >1000 mg/L. The 48-h EC₅₀ for *D. magna* was 32 mg/L. The 72-h EC₅₀ for *P. subcapitata* on growth and cell density values are 270 mg/L and 120 mg/L, respectively. In a 21-day *D. magna* reproduction study, LC₅₀ for parental survival was 1.0 mg/L; however, a clear dose-response relationship was not observed. The overall NOEC and LOEC were 0.46 mg/L (10% WAF) and 2.3 mg/L (50% WAF), respectively.

Exposure

DMTC is primarily used as an intermediate in the synthesis of organotin chemicals and, to a lesser extent, as a coating on glass. In 2000, worldwide production of DMTC was estimated at 1,000 to 5,000 metric tons [MT]. DMT(EHTG) is used in the production of films, sheets, injection moldings, pipes, sidings, and other applications where high thermostability is required. DMT(EHTG) has clearance in many countries for use in potable water pipes, and also is approved for use in food contact applications. In 2000, worldwide production of DMT(EHTG) was estimated at 5,000 to 10,000 MT. Use of DMT(IOTG) has been gradually replaced by DMT(EHTG) over approximately a ten year period.

DMT(EHTG)/(IOTG) is added to polyvinyl chloride (PVC) and chlorinated polyvinyl chloride (CPVC) as a heat stabilizer. After being blended into the PVC and CPVC resin, the stabilizers remain there throughout the subsequent processing steps. Dimethyltins may also be used in other PVC articles, such as window profiles, house siding, fences and decking. The amounts of stabilizer that can be used in the PVC, or the levels of dimethyltins that can be extracted into food and water are controlled. In one study, levels of dimethyltin extracted from PVC packaging materials by food simulants were below the specific migration limit established for methyltin compounds (0.18 mg Sn/kg).

Maximum dimethyltin concentrations of 400 ng Sn/L and 0.27 µg Sn/kg dry weight were reported in water and freshwater and marine sediment, respectively. Dimethyltin stabilizers occur occasionally in raw waste water; however, some research has shown that about 80% of organotins detected in untreated wastewater is associated with suspended solids and are removed from wastewater primarily by sedimentation and adsorption into sewage sludge. Studies have shown that dimethyltins have a half life of about 6 months in the environment.

Dimethyltin was not detected in saltwater in Western Florida or the Gulf of Mexico but was detected in Baltimore Harbor in Maryland with a maximum concentration of 0.1 µg/L. In a Canadian marina (freshwater), a maximum of 0.4 µg/L was found. In U.S. rivers, a mean of 0.004 µg/L was found; in German rivers a maximum of 0.26 µg/L, and in Florida lakes, ponds, and rivers none was detected (<0.008 µg/L).

In Turkey, the maximum sediment concentration of dimethyltin was 0.01 µg/L; in Great Bay, NW, the maximum sediment concentration was 0.06 µg/L, and in San Diego Bay, the maximum

concentration in sediment was 0.003 µg/L. Dimethyltin has been found in fresh water, seawater, and sediment in Canada in about 10 percent of all waters sampled.

In the Mediterranean, dimethyltin has been found in limpet (*Patella caerulea*) at 0.0002 mg Sn/kg in the shell and 0.009 mg Sn/kg in soft parts. In a forested area in Germany, dimethyltin compounds were detected in precipitation.

Dimethyltin compounds have been detected in Canadian drinking water at up to 49.1 ng Sn/L in one survey and up to 6.5 ng Sn/L in another study. In the United States, dimethyltin was found to range from 0.40 to 2.2 ng Sn/L in a limited number of tap water samples from Florida in 1977.

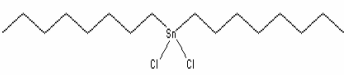
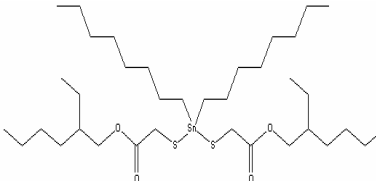
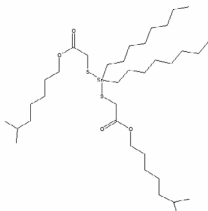
Most PVC and CPVC articles will either be recycled or landfilled at end of life. A portion of the PVC products entering the total solid waste stream will be incinerated, which destroys organotins and converts them to inorganic tin oxides. Concentrations of organotins in leachate samples from sanitary landfills were found to be in the low micrograms per liter range.

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

Human Health: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for human health (corrosivity, skin sensitization (EHTG/IOTG), neurotoxicity, and fetotoxicity at maternally toxic doses). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for the environment (toxicity to aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	Diocetyl tin dichloride and selected thioesters	
Structural Formulas Chemical Names and CAS Registry Numbers		Diocetyl tin dichloride [DOTC] CASRN 3542-36-7
		Diocetyl tin bis(2-ethylhexyl thioglycolate) [DOT(EHTG)] CASRN 15571-58-1
		Diocetyl tin bis(isooctyl thioglycolate) [DOT(IOTG)] CASRN 26401-97-8

SUMMARY CONCLUSIONS OF THE SIAR**Category Rationale**

DOTC, DOTC(EHTG), and DOT(IOTG) are considered one category of compounds for mammalian toxicology studies via the oral route. The justification for this category is based on structural similarities and the demonstrated rapid conversion of the thioesters to DOTC when placed in simulated mammalian gastric contents [0.07 M HCl] under physiological conditions. For DOT(EHTG), 100% conversion to DOTC occurred within 0.5 hours. Thus, DOTC is the appropriate surrogate for mammalian toxicology studies via the oral route.

Sensitization, irritation and *in vitro* genotoxicity are not covered under the category approach and the results of the mammalian *in vivo* tests via the oral route with the representative chloride cannot be extrapolated to the dermal or inhalation routes. However, the esters have much higher molecular weight and lower volatility than the chlorides, reducing the possibility of toxicity via inhalation and dermal routes.

The category approach was not used for the ecotoxicity and environmental fate endpoints. The considerable differences in the structures of the labile ligands cause differences in water solubility between the alkyltin chloride and thioesters affecting their respective bioavailabilities and distribution in the environment. Furthermore, DOT(EHTG) and DOT(IOTG) will degrade in aqueous solution such that organisms will be exposed to the parent material and their different degradation products. DOTC is not an appropriate surrogate for the thioesters for the ecotoxicity and environmental fate endpoints.

Analogue Rationale

Data for DOT(EHTG) and DOT(IOTG) are used interchangeably because they are isomers differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand. In addition, the breakdown products of DOT(EHTG) and DOT(IOTG) are the thioglycolate esters (EHTG and IOTG), which have the common degradates, thioglycolic acid and C-8 alcohols (either 2-ethylhexanol or isooctanol). EHTG and IOTG also have similar physicochemical and toxicological properties.

EHTG (CAS No. 7659-86-1) and IOTG (CAS No. 25103-09-7) form the Thioglycolic Acid Esters B Category, assessed in the OECD HPV Chemicals Program.

Human Health

The majority of toxicology studies were conducted with commercial mixtures having high dialkyltin to monoalkyltin ratios.

No toxicokinetic data are available for dioctyltins. However, a study under simulated gastric conditions was conducted with DOT(EHTG) (described above). *In vitro* data for DOTC and DOT(EHTG) indicate the dermal penetration of these dioctyltins is low. The acute inhalation LC50 for DOTC in rats is 390 mg/m³ for a 1-hr aerosol exposure to particles sizes of 3-10 microns, and 37,000 mg/m³ for a 1-hr aerosol exposure to particles sizes of 2.5-3.5 microns. The acute inhalation LC50 of DOT(EHTG)/(IOTG) is 470 mg/m³ in a study assigned a reliability of 4. The acute dermal LD50 of DOT(EHTG)/(IOTG) is > 2000 mg/kg bw in rats; there are no acute dermal toxicity data for DOTC. Acute oral LD50 values are 3300–7926 mg/kg bw in rats for DOTC, approx. 2000 mg/kg bw in rats and mice for DOT(EHTG), and 1120–3800 mg/kg bw in rats and 133-1400 mg/kg bw in mice for DOT(IOTG).

DOTC was not a primary skin or eye irritant in animal studies; DOT(EHTG) was found to be a irritant to the skin and eyes of test animals; and undiluted DOT(IOTG) was slightly irritating to the skin and not irritating to the eyes of test animals. No data on sensitization are available on DOTC, but the hydrolysis products EHTG or IOTG are sensitizers. DOT(EHTG)/(IOTG) was a skin sensitizer in two OECD TG 406 studies.

There are no repeated dose studies for DOTC, DOT(EHTG) or DOT(IOTG) via the dermal or inhalation routes.

The repeated dose toxicity of DOTC has been evaluated in a number of studies of varying duration. In the critical study for this endpoint, DOTC (92.1% purity) was evaluated in a GLP 90-day dietary study (OECD TG 408). The NOAEL for sub-chronic toxicity could not be established for this study, and the LOAEL was 10 ppm diet (0.7 mg/kg bw/day). The critical treatment-related changes included a reduction of thymus weight at all doses (10, 100, and 300 ppm diet) and lymphoid depletion of the thymus at 100 (6.5-6.8 mg/kg bw/day) and 300 ppm (19.3-19.8 mg/kg bw/day) diet. Other treatment-related effects included changes in clinical chemistry (ALP, bilirubin, cholesterol, total protein, bile acids, phospholipids, calcium, sodium, A/G ratio), hematology (Hb, PCV, MCV, MCH, reticulocytes, prothrombin time, lymphocytes, monocytes, total WBC), urinalysis (urinary crystals), and changes in organ weights (adrenals, thymus, spleen, kidneys, testes). Histopathological changes observed in the thymus included lymphoid depletion, characterized by a decrease in the size of the thymic lobules which can be ascribed to extensive loss of cortical and medullary small lymphocytes. Consequently, the distinction between the cortical and medullary areas was blurred. Although not accompanied by histopathological effects, the reduction of absolute and relative thymus weights in females at 10 ppm (0.7 mg/kg bw/day) was considered toxicologically relevant. An analysis of the critical toxic effect in this study (absolute and relative thymus weights of females) was performed using Benchmark Dose software developed by EPA; a putative NOAEL of 0.45 mg/kg/day was recommended for DOTC.

No NOAEL was determined in a 6-week dietary study of DOTC (>98% purity) in male and female rats, and the LOAEL was determined to be 50 ppm diet (estimated at 2.5 mg/kg/day). In the 6-week study, treatment-related thymic changes included thymic atrophy and lymphocyte depletion in the thymus-dependent paracortical areas of peripheral lymph nodes. In a 2-week dietary study of DOTC in male rats, 50 or 150 ppm in the diet resulted in reduced thymus and spleen weights (LOAEL was 50 ppm diet, estimated at 2.5 mg/kg/day).

Two 90-day repeated dose oral toxicity studies of DOT(EHTG) resulted in NOAELs of 10 ppm (0.5 mg/kg/bw/day) and 25 ppm (estimated at 1.25 mg/kg/day) in the diet. Both studies reported reductions in thymus weights (≥ 25 ppm diet). Thymic atrophy and lymphoid depletion were reported at ≥ 100 ppm diet (approximately 7 mg/kg bw/day). For DOT(IOTG), a 30-day repeated dose oral study in male rats and a 90-day repeat dose oral study in male and female rats reported NOAELs of 25 ppm diet (approximately 1.25 mg/kg bw-day) and 150 ppm diet (approximately 3.8-12.2 mg/kg bw-day for males, and 4.8-12.8 mg/kg bw/day for females); effects on the thymus were not investigated in either of these studies.

DOTC, DOT(EHTG) and DOT(IOTG) were negative in 4 of 16 *in vitro* genetic studies, including standard Ames assays (all), HGPRT assays (DOTC), a point mutation test (DOTC), and DNA binding and repair studies

(DOTC). DOTC was positive in the absence of metabolic activation in an *in vitro* mouse lymphoma assay and a gene mutation assay with *Saccharomyces cerevisiae*. DOT(EHTG) was weakly positive in the absence of metabolic activation to *S. typhimurium* strain TA100. DOTC was negative in an *in vivo* mouse micronucleus assay (OECD TG 474) and an *in vivo* DNA-binding assay, and did not increase the number of sister chromatid exchanges. A DOT(IOTG):MOT(IOTG) (80:20) mixture was negative in two *in vivo* mouse micronucleus assays. No *in vivo* genetic study of DOT(EHTG) was conducted; however, data for the analogue DOT(IOTG) is relevant for this endpoint. Based on these observations the overall conclusion is that DOTC does not have genotoxic potential.

The potential reproductive and developmental toxicity of DOTC was investigated in rats in an OECD TG 421 study. DOTC was maternally toxic at all dose levels – 10 (0.5-0.7 mg/kg bw/day), 100 (4.2-6.2 mg/kg bw/day) and 300 ppm diet (8.4-17.0 mg/kg bw/day). One or 2 animals of the 100 ppm and 300 ppm groups showed indications of treatment-related clinical effects, i.e., thin, pale appearance, piloerection and blepharospasm. Body weights were reduced at 100 and 300 ppm diet, thymus weights were decreased 33-38% at 100 ppm diet and 62-69% at 300 ppm diet, and severe to very severe treatment-related lymphoid depletion in dams was observed in the 10 ppm (5/10 animals), 100 ppm (10/10 animals), and 300 ppm (10/10 animals) dietary groups. The NOAEL for maternal toxicity was not established in this study, and the LOAEL was 10 ppm diet (0.5-0.7 mg/kg bw/day).

Treatment-related effects of DOTC on reproduction and development (OECD TG 421) of the pups were limited to the 100 and 300 ppm groups. Effects at 100 ppm diet included decreased gestation index (71% vs. 86% in controls), decreased live birth index (53% vs. 99%), decreased viability index (74% vs. 94%), increased post-implantations loss (49.2% vs. 22.3%), increased number of runts (PN1 and 4), and 2 dams delivered only dead pups. At 500 ppm diet, treatment-related effects included decreased gestation index (50% vs. 86% in controls), decreased live birth index (60% vs. 99%), decreased viability index (12% vs. 94%), increased post-implantations loss (70% vs. 22.3%), increased number of runts (PN1 and 4), and 1 dam delivered only dead pups. The NOAEL for reproduction and developmental effects was 10 ppm diet (0.5-0.7 mg/kg bw/day); LOAEL was 100 ppm diet (4.2-6.2 mg/kg bw/day).

A 2-generation study and developmental toxicity studies in mice, rats and rabbits with mixed DOT(IOTG):MOT(IOTG) (78.8:16.9, 80:20 ratio) showed maternal effects on the thymus, dose-related developmental abnormalities of bone formation in mice and rabbits, increased post-implantation losses, and decreased fetal weight plus decreased fetal viability in mice and rabbits. Compared to the screening study with DOTC, the conclusion was that in the comparable period of pregnancy, the effects on fetal weight and viability were basically the same. In contrast, rats did not show any of the abnormalities of bone formation seen in mice and rabbits.

In the 2-generation study with the DOT(IOTG):MOT(IOTG) mixture (78.8:16.9) the NOAEL for the F0 and F1 generations was 20 ppm (1.5 mg/kg bw/day), and the LOAEL was 60 ppm (4.7 mg/kg bw/day), based on reduced thymus weights of F0 males, and reduced thymus weights of both sexes and an increased incidence of stillbirths in the F1 generation. This response is not inconsistent with the result in the screening study with DOTC even though the doses in the 2-generation study were lower than the DOTC study. In the DOTC study, dose-related effects were seen at 10, 100 and 300 mg/kg/day, with post-implantation losses in the top two dose groups. This compares to the absence of such effects in the 2-generation study at the top dose of ~24 mg/kg/day. No teratogenicity was seen in either rat reproduction study; however, dose-related effects on bone formation with resulting severe birth deformations were seen in mice and rabbits. The origin of this interspecies difference is as yet unclear. NOAELs for developmental studies with mixed DOT:MOT esters (78.8:16.9, 80:20) were: 5 mg/kg/day in rats, based on maternal toxicity alone; 45 mg/kg/day in mice, based on the incidence of cleft palate; and 1 mg/kg/day in rabbits, based on the incidence of skeletal head anomalies.

Environment

The EPIWIN suite developed by Syracuse Research Corporation has not been validated for chemicals that contain metals 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. This could be especially pertinent to estimation of the BCF. This is being investigated in other assessment fora.

DOTC is a solid at room temperature, it melts at 45–47°C, boils at 175°C at 1.3 hPa, has a relative density of 1.15–1.18 g/cm³ at 50°C, and a vapour pressure of 5.16×10^{-6} hPa at 25°C. DOT(EHTG)/(IOTG) is a solid at room temperature, it freezes at -90° to -70°C, decomposes at $\geq 260^\circ\text{C}$, has a relative density of 1.08 g/cm³ at 20°C, and has an estimated vapour pressure of 0.02 hPa at 25°C.

DOTC and DOT(EHTG)/(IOTG) are low to poorly soluble in water with estimated solubilities of 0.3–1.6 mg/L (DOTC) and 1.0 mg/L [DOT(EHTG)/(IOTG)]. The inherent chemistry of organotins in water casts doubt on reported water solubility values.

In water, DOTC and DOT(EHTG)/(IOTG) undergo rapid degradation by hydrolysis. Although there is no stability data for DOT(EHTG)/(IOTG), data for DOTC and other organotins [DBTL, and DBT(EHTG)] indicate that the dioctyltin compounds are expected to hydrolyze within minutes to hours in water. It is expected that the chlorines in DOTC will be displaced to form dioctyltin hydroxide which eventually precipitates as the oxide. The thioester ligands on DOT(EHTG)/(IOTG) will be similarly rapidly displaced. It is also possible that the labile ligands can be displaced by other anions in the medium. The displaced thioester ligands, EHTG/IOTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid and either ethylhexanol or isooctanol, respectively.

Calculated Log Kows are 5.82 for DOTC and 15.35 for DOT(EHTG)/(IOTG), and log BCFs are 2.8 (DOTC) and 2.0 [DOT(EHTG)/(IOTG)]. These values should be seen with caution (refer to the EPIWIN discussion above).

With Henry's Law constants of 5.35×10^{-8} and 1.33×10^{-6} atm-m³/mol, respectively, DOT(EHTG) and DOTC would be expected to volatilize from surface water, with volatilization half-lives for a model river or lake of 38 days and 1 year, respectively, for DOTC, and 3 hours and 11 days, respectively, for DOT(EHTG).

If released to the environment, DOTC and DOT(EHTG)/(IOTG) will partition primarily to sediment [45% DOTC, 70% (DOT(EHTG)/(IOTG))] and soil [38% DOTC, 26% DOT(EHTG)/(IOTG)]. DOTC and DOT(EHTG)/(IOTG) were not readily biodegradable; however, the dioctyltins are atmospherically degraded by photochemically induced hydroxyl radicals [$t_{1/2} = 6.5$ hours for DOTC, 3.9 hours for DOT(EHTG)/(IOTG)].

In the ecotoxicity tests the organisms were most likely exposed to parent substance as well as hydrolysis/degradation products.

For DOTC, the acute aquatic toxicity is as follows: in zebra fish (*B. rerio*) the 96-h LC₅₀ > 0.24 mg/L; in *D. magna* the 48-h EC₅₀ > 0.28 mg/L; for green algae (*S. subspicatus*) the 72-h EC₅₀ for growth rate > 0.002 mg/L and NOEC $\geq$ 0.002 mg/L.

For DOT(EHTG), the acute aquatic toxicity is as follows: in zebra fish (*B. rerio*) the 96-h LC₅₀ > 25 and mg/L; in *D. magna* the 48-h EC₅₀ = 0.17 mg/L; for green alga *S. subspicatus* the 72-h EC₅₀ for growth rate = 0.17 mg/L and NOEC = 0.04 mg/L.

In 21-day chronic daphnia tests, the toxicity of DOTC is reported as LOEC = 0.87 mg/L and NOEC = 0.41 mg/L, and the toxicity of DOT(EHTG) is reported as LC/EC₅₀ (parental survival and reproduction) > 3.2 mg/L, LOEC = 1.4 mg/L, and NOEC = 0.29 mg/L.

Exposure

DOTC (always manufactured as a mixture with MOTC) is used as an industrial intermediate in the synthesis of organotin chemicals. In 2000, worldwide production of DOTC was estimated at 5,000 to 10,000 metric tonnes. DOT(EHTG) is always manufactured as a mixture with MOT(EHTG) and is added to polyvinyl chloride (PVC) and chlorinated PVC (CPVC) as a heat stabilizer. After being blended into the PVC and CPVC resin, the stabilizers remain there throughout the subsequent processing steps. In 2000, worldwide production of DOT(EHTG) was estimated at 7,500 to 12,500 metric tonnes. Production of DOT(IOTG) has been gradually decreasing over approximately ten years and is being replaced by DOT(EHTG).

The most prominent routes of potential exposure to dioctyltins in an occupational setting are inhalation and dermal contact. Exposure in the workplace is controlled through equipment design, as well as regular air monitoring. Consumer exposure to dioctyltins is primarily from PVC used in potable water pipes, other PVC plastic consumer products, and from PVC used in indirect food packaging applications. Dioctyltin chemicals either leach out of PVC and CPVC articles, or are released into the atmosphere during processing. Releases from production facilities are regulated in many countries. All processing systems are designed and maintained to

ensure that moisture is kept away from the resin compound, since the presence of water creates significant problems during processing. Therefore, losses to water during blending and melt processing are expected to be low, as these are designed to be “dry” processes. Furthermore, water is not used on a regular basis to clean equipment, wash out vessels, etc., and no wastewater is generated. Compounded PVC and CPVC material is solid and any spillage is cleaned up by vacuum or sweeping. Once the PVC or CPVC is melt processed into a final part, the dioctyltin chemicals are held within the resin although leaching may occur.

When tested, PVC water pipes showed an initial release of dioctyltins, which is followed by decreased releases until lower levels of release are reached. All regulatory bodies that have approved of the use of dioctyltins in potable water systems set limits on the amount of tin that can migrate, and in some cases the time over which such migration must fall to a small number. Other articles, such as window profiles and building siding that have dioctyltin stabilizers are expected to show the same type of leaching behavior, i.e., initial level falling to a lower level. Exposure from food packaging also is regulated, with limits on either the amount of migrated dioctyltin or the amount of dioctyltin the food packaging material can contain. Extraction work has shown that levels of dioctyltin extracted from PVC packaging materials by food simulants were below the specific migration limit (SML) established for dioctyltin compounds (0.04 mg/kg as Sn).

Although the above leaching pattern is observed, some studies have found dioctyltins in consumer products. In a study of organotins in food in Canada, five of 15 samples of edible oils contained dioctyltin (25.2 to 113 ng/g). Also, a limited number of fruit drinks (3 of 42 samples) contained dioctyltin at 0.9 to 4.3 ng/mL. Dioctyltins have also been found in all indoor dust samples collected from 10 regions from the United Kingdom in 2002, with a mean of 0.130 µg/g. Another study of indoor dust in the United States found an average dioctyltin concentration of 0.11 µg/g (with range of 0.072 to 0.20 µg/g). Other research did not find dioctyltin in fish or fishery products.

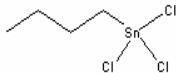
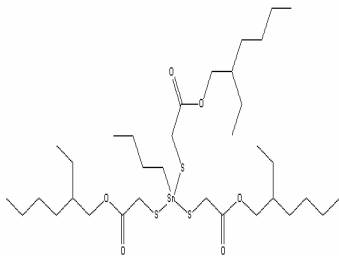
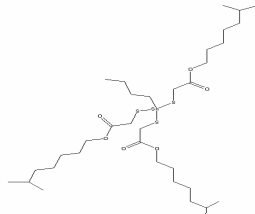
Most PVC and CPVC articles will either be recycled or landfilled at end of life. PVC products are not usually incinerated, but other organotin products that might be incinerated would be destroyed and converted to inorganic tin oxides. Landfill leachate may directly enter the environment. Concentration of organotins in leachate samples from sanitary landfills were found to be in the low micrograms per liter range. In addition, it is expected that most leachate would be treated at on-site water treatment facilities or released into a municipal sewer. If landfill leachate should directly enter the environment, there would be dilution of the leachate resulting in lowered environmental concentrations.

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

Human Health: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for human health (skin and eye irritation, dermal sensitization, acute inhalation toxicity, repeated-dose, and reproduction/developmental toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for the environment (toxicity to fish, aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	Monobutyltin trichloride and selected thioglycolate esters	
Structural Formula		Monobutyltin trichloride (MBTC, CASRN 1118-46-3)
		Monobutyltin tris(2-ethylhexyl thioglycolate), [MBT(EHTG), CASRN 26864-37-9]
		Monobutyltin tris(isooctyl thioglycolate), [MBT(IOTG), CASRN 25852-70-4]

SUMMARY CONCLUSIONS OF THE SIAR**Category Rationale**

MBTC, MBTC(EHTG), and MBT(IOTG) are considered one category of compounds for mammalian toxicology studies via the oral route. The justification for this category is based on structural similarities and the demonstrated rapid conversion of the thioesters to MBTC when placed in simulated mammalian gastric contents [0.07 M HCl] under physiological conditions. For MBT(EHTG), 98% conversion to MBTC occurred within 0.5 hours. Thus, MBTC is the appropriate surrogate for mammalian toxicology studies via the oral route.

Sensitization, irritation and *in vitro* genotoxicity are not covered under the category approach and the results of the mammalian *in vivo* tests via the oral route with the representative chloride cannot be extrapolated to the dermal or inhalation routes. However, the esters have much higher molecular weight and lower volatility than the chlorides, reducing the possibility of toxicity via inhalation and dermal routes.

The category approach was not used for the ecotoxicity and environmental fate endpoints. The considerable difference in the structures of the labile ligands causes differences in water solubility between the alkyltin chloride and thioesters affecting their respective bioavailabilities and distribution in the environment. Furthermore, MBT(EHTG) and MBT(IOTG) will degrade in aqueous solution such that organisms will be exposed to the parent material and their different degradation products. MBTC is not an appropriate surrogate for the thioesters.

Analogue Rationale

Data for MBT(EHTG) and MBT(IOTG) are used interchangeably because they are isomers, differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand. In addition, the breakdown products of MBT(EHTG) and MBT(IOTG) are the thioglycolate esters (EHTG and IOTG), which have the common degradates, thioglycolic acid and C-8 alcohols (either 2-ethylhexanol or isooctanol). EHTG and IOTG also have similar physicochemical and toxicological properties.

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EHTG (CAS No. 7659-86-1) and IOTG (CAS No. 25103-09-7) form the Thioglycolic Acid Esters B Category, assessed within the OECD HPV Chemicals Program.

Human Health

The majority of toxicology studies were conducted with commercial mixtures having high monoalkyltin to dialkyltin ratios. There are no available data on absorption, distribution, metabolism, or excretion; however, simulated gastric hydrolysis studies were conducted, as described above. For MBTC and MBT(EHTG)/(IOTG), acute oral LD₅₀s are > 1000 mg/kg bw in mice and > 2000 mg/kg bw in rats. Acute dermal and inhalation data are not available. MBTC is corrosive and MBT(EHTG)/(IOTG) is irritating to the skin and eyes of rabbits. No data on sensitization are available, but the hydrolysis products EHTG or IOTG are sensitizers.

Rats exposed to an aerosol of MBTC (1, 10, or 30 mg/m³, 6h/day, 5 days/week) for up to 28 days exhibited clinical signs and histopathologic changes consistent with exposure to corrosive substance. In the 90-day rat dietary study of MBTC (purity = 99.7%, the concentrations were 300, 1500, and 7500 ppm diet (equivalent to 19-25, 96-101, and 521-553 mg/kg bw/day, respectively). Treatment-related effects were limited to the high dose (7500 ppm) group. The NOAEL was 96-101 mg/kg bw/day. Hematological changes included increased reticulocytes in males, decreased mean corpuscular hemoglobin in females, decreased prothrombin time in both sexes, and increased WBC and lymphocytes in males; clinical chemistry changes included increased ALP, GGT, A/G ratio, bile acids, phospholipids and potassium in males; increased ASAT and triglycerides in both sexes; decreased sodium in males.

MBTC and MBT(EHTG) were negative in standard Ames assays (*S. typhimurium* strains) conducted with and without metabolic activation. MBTC was negative in two *in vitro* assays for chromosomal aberrations conducted with and without metabolic activation, and a Rec-assay conducted without metabolic activation. MBTC was positive as an SOS inducer and MBTC induced gene mutations in *Salmonella typhimurium* strain TA100, when tested in the absence of metabolic activation. MBTC was negative in an *in vivo* mouse micronucleus assay. The thioester ligands showed no evidence of genotoxicity in *in vitro* or *in vivo* studies. Overall, this category is considered not to be genotoxic.

No treatment-related effects were observed in a reproduction/developmental screening study (OECD TG 421), and the NOAEL for maternal toxicity and reproductive effects was the high dose of 7500 ppm diet (433-685 mg/kg bw/day).

Other studies confirmed that MBTC was not a developmental toxicant to pregnant rats exposed during the entire or selected segments of the period of organogenesis. MBT(EHTG) and MBT(IOTG) may have potential to cause adverse reproductive/developmental effects, based on the screening data for the hydrolysis product, 2-ethylhexyl thioglycolate (EHTG).

There is no available information on carcinogenicity of the monobutyltin compounds.

Environment

The EPIWIN suite developed by Syracuse Research Corporation has not been validated for chemicals that contain metals 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 of the monobutyltin category members are liquids at room temperature. MBTC has a freezing point of -63°C, a boiling point of 98°C at 13 hPa, the specific gravity is 1.71, and the measured vapor pressure is 0.06 hPa at 25°C. MBTC is completely soluble in water (1000 to 10,000 mg/L). Log BCF of 0.5 (calculated) and 1.7 and 2.1 (measured) for MBTC indicate a low to moderate potential to bioaccumulate in the tissues of aquatic organisms. Calculated log Kow value for MBTC is 0.18.

In water, MBTC undergoes rapid degradation by hydrolysis and is expected to hydrolyze within minutes. It is expected that the chlorines in MBTC will be displaced to form mono-butyltin hydroxide which eventually precipitates as the oxide. (The alkyltin moiety (MBT) was hydrolytically stable at pH 4, 7, and 9 ($t_{1/2}$ > 1 year at 25°C)).

Monobutyltin chloride has sufficient water solubility that it can be studied in water using analytical methods that involve derivitization. This analysis method only measures the amount of the alkyltin moiety, and can determine if the alkyltin itself is degrading. This method does not identify the other ligands attached to the tin, and thus hydrolysis of the chloride on tin to the hydroxide is not detected using this method.

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MBTC is not readily biodegradable. MBTC is atmospherically degraded by photochemically induced hydroxyl radicals and UV radiation half-life = 18 hours. Based on Henry's Law constants, volatilization of the monobutyltin compounds from surface water is predicted to occur; half-lives from a model river and lake are 31 and 340 days, respectively. Level III distribution modeling predicts that MBTC will partition primarily to water (54%) and soils (44%).

MBT(EHTG) has a melting point range of -85 to -65°C, decomposes at $\geq 260^\circ\text{C}$, has a relative density is 1.14 g/cm³, and an estimated vapor pressure of 0.02 hPa at 25°C. Measured vapor pressure values for the organotin compounds are difficult to obtain, and similar problems exist for measuring water solubility and partition coefficient. The low molecular weight impurities in the named substance (MBT(EHTG)) will volatilize (or solubilize) more readily and, therefore, influence the reported values. MBT(EHTG) is only slightly soluble in water (0.06–4.4 mg/L). Calculated log Kow values for MBT(EHTG)/(IOTG) are 12.45. Log BCFs of 2.0 (calculated) for MBT(EHTG) indicate a low to moderate potential to bioaccumulate in the tissues of aquatic organisms.

In water, MBT(EHTG)/(IOTG) undergo rapid degradation by hydrolysis. Although there is no stability data for MBT(EHTG)/(IOTG), data for other organotin compounds (DOTC, DBTL, DBT(EHTG)), indicate that the monobutyltin compounds are expected to hydrolyze within minutes to hours. The thioester ligands on MBT(EHTG)/(IOTG) will be similarly rapidly displaced to form mono-butyltin hydroxide which eventually precipitates as the oxide. It is also possible that the labile ligands can be displaced by other anions in the medium. The displaced thioester ligands, EHTG/IOTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid and either ethylhexanol or isooctanol, respectively.

MBT(EHTG) is readily biodegradable and MBT(IOTG) is expected to be biodegradable based on the data for IOTG and analogy to MBT(EHTG). Most of the degradation of MBT(EHTG)/(IOTG), as measured by CO₂ release, is from the breakdown of the thioester (EHTG/IOTG) ligands on the monobutyltin.

MBT(EHTG)/(IOTG) is atmospherically degraded by photochemically induced hydroxyl radicals and UV radiation half-life = 4.8 hours. Based on Henry's Law constants, volatilization of the monobutyltin compounds from surface water is predicted to occur; half-lives from a model river and lake are 340 days and 11 days, respectively. Level III distribution modeling predicts that MBT(EHTG)/(IOTG) will partition primarily to sediment (71-78%) and soil (20-25%).

MBTC contains technical impurities, including tributyltin chloride (TBTC). Because of its high toxicity, the level of this impurity should be taken into account when assessing the ecotoxicological profile of commercial products. Typically the MBTC commercially produced contains less than 1% TBTC by weight. Also, in the ecotoxicity tests the organisms were most likely exposed to parent substance as well as hydrolysis/degradation products.

MBTC was not acutely toxic to zebra fish (*Brachydanio rerio*) (96-h LC₅₀ > 100 mg/L), affected *Daphnia magna* condition (48-h EC₅₀ = 85 mg/L) and inhibited the growth (72-h EC₅₀ = 0.31 mg/L) and biomass (72-h EC₅₀ = 0.11 mg/L) in the green alga *Scenedesmus subspicatus* (NOEC = 0.12 mg/L). A 100% WAF (water accommodated fraction) of MBT(EHTG) was not acutely toxic to zebra fish (*B. rerio*) (96-h LC₅₀ > 2.3 mg/L), and the 99% WSF (water soluble fraction) produced inhibition to growth (72-h EC₅₀ > 0.36 mg/L) and biomass (72-h EC₅₀ = 0.20 mg/L) of the green alga *S. subspicatus* (NOEC = 0.025 mg/L). The concentrations in the WSF were based on measurement of total tin. The concentration of dissolved tin in the algae study was not stable over the duration of the test. It is known that dissolved MBT compounds hydrolyze rapidly to MBT hydroxide, and the hydroxide remains in solution for a short period, depending on pH, but does eventually precipitate as a solid oxide.

The 21-d EC₅₀ of MBT(EHTG) for *D. magna* reproduction was 0.103 mg/L, and the NOEC and LOEC were 0.049 and 0.117 mg/L, respectively. The data for MBT(EHTG) are considered applicable to MBT(IOTG).

Exposure

In 2000, global production was estimated at 10,000-15,000 tonnes of MBTC, and 2500-7500 tonnes of MBT(EHTG). MBTC is used as an industrial intermediate in the production of organotin compounds by the manufacturer, or is sold to other chemical companies for conversion to other products. MBTC also is marketed for use in glass coatings applications. The MBT(EHTG) stabilizer is added to polyvinyl chloride (PVC) and chlorinated polyvinyl chloride (CPVC) to preserve the polymeric structure and properties of the resins during the final stages of fabrication into finished articles. After being blended into the PVC and CPVC resin, the stabilizer remains there throughout the subsequent processing steps. All systems are designed and maintained to ensure that moisture is kept away from the resin compound, because the presence of water creates significant problems during

processing. Therefore, losses to water during blending and melt processing are low, as these are designed to be "dry" processes.

Over a period of approximately ten years, use of MBT(IOTG) has gradually decreased, and MBT(EHTG) is being used instead.

Monobutyltin chemicals either leach out of PVC and CPVC articles or are released into the atmosphere during processing. The monobutyltin compounds that leach out of PVC/CPVC articles into the environment will be hydrolyzed to the monobutyltin cation and associated anions. When tested, PVC/CPVC water pipes showed an initial release of monobutyltins, which is followed by decreased releases until lower levels of release are reached. Other articles that have monobutyltin stabilizers, such as window profiles and building siding, will show the same type of leaching behavior, i.e., initial level falling to lower levels.

MBT concentrations in drinking water passed through new CPVC pipe at two temperatures initially ranged from 1.2-2.7 ng Sn/g and 5.5-13.4 ng Sn/g at 24 and 65°C, respectively, and declined to 0.2-0.4 ng Sn/g and 0.3-0.6 ng Sn/g, respectively, over a period of 28 days. MBT concentrations measured in potable water in Canada range from non-detected (< 0.5 ng Sn/L) to 52 ng Sn/L. In the U.S., organotin is on the contaminant candidate list (published in February 2005) because they are known or anticipated to occur in public drinking water systems and are of sufficient concern to warrant further investigation. BT was detected at a frequency of 16% (4/25) in a winter-spring survey and 7% (2/28) in an autumn survey of Canadian drinking water samples. MBT concentrations ranged from not detected (< 0.5 ng Sn/L) to 28.5 ng Sn/L. MBT concentrations in distributed water samples from 5 municipalities in Canada ranged from not detected (< 0.5 ng Sn/L) to 3.1 ng Sn/L.

Consumers may be exposed to butyltins in food products. MBT was found in 15.6% of 90 blended wine samples at concentrations ranging from not detected (< 0.05 ng Sn/ml) to 0.50 ng/ml. The source of the butyltins was believed to be from the PVC transportation tanks used import wines for blending. MBT was only detected in 4 of 42 fruit juices at levels of 0.1-0.2 ng/cm³, and no MBT was found in edible oils sold in PVC containers.

MBT has been found in fish and various seafood products. In Europe, MBT concentrations in fish from 6 European countries ranged from 0.1 to 1920 µg/kg whole weight, with a mean of 10.1 and a median of 2.4 µg/kg. Eleven samples of fish products collected in 1996 (representative of the Japanese fish market) had MBT concentrations from not detected (~ <1.0 ng/g) to 31.8 ng/g (cultured oysters). MBT levels in seafood collected from several locations throughout Asia-Pacific ranged from <5.6 µg/kg (several species of fish and invertebrates) to up to 42 µg/kg (blue groper). MBT concentrations found in mussels, oysters, clams, Dungeness crab range from not detected to 2.6 µg/kg (tissue wet weight).

Exposure in the workplace is controlled through equipment design and administrative controls such as the use of personal protective equipment. Based on an air monitoring survey in 2003, workers in PVC processing facilities that manually handled the stabilizer had exposures ranging from 50 percent of the threshold limit value (TLV) to just at the TLV.

Most PVC and CPVC articles will either be recycled or landfilled at end of life. Landfill leachate may directly enter the environment. Concentrations of organotin in leachate samples from sanitary landfills were found to be in the low parts per billion range. Butyltins were not found in 5 Canadian landfill leachate samples. If landfill leachate should directly enter the environment, the leachate would likely be more dilute, resulting in lowered environmental concentrations.

Of organotin detected in untreated wastewater, 80% is associated with suspended solids and are removed from wastewater primarily by sedimentation and adsorption into sewage sludge. Sediments were found to have varying concentrations of butyltins.

Higher concentrations are typically found in and around harbors, marinas, dry docks, etc., where TBT was used as an antifouling paint. TBT degrades via debutylization to DBT and MBT. MBT concentrations in sediments are generally in the low mg/kg range; and MBT concentrations in fresh and marine waters are in the low µg Sn/L range.

A multi-year national U.S. monitoring program measured MBT in water, sediment, and bivalve tissue. In 1999, mean measured MBT concentrations ranged from ≤ 3.2-3.1 ng/L in surface waters regardless of depth, 2.5-5.9 ng/g in surface sediments, 2.7-6.5 ng/g in deep sediments, and 25-54 ng/g in bivalve tissue.

Other monitoring studies have also been conducted; several studies have been conducted in areas where antifouling paints have been used. In a review of several studies, maximum concentrations of monobutyltins reported in freshwater, coastal waters, and in sediments were 1.9 µg Sn/L, 2.8 µg Sn/L, and 6.8 mg/kg,

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respectively. In another study, a maximum concentration of monobutyltins in water of 0.076 µg Sn/L and 3.36 µg Sn/kg dry weight in sediment were observed. In half of seawater samples collected near Japan, a maximum concentration of 5.9 ng/L was seen.

Several studies in sediments have been conducted within the last several years. MBT was detected in some sediment samples in rivers in southwest France that were sampled in 2001, ranging from 0.001 to 0.125 mg Sn/kg dry weight. Also, in Spain, MBT concentrations ranged from 0.86 to 2.9 mg Sn/kg dry weight in five river estuaries; MBT accounted for the largest percent (47 percent) of total butyltin at all but one sampling site.

In the U.S., MBT in surface sediments (0-5 cm) in six cities near the Tennessee River and Kentucky Lake ranged from < 0.003 to 0.320 mg/kg dry weight (expressed as the butyltin ion). In the St. Lawrence River in Canada, surface sediments ranged from 0.006 to 0.989 MBT, expressed as mg Sn/kg dry weight,

MBT has also been found in seabirds, targeted organs in sea otters and other mammals, and in precipitation. Although sewage treatment can remove MBT, sludge has been found to have measurable concentrations.

Tin is not listed as a hazardous waste constituent by the U.S. EPA; therefore, its disposal is not restricted by federal land disposal restrictions. The recommended method of disposal of organotins is incineration in an approved hazardous waste incinerator, which converts the organotin to inorganic tin. Most PVC and CPVC articles will either be recycled or landfilled at end of life.

Exposure and risk assessments specific to several countries are available. These assessments have been performed in countries that produce monobutyltins for use in PVC.

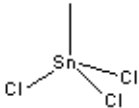
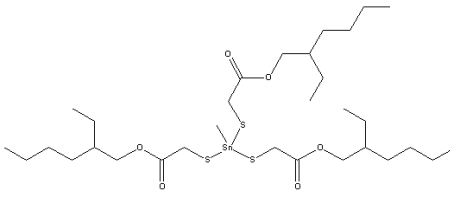
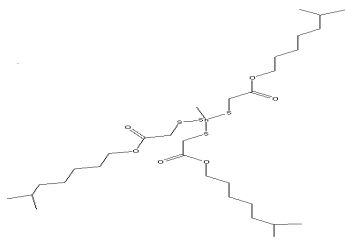
RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: MBTC is of low priority for further work. This chemical possesses properties indicating a hazard for human health (skin and eye irritation). These hazards do not warrant further work as they are related to reversible effects which may become evident only at high exposure levels. They should nevertheless be noted by chemical safety professionals and users.

MBT(EHTG) and MBT(IOTG) are candidates for further work. These chemicals possess properties indicating a hazard for human health (skin and eye irritation; skin sensitization and reprotoxicity of the EHTG and IOTG ligands). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for the environment (toxicity to fish, aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

Category Name	Monomethyltin chloride, thioglycolate esters, and tall oil ester reaction product	
Structural Formula, Chemical Names and CAS Registry Numbers		Monomethyltin trichloride, MMTC, CASRN 993-16-8
		Monomethyltin tris[2-ethylhexylmercaptoacetate], MMT(EHTG), CASRN 57583-34-3
		Monomethyltin tris[isooctylmercaptoacetate], MMT(IOTG), CASRN 54849-38-6
	This compound is a reaction product; therefore, the molecular structure will vary depending on the precursors (See SIAR)	Methyltin reverse ester tallate reaction product, TERP, CASRN 201687-58-3 201687-57-2; 68442-12-6; 151436-98-5 [mixture of CASRN 13269-74-4; 33397-79-4; 59118-79-5; 67859-63-6; 67859-64-7; 68928-40-5] See note for description of TERP

Note: The CASRN cited in the OECD SIAP for this substance refers to the descriptions of TERP from all national regulatory bodies. Therefore, this SIAP applies to TERP globally, whether described as a reaction product or described as a mixture of components. The CASRN of TERP described as a reaction product are: 201687-58-3; 201687-57-2; 68442-12-6; 151436-98-5. The CASRN of the individual components which, taken together as a mixture, describe TERP are: 13269-74-4; 33397-79-4; 59118-79-5; 67859-63-6; 67859-64-7; 68928-40-5. TERP described as a mixture of Japanese MITI numbers 2-3207 and 2-3208 is also included in the OECD definition of TERP.

The chemical definition of the substance described above is the reaction product of monomethyltin trichloride and dimethyltin dichloride, sodium sulfide (Na₂S) and various organic carboxylic acids including oleic acid and tall oil fatty acid (CASRN 8002-26-4), which are within the definition of C13 to C23 fatty acid used by Japan.

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

MMTC, MMT(EHTG), MMT(IOTG), and TERP are considered one category of compounds for mammalian studies via the oral route. The justification for this category is based on structural similarities and the demonstrated rapid conversion of all of the esters to the MMTC when placed in simulated mammalian gastric contents [0.07M HCl] under physiological conditions. For the MMT(EHTG) >90% conversion to MMTC occurred within 0.5 hours. For TERP, 68% of the monomethyltin portion of the compound was converted to MMTC within 1 hour. Thus, MMTC is the appropriate surrogate for mammalian toxicology studies via the oral route.

TERP is a reaction product of MMTC and dimethyltin dichloride (DMTC), Na₂S, and tall oil fatty acid [a mixture of carboxylic acids, predominantly C-18]. The reaction product is a mixture of carboxylic esters and includes short oligomers of mono/dimethyltins bridged by sulfide groups. Although the tall oil component of TERP is not structurally similar to EHTG, TERP's conversion to MMTC justifies its inclusion. While the contribution of the various ligands to the overall toxicity may vary, the contribution is expected to be small relative to that of the MMTC. Further, the EHTG ligand from MMT(EHTG) is likely to be more toxic than the oleic or linoleic acid from TERP so inclusion of TERP in the category is a rather conservative approach. The other possible degradate of tall oil and EHTG is 2-mercaptoethanol (2-ME), and it is common to both ligands.

Sensitization, irritation and *in vitro* genotoxicity are not covered under the category approach and the results of the mammalian *in vivo* tests via the oral route with the representative chloride cannot be extrapolated to the dermal or inhalation routes. However, the esters have much higher molecular weight and lower volatility than the chlorides, reducing the possibility of toxicity via inhalation and dermal routes.

The category approach was not used for the ecotoxicity and environmental fate endpoints. The considerable difference in the structures of the labile ligands causes differences in water solubility between the alkyltin chloride and thioesters affecting their respective bioavailabilities and distribution in the environment. Furthermore, MMT(EHTG) and MMT(IOTG) will degrade in aqueous solution such that organisms will be exposed to the parent material and their different degradation products. MMTC is not an appropriate surrogate for the thioesters or TERP for the ecotoxicity and environmental fate endpoints.

Analogue Rationale

Data for MMT(EHTG) and MMT(IOTG) are used interchangeably because they are isomers differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand. In addition, the breakdown products of MMT(EHTG) and MMT(IOTG) are the thioglycolate esters (EHTG and IOTG), which have the common degradates, thioglycolic acid and C-8 alcohols (either 2-ethylhexanol or isooctanol). EHTG and IOTG also have similar physicochemical and toxicological properties.

EHTG (CAS No. 7659-86-1) and IOTG (CAS No. 25103-09-7) form the Thioglycolic Acid Esters B Category, assessed within the OECD HPV Chemicals Program.

Human Health

The majority of toxicology studies were conducted with commercial mixtures having high monoalkyltin to dialkyltin ratios.

Gastric hydrolysis studies were conducted with TERP and MMT(EHTG) in which simulated gastric fluid [0.07M HCl under physiological conditions] converted these substances to methyltin chloride and the respective organic acids. Based on data for DMTC and DMT esters the dermal penetration of MMTC and its esters is expected to be low.

Acute oral LD₅₀ values for MMTC, MMT(EHTG), MMT(IOTG), and TERP indicated low to moderate toxicity; the most reliable data place the LD₅₀s in the range of 1000 mg/kg. Acute dermal LD₅₀ values were ≥1000 mg/kg bw, and inhalation LC₅₀ was >200 mg/L. MMTC was corrosive to skin and assumed corrosive to eyes. MMT(IOTG)/(EHTG) are irritating to skin, but not to eyes. No data on sensitization are available on MMT(EHTG)/(IOTG), but the hydrolysis products EHTG or IOTG are sensitizers. No primary irritation data

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were available for TERP, but it was a sensitizer in the mouse Local Lymph Node Assay.

There are no repeated-dose studies for the category members via the dermal or inhalation routes.

In a 90-day repeated dose oral study of MMTC, treatment-related changes were limited to the high dose group (750 ppm in diet; 50 mg/kg bw/d with some gender-related variation). Organ weight changes (adrenal, kidney, thymus, spleen, brain, epididymides), haematology, clinical chemistry, and urinalysis changes were noted, but histopathology only confirmed effects in the thymus and brain. The critical toxic effects were neurotoxicity and thymic atrophy. Both sexes had decreased cortex/medulla ratios in the thymus. In the brain there was loss of perikarya of neuronal cells in the pyramidal layer of the Hippocampus CA1/2 in both sexes, and in males there was loss of perikarya in the piriform cortex. The NOAEL was 150 ppm (10 mg/kg bw/d). Another 90-day dietary study using MMTC showed increased relative kidney weights and slight to moderate epithelial hyperplasia of the bladder in females at the lowest dose (NOAEL <20 ppm in diet [$<1\text{-}3.6$ mg/kg bw/d]) and additional effects including increased relative thymus weights in females and urinalysis results in both sexes at higher doses.

A 90-day dietary study with dose levels of 30, 100, 300, and 1000 ppm TERP in the diet resulted in slightly decreased food intake, body and organ weight changes, and decreased specific gravity of the urine at the highest dose. The NOAEL was 300 ppm in diet (equivalent to 15 mg/kg bw/d). A 28-day gavage study using TERP showed changes in clinical chemistry and slight differences in hematology at 150 mg/kg bw/d and higher. The NOAEL was 50 mg/kg bw/d.

The effects of MMT(IOTG) were evaluated in a 90-day dietary study using doses of 100, 500, and 1500 ppm (decreased from 2500 ppm) in the diet. Based on clinical chemistry effects at 500 ppm and other effects at higher doses, the NOAEL was 100 ppm in diet (approximately 6-21 mg/kg bw/d).

The monomethyltin compounds as a class are not mutagenic in the Ames test. TERP was positive in a human lymphocyte assay. MMTC was equivocal for induction of micronucleated polychromatic erythrocytes (MPEs) in an *in vivo* rat micronucleus test (OECD 474). In this study a statistically significant increase in MPE was observed only at 24 h and not at 48 h after treatment and there was no dose-response. Based on these observations the overall conclusion is that MMTC does not have genotoxic potential.

In a limited carcinogenicity study, MMT(EHTG) produced no compound-related macroscopic or microscopic changes in rats fed 100 ppm in the diet for two years.

In the reproductive satellite portion of the 90-day study using MMTC (with dose levels of 30, 150, and 750 ppm in the diet), post-implantation loss, decreased litter size and increased neonatal mortality occurred at 750 ppm (26-46 mg/kg bw/d for females). Maternal gestational body weights were transiently suppressed and other maternal toxicity was inferred from the repeated dose results at this dose. There were no malformations observed at any dose. The NOAEL for maternal toxicity, and reproductive, and fetotoxic effects was 150 ppm in the diet (6-12 mg/kg bw/d).

Environment

The EPIWIN suite developed by Syracuse Research Corporation has not been validated for chemicals that contain metals 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.

MMTC is a solid at room temperature and melts at 43°C, boils at 171°C, has a calculated vapor pressure of 1.7 hPa at 25 °C, and is soluble in water (1038 g/L at 20°C). The measured log Kow is -0.9 and MMTC is not readily biodegradable. Atmospheric degradation occurs by photochemical induced hydroxyl radicals, with a half-life of 15.7 days. A Henry's Law constant of 3.83×10^{-7} atm-m³/mol predicts MMTC will volatilize from surface water ($t_{1/2}$ = 99 days and 3 years for model river and lake, respectively). If released to the environment, MMTC is expected to partition primarily into water (54%) and soil (43%).

In water, MMTC undergoes rapid degradation by hydrolysis and is expected to hydrolyze within minutes. It is expected that the chlorines in MMTC will be displaced to form mono-methyltin hydroxide which eventually precipitates as the oxide (the alkyltin moiety (MMT) was hydrolytically stable at pH 4, 7, and 9 ($t_{1/2}$ > 1 year at 25°C)).

MMTC has sufficient water solubility that it can be studied in water using analytical methods that involve derivatization. This analysis method only measures the amount of the alkyltin moiety, and can determine if the alkyltin itself is degrading. This method does not identify the other ligands attached to the tin, and thus hydrolysis of the chloride on tin to the hydroxide is NOT detected using this method.

MMT(IOTG), MMT(EHTG), and TERP are sparingly soluble in water (0.6-10.7 mg/L). In water, these monomethyltin compounds undergo rapid degradation by hydrolysis. Although there is no stability data for MMT(EHTG)/(IOTG) or TERP, data for other organotins [DOTC, DBTL and DBT(EHTG)] indicate that the monomethyltin compounds are expected to hydrolyze within minutes to hours in water. The thioester ligands on MMT(EHTG)/(IOTG) will be rapidly displaced to form mono-methyltin hydroxide which eventually precipitates as the oxide. It is also possible that the labile ligands can be displaced by other anions in the medium. The displaced thioester ligands, EHTG/IOTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid and ethylhexanol or isooctanol, respectively.

TERP is a liquid at room temperature, boils at 216°C, and has a calculated vapor pressure of 0.2 hPa at 25°C. TERP is slightly soluble in water (4.4 mg/L), highly hydrophobic (log Kow = 25.5), has low potential for bioaccumulation (log BCF = 2.0), and is readily biodegradable. It is degraded atmospherically by hydroxyl radicals and ozone, with a half-life of 0.5 hours. If released to the environment, TERP is predicted to partition primarily to sediment (99%).

MMT(EHTG) is a liquid at room temperature and has a freezing point of -85 to -65°C, decomposes at $\geq 260^\circ\text{C}$, has a derived vapour pressure of 0.02 hPa at 25°C, a calculated log Kow of 10.98, is slightly soluble in water (1.8-6 mg/L), and is readily biodegradable. MMT(EHTG) is also degraded atmospherically, with a half-life of 6.3 hours. A Henry's Law constant of $3.18 \times 10^4 \text{ atm}\cdot\text{m}^3/\text{mol}$ predicts MMT(EHTG) will volatilize from surface water ($t_{1/2} = 8$ hours and 11 days for a model river and lake, respectively). If released to the environment, MMT(EHTG) is expected to partition primarily into sediment (71%) and soil (25%).

In the ecotoxicity tests the organisms were most likely exposed to parent substance as well as hydrolysis/degradation products. MMTC was not acutely toxic to zebra fish (*Brachydanio rerio*) (96-h $\text{LC}_{50} > 102 \text{ mg/L}$) or *Daphnia magna* (48-h $\text{EC}_{50} > 101 \text{ mg/L}$). MMTC inhibited the growth (72-h $\text{EC}_{50} = 0.03 \text{ mg/L}$) and biomass (72-h $\text{EC}_{50} = 0.02 \text{ mg/L}$) of the green alga *Scenedesmus subspicatus* ($\text{NOEC} = 0.007 \text{ mg/L}$). MMTC was not acutely toxic to earthworms at nominal concentrations up to 1000 mg/kg. TERP was not acutely toxic to rainbow trout (*Oncorhynchus mykiss*) (96-hr $\text{LC}_{50} > 4.4 \text{ mg/L}$), inhibited *D. magna* survival and mobility (48-h $\text{EC}_{50} = 0.27 \text{ mg/L}$), and inhibited growth of the freshwater green alga *Pseudokirchneriella subcapitata* was (72-h $\text{EC}_{50} = 0.64 \text{ mg/L}$; $\text{NOEC} = 0.28 \text{ mg/L}$). MMT(EHTG) was not acutely toxic to *B. rerio* ($\text{LC}_{50} > 6 \text{ mg/L}$; $\text{NOEC} = 3.6 \text{ mg/L}$) and did not inhibit the growth of *S. subspicatus* (72-h $\text{EC}_{50} > 1.84 \text{ mg/L}$; $\text{NOEC} = 0.6 \text{ mg/L}$). The 21-d EC_{50} for reproduction in a chronic *Daphnia magna* study was $> 0.134 \text{ mg/L}$ ($\text{NOEC} = 0.134 \text{ mg/L}$).

Exposure

In 2000, worldwide production was estimated at 1,000 to 5,000 metric tons for MMTC, 5,000 to 10,000 MT for MMT(2-EHTG), and 7,500 to 10,000 MT for TERP. MMTC is used as an industrial intermediate in the production of organotin chemicals; there are no commercial applications for this chemical. TERP and MMT(2-EHTG) are used in the production of polyvinyl chloride (PVC) films, sheets, injection moldings, pipes, sidings, and other applications where high thermostability is required. TERP and MMT(2-EHTG) have clearance in many countries for use in potable water pipes, and MMT(2-EHTG) also is approved for use in food contact applications. MMT(2-EHTG)/(IOTG) or TERP are added to PVC and chlorinated polyvinyl chloride (CPVC) as heat stabilizers. After being blended into the PVC and CPVC resin, the stabilizers remain there throughout the subsequent processing steps. Use of MMT(IOTG) has been gradually replaced by MMT(EHTG) over approximately a ten year period.

Consumers may be exposed to monomethyltins from PVC used in potable water pipes and fittings and from PVC used in food packaging applications. Monomethyltin stabilizers are used in the production of PVC water pipes, and these pipes are tested to insure that the amount of monomethyltin leaching into the water meets regulatory requirements. Monomethyltin chemicals can either leach out of PVC and CPVC articles, or are released into the atmosphere during the processing. However, monomethyltin compounds that leach out of PVC articles into the environment will be hydrolyzed to the corresponding monomethyltin and associated anions.

Monomethyltins may also be used in other PVC articles, such as window profiles, house siding, fences and decking. The amounts of stabilizer that can be used in the PVC, or the levels of monomethyltins that can be extracted into food and water are controlled.

In Canadian water samples from drinking distribution systems collected in 1996, monomethyltin was detected in 21 of 25 samples at 5.7 to 112 ng/L, and in 28 (100%) samples at concentrations of 2.1 to 129 ng Sn/L. Monomethyltin concentrations in distributed water systems from 5 Canadian municipalities ranged from not detected (< 0.5 ng Sn/L) to 257.4 ng Sn/L. Also, no organotin compounds were seen in raw water or water leaving the treatment plant, which suggests that the source was the distribution system. In the U.S., monomethyltin was found to range from 0.49 to 8.1 ng Sn/L in a limited number of tap water samples from Florida in 1977.

Monomethyltins are removed from wastewater primarily by sedimentation and adsorption onto sewage sludge. Regarding environmental fate, most PVC and CPVC articles will either be recycled or landfilled at end of life. PVC is not usually incinerated, but if other organotin products are incinerated, the organotins present are converted to inorganic tin oxides. Concentrations of organotins in leachate samples from sanitary landfills were found to be in the low micrograms per liter range. If landfill leachate should directly enter the environment, there would be dilution of the leachate entering the environment. The estimated half-lives of monomethyltin in a simulated landfill study ranged from 2 to 6 months.

Monomethyltins have been detected in fresh and marine waters and sediments. Concentrations of monomethyltins in fresh and marine waters are in the low micrograms per liter, and concentrations in sediments range from not detected (< 0.1 mg Sn/kg) to 0.3 mg Sn/kg. It has been found in precipitation in Germany and in limpet in the Mediterranean.

Tin is not listed as a hazardous waste constituent by the U.S. EPA. Therefore, its disposal is not restricted by federal land disposal restrictions.

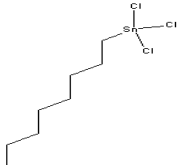
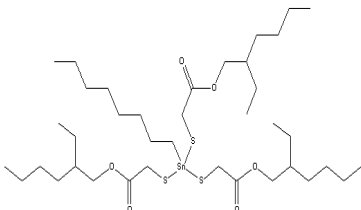
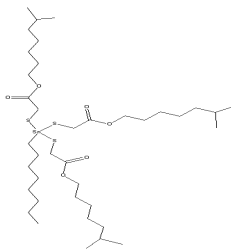
Exposure in the workplace is controlled through equipment design, as well as regular air monitoring, and worker exposure is confined to manual operations, such as material addition, transfer, or sampling.

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

Human Health: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for human health (corrosivity, skin sensitization, neurotoxicity, and reproductive toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for the environment (toxicity to aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	Mono-octyltin trichloride and selected thioglycolate esters
Structural Formula, Chemical Names and CAS Registry Numbers	 Mono-octyltin chloride [MOTC], CASRN 3091-25-6
	 Mono-octyltin tris[2-ethylhexyl thioglycolate] [MOT(EHTG)], CASRN 27107-89-7
	 Mono-octyltin tris[isooctyl thioglycolate] [MOT(IOTG)], CASRN 26401-86-5

SUMMARY CONCLUSIONS OF THE SIAR**Category Rationale**

MOTC, MOT(EHTG), and MOT(IOTG) are considered one category of compounds for mammalian toxicology studies via the oral route. The justification for this category is based on structural similarities and the demonstrated rapid conversion of the thioesters to MOTC when placed in simulated mammalian gastric contents [0.07 M HCl] under physiological conditions. For MOT(EHTG), 88% conversion to MOTC occurred within 0.5 hours. Thus, MOTC is the appropriate surrogate for mammalian toxicology studies via the oral route.

Sensitization, irritation and in vitro genotoxicity are not covered under the category approach and the results of the mammalian in vivo tests via the oral route with the representative chloride cannot be extrapolated to the dermal or inhalation routes. However, the esters have much higher molecular weight and lower volatility than the chlorides, reducing the possibility of toxicity via inhalation and dermal routes.

The category approach was also not used for the ecotoxicity and environmental fate endpoints. The considerable difference in the structures of the labile ligands causes differences in water solubility between the alkyltin chloride and thioesters affecting their respective bioavailabilities and distribution in the environment. Furthermore, MOT(EHTG) and MOT(IOTG) will degrade in aqueous solution such that organisms will be exposed to the parent material and their different degradation products. MOTC is not an appropriate surrogate for the thioesters for the ecotoxicity and environmental fate endpoints.

Analogue Rationale

Data for MOT(EHTG) and MOT(IOTG) are used interchangeably because they are isomers differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand. In addition, the breakdown products of MOT(EHTG) and MOT(IOTG) are the thioglycolate esters (EHTG and IOTG), which have the common degradates, thioglycolic acid and C-8 alcohols (either 2-ethylhexanol or isooctanol). EHTG and IOTG also have

similar physicochemical and toxicological properties.

EHTG (CAS No. 7659-86-1) and IOTG (CAS No. 25103-09-7) form the Thioglycolic Acid Esters B Category, assessed at the OECD HPV Chemicals Program.

Human Health:

The majority of toxicology studies were conducted with commercial mixtures having high monoalkyltin to dialkyltin ratios.

Toxicokinetic data are not available for the monoalkyltins. However, a study was conducted with MOT(EHTG) and in which simulated gastric fluid [0.07 M HCl under physiological conditions] converted MOT(EHTG) to MOTC and the respective organic acids. Within 0.5 hr, 88% of the MOT(EHTG) was converted to MOTC. This was a primary basis for creating the chemical category. In vitro data for DOTC and DOT(EHTG) indicate the dermal penetration of MOTC and MOT(EHTG)/(IOTG) is low.

There are no data on the acute dermal or inhalation toxicity of the monoalkyltin compounds. Acute oral toxicity studies have been conducted with MOTC, MOT(EHTG) and MOT(IOTG). Acute oral LD50 values are >2000 mg/kg bw in rats [MOTC and MOT(EHTG)], 980-5000 mg/kg bw in rats for MOT(IOTG), and 1500 mg/kg bw in mice for MOT(EHTG). MOTC is slightly irritating to skin and severely irritating to the eyes of rabbits; MOT(EHTG)/(IOTG) are skin irritants. No sensitization data on MOTC were available; MOT(EHTG) is a sensitizer in animal studies. The signs of irritation and sensitization are in keeping with the expectations based on the data for the hydrolysis products, MOTC and EHTG/IOTG.

There are no repeated dose studies for MOTC, MOT(EHTG) or MOT(IOTG) via the dermal or inhalation routes. Two repeated dose oral studies of MOTC were reported. The NOAELs from the two 90-day sub-chronic oral (dietary) studies of MOTC were < 30 ppm diet and 100 ppm diet. In the critical GLP study (OECD TG 408), treatment-related changes were limited to the high dose group (500 ppm in diet) and included increased ALP levels, organ weight changes (liver, thymus), thymic atrophy, and moderate to severe lymphoid depletion in the thymus of 9/10 females. Histopathology confirmed lymphoid depletion was characterized by a decrease in the size of the thymic lobules due to an extensive loss of cortical and medullary small lymphocytes. In severe cases, the cortex was very small or partially absent. Based on decreased thymic weights and associated histopathological findings in animals of the 500 ppm group, the NOAEL for sub-chronic toxicity was placed at 100 ppm in the diet (~7 mg/kg bw/day in males and females), and the LOAEL was ~32 mg/kg bw/day in males and females. In the second, non-GLP study, a definitive NOAEL could not be determined and the LOAEL was 30 ppm diet (~1.5-4.8 mg/kg bw/day in males and females). In this study, treatment-related effects included a dose-related decrease in relative thymus weights at ≥30 ppm diet in females and ≥100 ppm in males; decreased body weights; changes in hematology, clinical chemistry and urinalysis; and organ weight changes (thymus, liver, heart, spleen). A contributor to the differential toxicity seen in these two 90-day dietary studies is likely the age (size) of the exposed animals. In the GLP study, 7-week old rats (mean body weights: 122.4 and 135.1 g) were fed experimental diets of 10, 100 or 500 mg MOTC/kg diet for 13 weeks. In the non-GLP study, weanling rats (mean body weights: 59 and 64 g) were fed diets containing 30, 100, 300 or 1000 mg MOTC/kg diet for 13 weeks. Additionally, the critical GLP study contained ~10% (mass/mass) DOTC, and test diets were stable at room temperature (confirmed by analysis). No (or limited) data on test diet preparation and stability are available for the second 90-day study; however, it was reported to contain ~6% (mass/mass) DOTC.

The monoalkyltin compounds were not mutagenic in standard in vitro Ames assays conducted with and without metabolic activation. MOTC also was negative in an in vitro HGPRT assay, and in an in vivo mouse micronucleus test. These materials are not considered genotoxic.

In the reproduction/developmental screening study (OECD TG 421), MOTC administered in the diet was maternally toxic at 100 and 500 ppm diet, and embryo-toxic to the developing fetus at 500 ppm diet. Maternal toxicity was manifest as decreased absolute and relative thymus weights (300 and 500 ppm), and moderate to severe lymphoid depletion, which was characterized by severe thymic atrophy. Reproduction and fertility changes were limited primarily to the high dose (500 ppm diet) group and included slight decreases in gestation, live birth, fertility, and viability indices; increased post-implantations loss (41.3% vs. 6.4% in controls); increased number of stillborn pups (16 vs. 0 in controls); and decreased number of liveborn pups (46 vs. 104 in controls). The NOAEL for maternal toxicity was 10 ppm diet (0.5-0.7 mg/kg bw/day), and the NOAEL for reproductive effects was 100

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ppm diet (6.4 mg/kg bw/day in males, 4.8-7.7 mg/kg bw/day in females). The decreased incidence of pregnancy/lactation involution seen in animals of the 500 ppm group is likely due to the presence of overt treatment-related lymphoid depletion, which obscured the lactation-related involution. No developmental toxicity was observed in the OECD 421 study of MOTC.

Environment:

The EPIWIN suite developed by Syracuse Research Corporation has not been validated for chemicals that contain metals 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. This could be especially pertinent to estimation of the BCF. This is being investigated in other assessment foray.

All of the category members are liquids at room temperature. MOTC is always manufactured as a mixture with DOTC. MOTC melts at $< 10^{\circ}\text{C}$, boils at $150\text{--}159^{\circ}\text{C}$ at 13 hPa, and has a calculated vapor pressure of 0.005 hPa at 25°C , and a relative density of 1.41-1.45 g/cm³ at 20°C . MOT(EHTG)/(IOTG) melts at -80 to -70°C and decomposes at $\geq 250^{\circ}\text{C}$.

MOT(EHTG)/(IOTG) have an estimated vapor pressure of 0.04 hPa at 25°C and a relative density of 1.08 g/cm³ at 20°C . MOTC and MOT(EHTG)/(IOTG) are not readily biodegradable, but are atmospherically degraded by photochemically induced hydroxyl radicals; half-lives are 12.9 hours for MOTC and 4.3-4.5 hours for MOT(EHTG)/(IOTG). Calculated log Kow values for MOTC and MOT(EHTG)/(IOTG) are 2.14 and 14.1-14.4, respectively, indicating that MOT(EHTG)/(IOTG) is hydrophobic. Calculated log BCFs of approx. 1 (MOTC) and 2 [MOT(EHTG)/(IOTG)] should be seen with caution (refer to the EPIWIN discussion above).

MOTC and MOT(EHTG)/(IOTG) are sparingly soluble in water, with estimated values of 0.33 mg/L at 20°C (MOTC) and 0.5-2.7 mg/L [MOT(EHTG)/(IOTG)]. In water, MOTC and MOT(EHTG)/(IOTG) undergo rapid degradation by hydrolysis. Although there is no stability data for MOTC or MOT(EHTG)/(IOTG), data for other organotin [DOTC, DBTL and DBT(EHTG)] indicate that the monooctyltin compounds are expected to hydrolyze within minutes to hours in water. It is expected that the chlorine in MOTC will be displaced to form mono-octyltin hydroxide which eventually precipitates as the oxide. The thioester ligands on MOT(EHTG)/(IOTG) will be similarly rapidly displaced. It is also possible that the labile ligands can be displaced by other anions in the medium. The displaced thioester ligands, EHTG/IOTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid and either ethylhexanol or isooctanol, respectively.

Based on Level III distribution modeling, MOTC is predicted to partition primarily to water (69%) and soil (20%); MOT(EHTG)/(IOTG) are predicted to partition primarily to sediment (74-84%) and soil (15-22%). Under environmental conditions these compounds hydrolyze very quickly in water; therefore, the calculated partition coefficients may not be precise, but they do provide a reasonable estimation as to which compartments the named substance will migrate.

In ecotoxicity tests, the organisms were most likely exposed to the parent substance as well as hydrolysis/degradation products. A filtered, saturated solution of MOTC prepared at a loading rate of 100 mg/L was not toxic to zebra fish (*Brachydanio rerio*) (96-h LC₅₀ > 0.33 mg MOTC/L) or to *Daphnia magna* (48-h EC₅₀ > 0.33 mg MOTC/L). MOTC inhibited the growth (72-h EC₅₀ = 0.22 mg MOTC/L) and biomass (72-h EC₅₀ = 0.13 mg MOTC/L) of the freshwater green alga *Pseudokirchneriella subspicatus* (formerly known as *Scenedesmus subspicatus*) (NOEC = 0.045 mg MOTC/L).

A 100% Water-Accommodated Fraction (WAF) of MOT(EHTG) induced no visible effects in zebra fish (*B. rerio*) (96-h LC₅₀ > 2.3 mg MOT(EHTG)/L). The 48-h EC₅₀ for MOT(EHTG) for *D. magna* is 1.0 mg MOT(EHTG)/L, based on nominal concentrations. The 9.9% Water Soluble Fraction (WSF) inhibited *P. subspicatus* growth (72-h EC₅₀ > 0.44 mg MOT(EHTG)/L, NOEC = 0.007 mg MOT(EHTG)/L) and biomass (EC₅₀ = 0.18 mg MOT(EHTG)/L).

In a 21-day *D. magna* study, the LC₅₀ for parental survival was 0.23 mg MOT(EHTG)/L, the EC₅₀ for reproduction was > 0.34 mg MOT(EHTG)/L, and the overall NOEC and LOEC were 0.036 and 0.16 mg MOT(EHTG)/L, respectively. MOT(EHTG) and MOT(IOTG) are analogs and ecotoxicity data for MOT(EHTG) are representative of MOT(IOTG).

Exposure:

In 2000, global production was estimated at 1,000-5,000 metric tonnes (MT) for MOTC, and 2,500-7,500 MT for MOT(EHTG). Production of MOT(IOTG) ceased approximately 10 years ago and no production numbers are available for this compound.

MOTC [always manufactured as a mixture with DOTC] used as an industrial intermediate in the production of organotin chemicals such as MOT(EHTG); there are no commercial applications for MOTC. MOT(EHTG) [always manufactured as a mixture with DOT(EHTG)] is added to PVC and CPVC as a heat stabilizer intended to preserve the polymeric structure and properties of the resins during the final stages of fabrication into finished articles. After being blended into the PVC and CPVC resin, the stabilizers remain there throughout the subsequent processing steps. Mono-octyltin mercaptoacetate-based stabilizers are widely used in the production of films including indirect food contact applications, sheets, injection moldings, pipes, sidings, and other rigid PVC applications where high thermostability is required. All systems are designed and maintained to ensure that moisture is kept away from the resin compound, since the presence of water creates significant problems during processing. Therefore, losses to water during blending and melt processing are very low, as these are designed to be "dry" processes. Furthermore, water is not used on a regular basis to clean equipment, wash out vessels, etc., and no wastewater is generated. Compounded PVC and CPVC material is solid and any spillage is cleaned up by vacuum or sweeping. Once the PVC or CPVC is melt processed into a final part, most of the mono-octyltin chemicals are strongly held within the resin and are highly resistant to leaching although some leaching of mono-octyltin compounds may occur from some PVC products.

Mono-octyltin chemicals either leach out of PVC and CPVC articles, or are released into the atmosphere during processing. Releases from production facilities are low, and are regulated in many countries. There are a range of organotin chemicals that are in the PVC after processing which might leach out; however, the organotins will be hydrolyzed to the constituent alkyltin (MOT) and the relevant anion. Leaching of mono-octyltins from commercially available PVC products is low, and regulatory bodies that have approved of the use of mono-octyltins in potable water systems set limits on the amount of tin that can migrate, and in some cases, the time over which such migration must fall to a small number, for example ANSI/NSF Standard 60. When tested, PVC water pipes showed an initial release of mono-octyltins, which is quickly followed by decreased release until low levels of release are reached. No octyltins were detected in Canadian drinking water samples at concentrations above the detection limit of 0.5 ng Sn/L. No octyltins were detected in water passed through new CPVC pipe at 24 and 65°C under static and repetitive extractions. In the U.S., organotins were placed on the drinking water contaminant candidate list in 1998 partly because mono- and di-organotins used in chlorinated PVC pipes were of sufficient concern to warrant further investigation (63 FR 10273). Organotins remain on the contaminant candidate list (published in February 2005) because they are known or anticipated to occur in public drinking water systems (70 FR 9071). Other articles, such as window profiles and building siding that have mono-octyltin stabilizers will show the same type of leaching behavior, i.e., initial level falling to a very low level quite rapidly.

Exposure from food packaging also is regulated, with limits on either the amount of migrated mono-octyltin or the amount of mono-octyltin the food packaging material can contain. MOT levels extracted from olive oil packaged in PVC packaging materials were well below the specific migration limit (SML) established for mono-octyltins (1.2 mg/kg as Sn). Consumers may be exposed to octyltins in food products shipped in PVC containers or transportation tanks. MOT was detected in 5 of 15 edible oils (i.e., sunflower, peanut, corn, canola, soya, olive) at concentrations of 5.7 to 26.9 ng/g. MOTC was only found in 1 of 90 samples of blended wines from France, Greece, Italy, Germany, USA, China, and Canada at a concentration of 2.41 ng/mL. A variety of store-bought fruit juices were analyzed for organotins; MOT was detected in 5 of 42 samples at a maximum concentration of 16.3 ng/cm³.

In Japan, mono-octyltins were found in 16 of the 54 kitchen utensils, food packages and toys examined at a maximum concentration of 775 µg/g (PVC food container). PVC flooring was found to contain MOT at concentrations ranging from not detected (< 0.4 µg/g) to 91 mg/kg.

Individuals may be exposed to mono-octyltins from indoor dust. MOT was found in dust samples collected from private homes and business in the U.K. at a mean concentration of 0.45 µg/g dust, and from private homes in Germany at a maximum concentration of 0.04 µg/g. Possible sources were from stabilizers in PVC. Dust samples from other European countries showed a similar pattern.

Exposure in the workplace is controlled through equipment design and administrative controls such as the use of personal protective equipment. Based on an air monitoring survey in 2003, workers in PVC processing facilities that manually handled the stabilizer had exposures ranging from 50 percent of the threshold limit value (TLV) to just at the TLV. For general work in and around extruders, measured exposure levels were <0.0001 to 0.034 mg/m³.

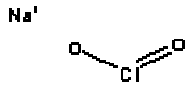
Tin is not listed as a hazardous waste constituent by the EPA; therefore, its disposal is not restricted by federal land disposal restrictions. The recommended method of disposal of organotins is incineration in an approved hazardous waste incinerator, which converts the organotin to inorganic tin. Most PVC and CPVC articles will either be recycled or landfilled at end of life. Although landfill leachate may directly enter the environment, tests have shown that very little organotin leaches out from PVC. Concentration of organotins in leachate samples from sanitary landfills were found to be in the low micrograms per liter range. In addition, it is expected that most leachate would be treated at on-site water treatment facilities or released into a municipal sewer. If landfill leachate should directly enter the environment, there would be dilution of the leachate resulting in substantially lowered environmental concentrations.

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

Human Health: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for human health (skin and eye irritation, skin sensitization, repeated-dose, and reproductive toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for the environment (toxicity to aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	Sodium chlorite 7758-19-2 Chlorine dioxide 10049-04-4
Chemical Name	Category Sodium chlorite and chlorine dioxide
Molecular Formula	Sodium chlorite Na ClO ₂
	 Chlorine dioxide ClO ₂ 

SUMMARY CONCLUSIONS OF THE SIAR**Category justification**

Chlorine dioxide and sodium chlorite are characterized together in this dossier because studies conducted with chlorite, the predominant reduction product of chlorine dioxide, are considered to be relevant in characterizing the toxicity of chlorine dioxide. In addition, studies conducted with chlorine dioxide may be relevant to characterize the toxicity of chlorite. Chlorine dioxide is fairly unstable and dissociates predominantly into chlorite (ClO₂⁻) and chloride (Cl⁻), and to a lesser extent, chlorate (ClO₃⁻). There is a ready interconversion among these species in both water and the human gut. Therefore, what exists in water or the body is a mixture of these chemical species. Toxicity information on sodium chlorite is also relevant and appropriate for assessing the effects of chlorine dioxide in man and the environment and *vice versa*. This category approach does not take into account local effects that would occur by dermal or inhalation exposure as they are specific to each substance.

Human Health

Both sodium chlorite and chlorine dioxide are rapidly absorbed following ingestion with chlorine dioxide being converted into chlorite and chloride ions with chlorate as a minor by-product.

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Both oral and dermal acute studies on sodium chlorite suggest that it is of moderate acute toxicity while chlorine dioxide gas is a potent respiratory toxicant. The oral LD₅₀ for sodium chlorite in rats was 284 mg/kg body weight and the 24-hour dermal LD₅₀ in rabbits was 134 mg/kg body weight. Acute oral and inhalation studies conducted with chlorine dioxide showed marked local toxicity and corrosive properties: The oral LD₅₀ for chlorine dioxide was 94 mg/kg body weight while the inhalation LC₅₀ was 0.089 mg/l. Two clinical acute oral studies of sodium chlorite and chlorine dioxide in humans gave no observed adverse effect levels (NOAELs) of 0.034 mg/kg body weight and 0.34 mg/kg body weight, respectively.

Sodium chlorite is non-sensitising to skin and is at worst, mildly irritating to skin (34.5%) and severely irritating to the eye (31% solution). Chlorine dioxide gas is classified as corrosive.

No repeat dose dermal and inhalation studies were available. In repeated-dose oral studies in rats and mice, the main target for both sodium chlorite and chlorine dioxide was the haematological system. Sodium chlorite was shown to induce a reduction in red blood cells, including decreased haemoglobin levels and haematocrit. This change was associated with morphological changes in the red blood cells, namely, polychromasia, poikilocytosis and macrocytosis. The NOAEL for sodium chlorite based on haematological effects observed in rats was 10 mg/kg body weight/day. Chlorine dioxide was also shown to induce decreased red blood cell counts, haemoglobin concentration and packed cell volume in addition to increased erythrocyte fragility and blood glutathione levels based on a limited study. Although this latter study with chlorine dioxide was limited in the number of animals, it gives important information in terms of comparable effects with sodium chlorite. The other specific toxicity observed in monkeys and in some reproductive studies was an effect on the thyroid system (with decreased T3 and T4), which was demonstrated to be reversible. A lower oral LOAEL (1.9 mg/kg bodyweight/day) for chlorine dioxide based on nasal inflammation in male rats only, was probably caused by chlorine dioxide gas being released from the solution.

There were no reliable *in vitro* mutagenicity tests for sodium chlorite while those for chlorine dioxide were inconclusive. There were however, a number of negative *in vivo* tests for sodium chlorite and chlorine dioxide and it is considered that they have a low potential for genotoxicity.

In a carcinogenicity drinking water study in mice, there were no significant dose-related increases in tumour incidence with sodium chlorite, and it was concluded that sodium chlorite had no carcinogenic potential.

In a two-generation oral study with sodium chlorite in rats, haematotoxic effects occurred at all dose-levels and no significant fertility, reproductive or developmental effects were observed at the highest concentration tested. The NOAEL for haematotoxicity was 3 mg/kg bodyweight/day. A rabbit developmental study in drinking water concluded that sodium chlorite was not considered to be teratogenic or a selective developmental toxicant.

Chlorine dioxide did not affect fertility in a one-generation study performed on rats by gavage. The NOAEL was 10 mg/kg bodyweight/day (highest dose tested).

Experiments on human volunteers suggest no effects in humans exposed in drinking water to 0.036 mg/kg of bodyweight/day of chlorine dioxide or sodium chlorite during a period of 12 weeks. An epidemiological study of 198 people exposed for 3 months to drinking water disinfected with chlorine dioxide (concentration of chlorite ion averaged 5 mg/l) also suggested no effects in humans.

Environment

Sodium chlorite at atmospheric pressure is solid with a melting point of 234°C, a vapour pressure of 1.1×10^{-7} Pa at 25°C and its relative density is 2.432 at 20°C. It is soluble in water (571 g/l) with a dissociation constant of 141 equating to a pKa of 2.15. Under laboratory conditions in pure water and using very high levels of UV radiation, sodium chlorite solutions have a photodegradation half-life of about 30 minutes with major products being identified as chlorine dioxide, hydroxide and chloride ions with chlorate and hypochlorite as minor products. The radiation dose required to degrade sodium chlorite suggest that doses required for drinking water disinfection would not significantly reduce chlorite concentrations. Sodium chlorite is expected to be rapidly reduced to sodium chloride in the environment especially in anaerobic conditions.

Chlorine dioxide at atmospheric pressure is a gas with a melting point of -59°C, vapour pressure of 975.9 hPa at 10 °C, a relative density of 1.6 at 0°C (relative vapour pressure 2.3) and it is soluble in water (7.5 g/l). A number of physicochemical parameters for chlorine dioxide cannot be directly measured owing to its explosive potential when air concentrations exceed 10%. Solutions are stable when kept cold and in the dark. These chemicals are

strong oxidising agents.

Sodium chlorite, in general, shows low acute toxicity to fish with LC₅₀ values above 100 mg/l for zebrafish, sheepshead minnow and rainbow trout and slightly lower for bluegill sunfish while chlorine dioxide appears to be highly toxic to fish. Due to extremely low lipophilicity and high instability in water, sodium chlorite is not expected to bioaccumulate in fish.

Sodium chlorite and chlorine dioxide are more toxic to invertebrates with high toxicity to *Daphnia magna* (sodium chlorite and chlorine dioxide, LC₅₀ 48-hour = 0.063 and 0.026 mg/l, respectively) and the crustacean, *Mysidopsis bahia* (sodium chlorite LC₅₀ 96-hour = 0.65 mg/l). However, the mollusc, *Crassostrea virginica* was much less sensitive (sodium chlorite 96 hours NOEC was 70.6 mg/l and the EC₅₀ (shell growth) was 129 mg/l). The green algae were more sensitive to sodium chlorite than fish or oyster and toxicity increased with time (ECr50 value at 72 hours was recorded as 1.2 mg/l). At present there are no data on the stability and exposure of sodium chlorite in the environment. However, the instability of these chemicals suggests that it would not be relevant to perform chronic experiments.

Studies on the effects of sodium chlorite on terrestrial species were not of sufficient quality to form conclusions on its toxicity. Sodium chlorite would be expected to rapidly reduce to sodium chloride in the environment.

Exposure

The commercial production of sodium chlorite is carried out in two steps: first, sodium chlorate is reacted with an acid to generate chlorine dioxide, and then, chlorine dioxide is reacted with caustic soda, catalysed by hydrogen peroxide, to form sodium chlorite. The industrial product formed is a solution of about 34.5% sodium chlorite; the commercial grades are obtained by dilution with water.

The total amount of sodium chlorite (as 100%) sold on average in the EU member countries (15) for the years 1998-2000 was 11 800 tonnes per year. This includes use as preservatives for liquid cooling and processing systems; food and feed area disinfectants; food or feedstocks; molluscicides; and slimicides and other non-defined biocidal use. The estimated total consumption of sodium chlorite in Japan is 4000 tonnes per year.

In the European Union, the total amount of chlorine dioxide produced per year (averaged from the years, 1998-2000) from sodium chlorite is 7859 metric tonnes and the amount for biocidal use is 6105 metric tonnes, approximately 78% of the total production.

Occupational exposure may occur during manufacturing, in the paper and pulp bleaching industries, during use as a sterilizing agent in hospitals, as a biocide in water treatment and as an improving agent in flour. Sodium chlorite and chlorine dioxide may also occur in foodstuffs as a result of their use in processing.

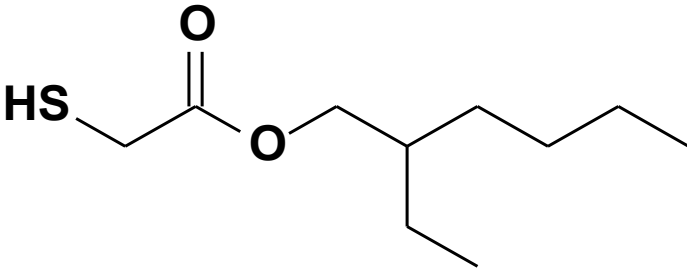
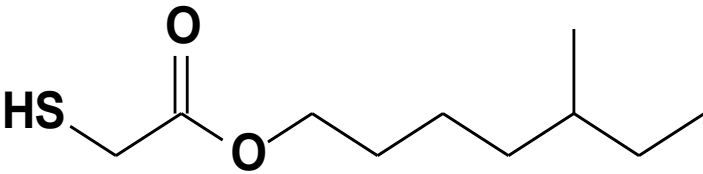
RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for human health (corrosivity, haematological toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if then indicated, a risk assessment.

Environment: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard to the environment (acute toxicity to aquatic invertebrates). An exposure assessment, and if indicated, an environmental risk assessment are recommended, especially since the substances have widespread uses as biocides. However, the fact that these substances are considered to be unstable in the environment and rapidly degrade to the non-toxic chloride ion should be taken into account.

Note: For both human health and environment, a risk assessment will be carried out under the European Union Biocidal Products Directive. (dossiers on biocidal products should be submitted at latest by July 2007).

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	ESTERS OF THIOGLYCOLIC ACIDS
CAS Numbers and Chemical Names	7659-86-1 Ethylhexyl Thioglycolate (EHTG) 25103-09-7 Isooctyl Thioglycolate (IOTG)
Structural Formula	EHTG:  IOTG (iso-octanol is a mixture of C-8 alcohol isomers: methylheptanols with methyl at 3, 4, or 5 carbon, methyl at 5 shown; and dimethylhexanols, no structure shown): 

SUMMARY CONCLUSIONS OF THE SIAR**Category/Analog Justification:**

This category contains two octyl [C-8] esters of thioglycolic acid ethylhexyl thioglycolate (EHTG) and isooctyl thioglycolate (IOTG). The thioglycolate segment of the molecules is identical as is the ester linkage. Both EHTG and IOTG are hydrolytically unstable, and have a common degradate, thioglycolic acid (TGA; CAS No. 68-11-1). The other hydrolysis product for EHTG is 2-ethylhexanol (CAS No. 104-76-7), an 8-carbon alcohol and for IOTG it is iso-octanol. The iso-octanol in this case is a mixture of 8-carbon alcohols, the major isomers being methylheptanols, and dimethylhexanols. Melting point, boiling point, vapor pressure and water solubility values are consistent, as expected for close structural analogs. Partition coefficients further suggest that their kinetic behavior in mammalian and aquatic biological systems would not be markedly different. These similarities suggest that the two compounds would be toxicologically similar. Therefore, biodegradation and acute fish toxicity data for IOTG are used to address these endpoints for EHTG. Similarly, acute aquatic toxicity to alga, in vivo mammalian genetic toxicity, reproductive and developmental toxicity data for EHTG are considered to be representative of IOTG.

Human Health

Toxicokinetics data are not available. Acute toxicity studies have been conducted with EHTG and IOTG by the dermal, inhalation and oral routes of exposure. Acute dermal and inhalation toxicity is low, with inhalation LC50 values in rats ranging from 0.4 mg/L (IOTG) to >0.51 mg/L (EHTG) and dermal LD50 values in rats or rabbits greater than 2000 mg/kg bw for both substances. The acute oral toxicity values indicate moderate toxicity, with LD50 values in rats ranging from 303 – 334 mg/kg bw (EHTG) to 485 mg/kg bw (IOTG). EHTG and IOTG are slightly irritating to the skin. EHTG has no to slight eye irritation potential, similar signs of eye irritation are seen with IOTG.

In animals, EHTG is a skin sensitizer while IOTG showed a weak response.

Repeated inhalation of up to 3.2 ppm IOTG did not cause any clinical signs of irritation or toxicity. There were no

exposure-related effects on hematology, urinalysis, clinical chemistry, organ and terminal body weights for male and female rats. There were no exposure-related lesions observed in any rats at necropsy. The No Observed Adverse Effect Level (NOAEL) for repeated inhalation of IOTG was 3.2 ppm (0.38 mg/m³; the highest concentration tested). The administration of up to 0.2% EHTG in the diet of rats for 28 days did not lead to a proliferation of hepatic peroxisomes, and did not produce any treatment-related effects. The 28 day NOAEL was 0.2% EHTG in the diet (the highest dose tested; 168 mg/kg bw for males; 173 mg/kg bw for females). The administration of up to 150 mg/kg bw EHTG by gavage to rats for 7 days did not produce any treatment-related effects. Higher doses (up to 250 mg/kg bw/d) produced mortality but no other effects that could be unequivocally attributed to the treatment. The 7 day NOAEL was 150 mg/kg bw. In an OECD guideline 421 study, groups of male and female rats were exposed to doses of EHTG of 0, 10, 50 and 150 mg/kg bw /day by gavage. Systemic toxicity was observed in the 150 mg/kg/day group. It was characterized by mortality, moribundity, decreased mean body weight gain, decreased consumption of feed, increased liver and kidney weight, or hepatocellular vacuolization in at least one sex of the F0 animals. The systemic NOEL was established at 50 mg/kg/day based on the hepatocellular effects at 150 mg/kg/d.

In an *in vivo* micronucleus assay, EHTG was not considered to be an inducer of micronuclei in male and female mice or rats up to 700 or 900 mg/kg bw, respectively. In *in vitro* bacterial mutation assays EHTG and IOTG did not induce mutagenicity in *Salmonella* bacterial strains with or without metabolic activation.

In an OECD guideline 421 study, groups of male and female rats were exposed to doses of EHTG of 0, 10, 50 and 150 mg/kg bw/day by gavage. Parental systemic toxicity was observed in the 150 mg/kg/day group. It was characterized by: mortality, moribundity, decreased mean body weight gain, decreased consumption of feed, increased liver and kidney weight, or hepatocellular vacuolization in at least one sex of the F0 animals. Increased mucification of the cervical and vaginal epithelium were noted in post-partum F0 dams. Decreased viability and growth of the F1 animals through post-partum day 4 also occurred at the 150 mg/kg bw/day dose. At doses producing maternal mortality, EHTG is considered to have a reproductive effect (dystocia in the 150 mg/kg/day group was considered test article-related). EHTG also reduced post-natal survival at 150 mg/kg bw/d but was not teratogenic. It is possible that maternal toxicity and direct neonatal exposure contributed to decreased viability and growth of F1 animals. Within the limits of the experimental design, a dosage level of 50 mg/kg bw/day was considered to be a NOAEL for reproductive or developmental effects, neonatal toxicity and systemic (maternal) toxicity resulting from exposure to EHTG when administered orally by gavage to rats.

Environment

The melting point of EHTG and IOTG is <-50°C and the boiling points are 119.5-171.1 °C at 1013 hPa and 117.5 – 161.8 °C at 1013 hPa, respectively. The vapor pressure for EHTG is 0.966 hPa at 25 °C; the vapor pressure of IOTG is 0.191 hPa at 25 °C. The water solubility of EHTG is 4.73 mg/L at 20°C; the water solubility for IOTG is 10.6 mg/L at 20°C. The partition coefficient (log Kow) of EHTG is 2.4; the partition coefficient (log Kow) for IOTG is 3.68 to 3.96 (at 25 °C; both values estimated). The overall OH rate constant for EHTG and IOTG is 45 x 10⁻¹² cm³/molecule-sec with half-lives of 2.8 hrs (EHTG) and 2.9 hrs (IOTG). The hydrolysis t_{1/2} of EHTG and IOTG at pH 7 and at 25 °C are 12 and 7.2 hrs, respectively. Hydrolysis of IOTG produces a mixture of C8 alcohols, with the major products being methylheptanols and dimethylhexanols. Hydrolysis of EHTG produces 2-ethylhexanol. Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 1000 kg/h for each media, shows the following percent distribution for EHTG: Air = 3.84%; Soil = 49%; Water = 45.6%; Sediment = 1.57%; for IOTG the values are Air = 1.83%; Soil = 68.2%; Water = 29%; Sediment = .995%. However, EHTG and IOTG are unlikely to be found in the environment, as these materials are hydrolytically unstable. IOTG is not readily biodegradable (18% degradation after 26 d; 45% degradation after 28 d). EHTG is also expected to be not readily biodegradable. Based on modeling results, bioconcentration is likely to be low for both materials (BCF = 136). The Henry's Law Constant for both EHTG and IOTG is 4.6 Pa m³/mole.

The 96-hr LC₅₀ of IOTG in fathead minnows was 4.4 mg/L under static conditions. Acute fish aquatic toxicity data for IOTG are considered to be representative of EHTG. The 48 hr EC₅₀ for EHTG to *Daphnia magna* was 0.38 mg/L under static conditions. The 48 hr EC₅₀s for IOTG are 0.39 mg/L and 2.4 mg/L, both under static conditions. The 72 hr ErC₅₀ for EHTG to *Pseudokirchneriella subcapitata* was 0.91 mg/L; the 72 hr EbC₅₀ was 0.41 mg/L. Acute aquatic toxicity to alga data for EHTG are considered to be representative of IOTG. Based on the hydrolysis of these substances, the test organisms were most likely exposed to both parent substance and hydrolysis/oxidation products.

Exposure

There is no direct environmental exposure to EHTG or IOTG as a commercial end-products because they are mainly used to produce organotin stabilizers for polyvinylchloride (PVC). These stabilizers are used in processing of PVC and are strongly held by the resin so very little is released into the environment. EHTG and IOTG are also used as

chain length transfer agents during polymerization to control molecular weight. IOTG was used in permanent wave solutions in the past, but it is no longer sold for that application or other personal care/cosmetic applications. In production, EHTG and IOTG are handled in closed systems. Air streams and waste water are treated prior to release to the environment. Air emissions from manufacturing processes are controlled by a 99% efficient Thermal Oxidizer. Odors from the manufacturing process are controlled by a Sodium Hypochlorite scrubber. Wastewater from the process area is treated on site in a biological wastewater treatment system using primary and secondary treatment.

Personal protective equipment is recommended for use during production to minimize exposure. Potential routes of exposure to workers during manufacture include dermal and inhalation routes, however low vapor pressure diminishes the potential for inhalation exposure. EHTG and IOTG are stored at ambient temperature and atmosphere in bulk storage tanks with atmospheric vents, drums and rail cars. These materials are transported from the manufacturer by road, marine, rail and air in several container types and sizes.

At the industrial consumer level, EHTG and IOTG are handled in closed systems. Engineering controls and personal protective equipment are recommended for use by the industrial consumer to minimize exposure. Exposure to EHTG or IOTG is possible during handling at the industrial consumer level (sampling raw materials or charging drummed material into reactors). Potential routes of exposure to industrial consumer workers during use include dermal and inhalation routes. While inhalation exposure may be possible, the vapor pressures are very low. Because water is not used in PVC processes there are no water emissions of EHTG or IOTG in PVC processing.

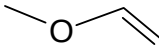
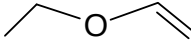
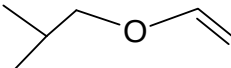
There are no direct consumer exposures to EHTG or IOTG as end-products. The primary use for these materials is to be reacted with organotin to produce PVC heat stabilizers for PVC extrusion. Use as chain length transfer agents during polymerization is also a significant application. None of these are consumer products.

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

Human Health: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for human health (skin sensitization potential, acute, repeated-dose/reproductive/neonatal toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for the environment (toxicity to fish, aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

Chemical category	Vinyl Ethers	
Category Members: CAS Registry Numbers and Chemical Names	107-25-5 Methyl vinyl ether (MVE) 109-92-2 Ethyl vinyl ether (EVE) 109-53-5 Isobutyl vinyl ether (IBVE)	
Category Members: Structural Formulas	107-25-5  109-92-2  109-53-5 	
SUMMARY CONCLUSIONS OF THE SIAR Category justification The sponsored Vinyl Ether (VE) Category consists of short-chain (C3 to C6) vinyl ethers with a methyl (M), ethyl (E), or isobutyl (IB) group. The category members have similar structure and similar physico-chemical, environmental, and ecotoxicological properties, or follow a trend with respect to these properties. The toxicological profiles of all category members are very similar. Human Health Vapors of MVE, EVE and IBVE are rapidly absorbed after inhalation. All category members are aliphatic vinyl ethers and may undergo microsomal oxidation to unstable epoxides. IBVE hydrolyzes rapidly and completely to acetaldehyde and isobutanol in simulated gastric fluid. Much less hydrolysis occurs in simulated intestinal fluid or saliva. The members of this category have a low order of acute toxicity. The acute inhalation LC₀-values (rat, 4 hrs) of MVE, EVE and IBVE were 47.9, 21.2 and 21.1 mg/l for MVE, EVE, and IBVE, respectively. There were no signs of toxicity noted in rats exposed to MVE; marked apathy and depressed breathing were seen during exposure to EVE. These signs subsided after the exposure ended and were absent on the next day. In humans, EVE has an anesthetic effect, and may cause salivation, nausea, vomiting, and circulatory and respiratory depression. Apathy, staggering and depressed breathing were noted in rats exposed to IBVE. No signs of toxicity were found in rabbits after 24 hours of occlusive treatment with 8.0 ml/kg bw of MVE, and no mortalities occurred after the same treatment with 15 080 mg EVE/kg bw or 15 380 mg IBVE/kg bw. The oral LD₅₀ values in rats for EVE and IBVE were determined as 6153 mg/kg bw and > 7700 mg/kg bw, respectively. Signs of toxicity were only reported for IBVE and included dyspnea, staggering, and reddish encrusted eyes. EVE was not irritating to the skin of rabbits. IBVE (of unknown purity) was a skin irritant in rabbits after 2 or 24 hours of occlusive treatment. Cold, liquid MVE, EVE and IBVE were all slightly irritating to the eyes of rabbits. There were no studies on the skin or respiratory sensitization potential of MVE, EVE or IBVE available. Repeated dose toxicity studies were performed on rats by the respiratory route with MVE and IBVE. MVE was tested in 28-day studies according to OECD TG 412, and IBVE in a 90-day combined repeated toxicity and reproduction/developmental toxicity screening study according to OECD TG 422. No mortalities occurred in any of these studies at concentrations up to and including 60 mg/l MVE, and 8.3 mg/l IBVE. Exposure to high concentrations of MVE (12 - 60 mg/l) led to increased liver weights in male and female rats. Blood clotting times		

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were increased and total protein decreased in all male dose groups in the study using 1.2 – 60 mg/l, but this effect was not confirmed in a second study using 0.36 - 3.6 mg/l MVE. Following inhalation of 60 mg/l, atrophy in the region of the olfactory epithelium was observed on histological examination of the nasal mucosae. The NOAEL values were 8.4 mg/l MVE for female rats and 3.6 mg/l MVE for male rats. The main target organ of IBVE was the upper respiratory tract (hyperplasia of the respiratory epithelium, decrease of the secretory mucous cells, slight degeneration of the olfactory epithelium) at 2.08 or 4.16 mg/l IBVE. Based on these findings the NOAEL was 0.208 mg/l IBVE. Furthermore, changes in some blood parameters were seen in female animals at 2.08 mg/l. High serum triglyceride and cholesterol levels were noted in high-dose parental females; the effect was less pronounced in non-pregnant females and absent in males. Increased liver and kidney weight changes were noted in high-dose males and intermediate and high-dose non-pregnant females. There was no treatment-related effect in the neurofunctional tests (Functional Observation Battery and Motor Activity Test) at any dose level. The systemic toxicity of EVE after repeated inhalation is expected to be similar to that observed with MVE and IBVE.

MVE, EVE and IBVE were not mutagenic in the Ames test or in mammalian cell systems (EVE, IBVE) both in the absence and presence of metabolic activation. EVE and IBVE did not induce chromosomal aberrations in Chinese Hamster cells. *In vivo*, MVE did not induce micronuclei in bone marrow of mice, exposed to MVE vapors at concentrations as high as 60 mg/l. The members of this category appear to have no potential to induce gene mutations or chromosomal aberrations.

No carcinogenicity study is known to exist on any of the category chemicals.

There were no specific fertility studies available for MVE and EVE. Testes weights and testes histology as well as sperm parameters were not affected in a 28-day inhalation study on rats up to and including the highest tested dose of 60 mg/l MVE. In female rats exposed during gestation days 5 through 15, the pregnancy rate, gestational parameters including resorptions, pre- and postimplantation losses, percentages of live fetuses, and sex ratios were not affected at any dose level up to the highest tested dose of 47 mg/l MVE. Because of the short exposure periods in these studies, no firm conclusions can however be drawn with regard to the reproductive toxicity of MVE. The toxicity of IBVE to reproduction was tested according to OECD TG 422 in a rat inhalation study with an extended exposure period of 90 days for parental animals at 50, 500, and 2000 ppm (i.e. 0.208, 2.08, and 8.3 mg/l). Reproduction parameters (male and female fertility indices, gestation index, and duration of gestation) and histology of male and female reproductive organs were not affected at any dose. Therefore, the NOAEL for reproduction toxicity was 2000 ppm IBVE for male and female rats, i.e. 8.3 mg/l. There is no data to suggest that members of this category will represent a hazard for fertility.

In a developmental toxicity study performed with MVE according to OECD TG 414, slight systemic toxicity (decreased corrected terminal body weight) was noted in all dams treated with 5000, 10 000, or 19 500 ppm (12, 24 or 47 mg/l). No malformations were noted in the offspring, but there was an increase in the incidence of skeletal variations (delayed ossification of neck, tail, paws and sternebra at 10 000 and 19 500 ppm). The developmental NOAEL was at 5000 ppm, i.e. 12 mg/l; the LOAEL for maternal toxicity was also at 5000 ppm (12 mg/l).

As noted above, a systemic NOAEL of 0.208 mg/l was derived for IBVE in the 90-day inhalation study on rats according to OECD TG 422. In the progeny, no other effect than a slightly, yet significantly reduced live born index (93 versus 100 % in controls) was noted at the highest tested dose of 2000 ppm (8.3 mg/l). Therefore, the developmental NOAEL was 500 ppm (2.08 mg/l). No reproduction and developmental toxicity data exist for EVE. Based on the structural similarities between the members of this category and the similarity of their toxicity profiles, data for the tested vinyl ethers are considered to be predictive for EVE, i.e. it is expected, that there will be no developmental toxicity in the absence of maternal toxicity.

Environment

The three members of the category, MVE, EVE, and IBVE, are colorless liquids. Above the boiling point (5.7 °C) MVE is a colorless gas. The boiling points for EVE and IBVE are 36 and 83 °C, respectively. The densities at 20 °C are 0.747 g/cm³ (MVE, liquefied gas), 0.754 g/cm³ (EVE) and 0.769 g/cm³ (IBVE). The substances are volatile with vapor pressures from ca. 90 hPa (IBVE) to ca. 1700 hPa (MVE) at 20 °C. The category members are soluble in water (0.7 – 17.1 g/l at 25 °C) and the Henry's Law constants of 264 – 680 Pa·m³/mol at 20 °C indicates high potential for volatilization. The log K_{OW} values of 0.4 (MVE, calculated), 1.6 (EVE, 25 °C, measured), and 3.1 (IBVE, 25 °C, measured) and the calculated BCF values of 1.3 – 81 (IBVE) show a low to moderate potential for bioaccumulation.

According to Mackay Level I, the category members would distribute to a great extent to air (98.7 – 99.6 %). On Mackay, Level III shared emissions (scenario 4) to air (60 %), water (30 %), and soil (10 %) would lead to a

predominant distribution into water for all category members, whereas in the other scenarios (1-3), the category members would remain in the compartment they were released into. In the atmosphere, the category members will rapidly be photodegraded by reactions with OH radicals (calculated half-lives ($t_{1/2}$) for a 24-h day: 8 – 11 hours).

Calculated half-lives for hydrolysis of EVE and IBVE at pH 7 are 42 d and 35 d respectively, and at pH 5 these are 10.0 h and 8.4 h, respectively.

As shown in ready (sealed system) and inherent biodegradability (unsealed system) tests, IBVE is biodegradable: 63 % biodegradation after 28 days in a OECD TG 310 test but failing the 10-days window, and 70 % BOD of COD after 5 days in a BOD₅ test following the German Industrial Standard DIN 38409, part 51. In a similar test, EVE was not biodegraded: 10 % BOD of COD after 5 days. However, the members of the category will also be easily eliminated from water by volatilization (EVE: 100 % elimination by volatilization after 5 days in an OECD TG 302B test). Experimental data are not available for MVE.

Acute aquatic toxicity studies in sealed test systems are available for IBVE. The results for fish (*Danio rerio*; LC₅₀ (96 hours): 28.3 mg/l), invertebrates (*Daphnia magna*; EC₅₀ (48 hours): 46.3 mg/l), and algae (*Desmodesmus subspicatus*; 72 h E_bC₅₀ = 32.2 mg/l; 72 h E_rC₅₀ = 45.9 mg/l) indicate moderate toxicity to aquatic life. The acute toxicity result for EVE on *Daphnia magna* (closed system; 48 hour EC₅₀: > 100 mg/l) showed that EVE is of less ecotoxicity than IBVE. The assumed trend in aquatic toxicity from MVE over EVE to IBVE was confirmed by QSAR predictions on aquatic toxicity. Concerning toxicity to microorganisms, only data from studies with unsealed test systems are available. According to the EU risk assessment procedure (EC, 2003) a PNEC_{aqua} of 0.028 mg/l was obtained by applying an assessment factor of 1000 on the lowest effect concentration, the result of the acute *Danio rerio* test with IBVE.

Exposure

The industrial method used for the production of vinyl ethers in the Sponsor country is the reaction of acetylene with the corresponding alcohols in the presence of potassium hydroxide in the liquid phase under pressure and temperatures between 150 and 180 °C (Repe vinylation). Because of the applied reaction conditions and the handling of gaseous compounds the manufacturing facilities are designed as closed systems. In the Sponsor Country, the vinyl ethers of this category are manufactured at one single site and processed in plants at the same location.

The annual world production capacity in 2004 for the members of the vinyl ethers category (MVE, EVE, IBVE) was estimated at 40 000 – 80 000 tons, subdivided into 10 000 – 20 000 tons/a for Europe, 10 000 – 20 000 tons/a for NAFTA (USA), and 20 000 – 40 000 tons/a for Asia/Pacific.

MVE is used as a starting material for polymers/copolymers (coatings, adhesives), leather processing agents, biocides, construction material, and personal care products. EVE is a starting material for polymers/copolymers (coatings, adhesives), flavors, and pharmaceuticals. IBVE is mainly used as starting material for copolymers (e.g. in coatings for food packaging materials, adhesives), pharmaceuticals, and dyes (fuel markers).

During manufacture and processing of vinyl ethers, worker exposure is controlled by the use of closed systems, industrial hygiene controls, and personal protective equipment. In the Sponsor country, any risk of accumulation of vinyl ethers or its impurities is minimized by natural ventilation, as the chemical is produced in closed systems installed in open air. At processing sites, the exposure of workers is minimized by vapor abstraction. Prior to repair and maintenance work, vessels, pipes and other equipment is rinsed to remove any residual vinyl ethers. In the Sponsor country, the main part of the production volume is processed internally and transferred via pipelines to other plants at the same site. Only small amounts are bottled in trading units in an air-conditioned room using an exhaust device. Dedicated systems designed to handle vinyl ethers are typically used for loading and unloading purposes, and spill prevention procedures are in place. Drum filling stations are fully encapsulated and vapor abstraction is in place to prevent the formation of explosive atmospheres and to minimize exposure. The vent gases are either incinerated or cleaned by means of a scrubber.

At the production and processing sites, workers wear personal protective equipment which includes gloves, face shields and safety goggles in view of the low pH during processing. During repair and maintenance operations, and during drum emptying operations, respiratory protective equipment is additionally used. Exposure to vinyl ethers via air is routinely controlled by personal air sampling.

Consumer exposure to residual MVE, EVE or IBVE may occur through the use of products made from vinyl ether polymers or copolymers. However, this exposure is considered to be very low, since most of the marketed vinyl ether polymers and co-polymers are heat-treated and potentially existing residual vinyl ethers are expected to evaporate during this process. In the EU, the use of IBVE in food packaging materials is restricted to a

maximum of 5 mg/kg in the finished article, because of limited data which did not allow establishing an acceptable daily intake.

Releases into the environment may occur during manufacturing and processing in the industry. According to the data reported to the German Emission Register, during production and internal processing at BASF AG, Ludwigshafen, 127 kg/a of MVE, less than 100 kg/a of EVE, and 3903 kg/a of IBVE were emitted to air in 2004. The mean measured IBVE concentrations in the effluent of the industrial wastewater treatment plant (wwtp) of BASF AG were below the limit of detection (20 µg/l) in 2004. Neither MVE nor EVE was monitored in the effluent of the WWTP at this production and processing site.

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

Human Health: The chemicals of this category are currently of low priority for further work. The chemicals possess properties indicating a hazard for human health (irritation, repeated-dose toxicity by high dose treatment, all category chemicals may produce explosive atmospheres with air, the lower explosive limits are in the range between 0.7 and 2.2 vol.%). Exposure in occupational settings is controlled, and consumer exposure is anticipated to be low. Countries may wish to investigate any exposure scenarios that have not been presented by the Sponsor country.

Environment: The chemicals of this category are currently of low priority for further work. The chemicals possess properties indicating a hazard for the environment (acute toxicity to fish, aquatic invertebrates and algae: LC/EC₅₀ between 10 and 100 mg/l). However, the chemicals are of low priority for further work for the environment because of their volatility, their fast photodegradation and limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category Name	Crystalline, Non-fibrous Zeolites (Zeolites A, P, X and Y)
CAS Nos.	1318-02-1 = Zeolites also: 1344-00-9 = Sodium aluminosilicates (for historical reasons)
Structural Formula	$ \begin{array}{c} \left[\begin{array}{ccccc} & \text{O} & & \text{O} & \\ & & & & \\ - & \text{O} - \text{Si} - & \text{O} - & \text{Al} - & \text{O} - \\ & & & & \\ & \text{O} & 2\text{Na}^{(+)} & \text{O} & \\ & & & & \\ - & \text{O} - \text{Al} - & \text{O} - & \text{Si} - & \text{O} - \\ & & & & \\ & \text{O} & & \text{O} & \\ & & & & \end{array} \right]_n \end{array} $ General formula of zeolites: $\text{Na}_x[(\text{AlO}_2)_x(\text{SiO}_2)_y] \cdot x \text{H}_2\text{O}$ Zeolite A: $\text{Na}_{12}[(\text{AlO}_2)_{12}(\text{SiO}_2)_{12}] \cdot 27 \text{H}_2\text{O}$ Zeolite P: $\text{Na}_6[(\text{AlO}_2)_6(\text{SiO}_2)_6] \cdot 15 \text{H}_2\text{O}$ Zeolite X: $\text{Na}_{86}[(\text{AlO}_2)_{86}(\text{SiO}_2)_{106}] \cdot 264 \text{H}_2\text{O}$ Zeolite Y: $\text{Na}_{56}[(\text{AlO}_2)_{56}(\text{SiO}_2)_{136}] \cdot 250 \text{H}_2\text{O}$

SUMMARY CONCLUSION OF THE SIAR**Category Justification:**

The members of the synthetic, non-fibrous crystalline zeolites category share the same basic structure. The production routes for the zeolites of this category are very similar with identical starting materials. They are "framework" aluminosilicates, which are based on an infinitely extending three-dimensional network of AlO_4 and SiO_4 tetrahedra. These are linked to each other by oxygen forming secondary building units (SBU). Further structural entities are polyhedra, which are built from the SBUs. The framework of all zeolites contains channels and inter-connected voids, which are occupied by the cation (e.g., sodium) and water molecules. The members of this category have similar physico-chemical, ecotoxicological and toxicological properties, which supports the approach of grouping these compounds into a category.

Human Health:

After inhalation, the zeolites of this category may reach the lungs, bronchi and alveoli, where the substances are deposited and later removed by macrophages. After oral exposure, the zeolites are hydrolyzed to silicates and aluminates in the stomach. No toxicologically relevant absorption of Al occurs, but increased Si levels may be found in the kidney. The major part of Si is rapidly excreted in urine and feces with excretion half-lives of between 6 and 8 hours.

No toxic effects were observed after acute exposure to the zeolites A, Y and X, with 1-hour inhalation LC_{50} values in rats of $> 18\,300 \text{ mg/m}^3$, and $> 2300 \text{ mg/m}^3$ for zeolites A and Y, respectively. The dermal LD_{50} values in rabbits were $> 2000 \text{ mg/kg bw}$ for both zeolite A and zeolite Y; and the oral LD_{50} in rats were determined to be

> 2000 mg/kg bw for zeolites A, Y, and X. Similar results are expected with zeolite P.

Zeolite A, Y and X were not irritating to the skin of rabbits, and slightly to moderately irritating to the rabbit eyes. Similar results are expected with zeolite P.

Zeolite A was not a skin sensitizer in limited animal tests, and there is no evidence from human experience that zeolites may induce respiratory sensitization.

In repeated dose inhalation studies with cynomolgus monkeys, exposed to 0, 1, 6 or 50 mg/m³ zeolite A dust for 6 hours per day, 5 days a week for periods of 6, 12 or 24 months, macrophage accumulation, bronchiolitis and alveolitis were found after 6 months down to the lowest tested zeolite concentration of 1 mg/m³ (LOAEL). A NOAEL could not be identified in this study.

Repeated dose toxicity studies were not available for the dermal route.

Chronic oral studies demonstrate that zeolite A causes adverse effects at high doses in the kidney and urinary bladder, probably due to the absorption of SiO₄ after zeolite dissociation. The subsequent deposition of crystalline material in the kidney and the excretion of this material via the urine may cause mechanical damage to the kidney and bladder associated with concurrent epithelial hyperplasia in these organs. The NOAEL for these effects in rats was determined as 75 mg/kg bw/day in a 200-day study. No adverse effects were found in a two-year study with rats at the highest tested dose (60 mg/kg bw/day). Similar results are expected for zeolites X, P, and Y.

Zeolites A and X (silver exchanged), which were the only zeolites tested for genetic toxicity, induced no gene mutations in several guideline tests on bacteria and mammalian cells in culture (only Zeolite X was tested in the latter). Zeolite A was not clastogenic *in vitro*. *In vivo* clastogenesis studies considered to be reliable showed no evidence of induction of chromosomal aberrations by either Zeolite A or X. However, a reliable *in vitro* study of Zeolite X showed clear induction of chromosomal aberrations. While the difference in response between *in vitro* and *in vivo* is of interest, the important conclusion is that this category of chemicals lacks the potential to induce chromosomal aberrations *in vivo*.

Limited carcinogenicity studies with zeolite A by the oral and inhalation routes did not indicate a carcinogenic potential.

There were no fertility studies available. In 6-, 12-, and 24-month inhalation studies with cynomolgus monkeys, zeolite A has not shown any adverse effects on testes and ovaries up to and including a concentration of 50 mg/m³. No treatment related effects on the testes of rats were observed after exposure to up to 2.0 % zeolite A in the diet (corresponding to ca. 1250 mg/kg bw/day) for up to 200 days. Therefore the NOAEL for male reproduction organs was determined to be 1250 mg/kg bw/day.

In studies which were performed similarly to OECD TG 414, zeolite A was not shown to be a developmental toxicant in rats, rabbits, hamsters and mice. For all species, the NOAEL was 1600 mg/kg bw/day (highest tested dose) for maternal and developmental toxicity. Thus, the members of this category are considered to have neither reproductive nor developmental toxicity.

Environment

Zeolite A as category representative is an inorganic solid with a melting point of 1700 °C, a solubility in water of 1.4 mg/l at 25 °C, and a negligible vapour pressure. Data for zeolites P, X, and Y are not available but assumed to be very similar. The densities are 1.99 g/cm³ (zeolite A), 2.01 g/cm³ (zeolite P), 1.93 g/cm³ (zeolite X), and 1.92 g/cm³ (zeolite Y) and the ion exchange capacities (in mequiv/g) are 7 (zeolites A and P), 6.4 (zeolite X), and for zeolite Y 4.4 or 5.0. Partition coefficients such as log K_{OW} and the Henry's Law constant are not applicable to zeolites. Bioaccumulation of zeolite A was not observed in clams and tubifex.

Photodegradation and biodegradation are not applicable as environmental fate processes for zeolites because they are nearly insoluble inorganic solids. Hydrolysis has a half-life of about 1 - 2 months depending on pH values (lower pH values accelerate the hydrolysis) and transforms zeolites into natural aluminosilicates, which are indistinguishable from natural soil and sediment silicates.

Zeolites are a constituent of the wastewater stream. Removal of zeolites from the wastewater during the treatment process by gravitational settling is the dominant fate process for zeolites. As a result, 72 - 90 % of the zeolites are transferred from the wastewater stream to the sludge. Via sludge disposal the major fraction of zeolites ends up in the terrestrial environment. However, this is not considered as an issue of concern as zeolites are listed as inert ingredients of minimal risk by US-EPA and may subsequently be used as additives to plant protection products for the terrestrial environment without limit, and hence are considered as ingredients without significant adverse impact to environment.

The acute data for fish and *Daphnia* indicate low aquatic toxicity of zeolites (> 100 mg/l) towards these species. The key studies for chronic effects related to physical effects of suspended crystals in fish and *Daphnia* yield NOEC values in the range of 32 - 129 mg/l indicating that zeolites do not pose a significant hazard to aquatic life. Algae turned out to be most susceptible group of organisms (NOEC 18 mg/l); however this is not a response to toxicity, but a result of nutrient depletion of the nutrient-poor media used in the tests.

The Ca²⁺-exchanged form of zeolites as the environmentally prevalent species displays low toxicities (NOEC: 60 000 mg/kg) to terrestrial organisms. Hence, zeolites do not pose a significant hazard to terrestrial life.

Exposure

The annual consumption of all zeolites used in the European detergent market has been relatively constant for a number of years. The figures for the years 1993 - 2000: were in the range 620 000 - 650 000 metric tonnes. Production by CEFIC members only in 2002 was 500 000 metric tonnes of zeolite A and 75 000 metric tonnes of zeolite Y.

Zeolites are listed in the Swiss and Swedish Product Register as well as the SPIN database for different uses, e.g., in adhesive and auxiliary products, paint, lacquers, varnishes, detergents, soaps and consumer products. Zeolites, especially zeolite A and P, are used in concentrations of up to 30 % in household detergents to decrease the water hardness by exchanging the Ca-ions for Na-ions. The major part of phosphate-free household detergents is based on the use of zeolites A and P as builders. Moreover, zeolites are also used as catalysts (petrochemicals processing for aromatics, olefins, and detergents production; and zeolites X and Y in the mineral oil industry for fuel production) or molecular sieves.

Occupational exposure may occur during manufacture and production of zeolite powder, paste or granulate and through the professional use of zeolite containing products. Exposure is most likely to occur through inhalation and dermal contact. Measured occupational exposure concentrations in a French Molecular Sieves workshop were < 6.7 mg/m³ for inhalable dust, and < 4.1 mg/m³ for respirable dust, respectively. In the Sponsor country, total dust measurements in a producing facility resulted in values between 0.58 and 9.6 mg/m³ for respirable dust, and between 0.69 and 2.0 mg/m³ for inhalable dust.

Consumers are exposed to zeolites A and P through the use of household detergents, mainly through the dermal and inhalational routes. A worst-case consumer exposure has been estimated to be about 0.09 µg/m³ per use for the respiratory route, less than 12.2 µg/kg bw/day for the dermal route and 0.5 µg/kg bw/day for the oral route.

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

Human Health: The chemicals of this category are candidates for further work.

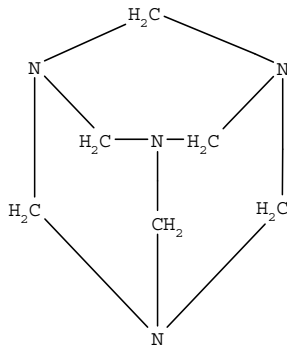
The chemicals possess properties indicating a hazard for human health (repeated dose inhalation toxicity). While consumer exposure by the inhalational route is considered to be negligible, workplace exposure may not be well enough controlled as there is no specific OEL for zeolites in the Sponsor country, and the LOAEL derived in repeated dose inhalation studies for (in animals reversible) lung effects is below the OEL for general dust in the Sponsor country. Member countries are invited to perform an occupational exposure assessment, and, if then indicated, a risk assessment.

Environment: The chemicals of this category are currently of low priority for further work due to their low hazard profile.

The observed effects occurred well above water solubility and are related to nutrient depletion in the case of algae and physical effects (suspended crystals) in the case of daphnids and fish.

Note: There is a HERA (Human and Environmental Risk Assessment) report available for Zeolite A, produced by A.I.S.E. and Cefic in 2004 and there is a preliminary Environmental Risk Assessment report available for Zeolites P and X, also produced by A.I.S.E. and Cefic (<http://www.heraproject.com>).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-97-0
Chemical Name	Methenamine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Methenamine is rapidly absorbed and excreted (90% of the dose within 12 h) after oral uptake in man. The mean half-life in blood was reported as 4.3 h. Methenamine can pass the placenta and is detectable in breast milk of lactating women; however, no accumulation was seen. Toxicokinetic data were not available for dermal administration or inhalation exposure of methenamine.

Formaldehyde is formed via hydrolytic cleavage of methenamine at acidic pH values, thus formaldehyde formation occurs after oral administration at the acidic pH of the stomach. However, formaldehyde can be absorbed into the bloodstream, where it is converted to formic acid very rapidly. The half-life of formic acid is reported to be 90 min. It can be excreted through the kidneys or be further oxidised to carbon dioxide and water.

In limited studies, acute toxicity of methenamine in rats has been demonstrated by oral and dermal application (acc. to OECD TG 402) with LD₅₀ values of > 20 g/kg bw and >2 g/kg bw, respectively. Data on acute inhalation toxicity are not available. Limited data on the acute toxicity of methenamine in humans show an acute dermatitis of the exposed surfaces as the main symptom.

Methenamine does not exhibit local irritation by contact with skin and eyes of rabbits under the conditions of tests according to OECD TGs 404 and 405. However, acute dermal exposure in humans causes local irritancy.

Guinea pigs exhibited strong skin sensitization in a maximization test according OECD TG 406. The substance does not clearly demonstrate skin sensitizing properties in humans. In a number of human cases, allergic symptoms such as wheezing and asthma were reported upon exposure to methenamine. However, in all cases simultaneous exposure occurred to other irritant and sensitizing chemicals. The respiratory hypersensitivity could not be specifically related to methenamine exposure.

In several early long-term studies with repeated application to rats and mice, no specific organ toxicity was recorded after oral administration of methenamine (gavage, feeding, or drinking water) up to doses of and including 2.5 g/kg bw/d. All in-life parameters, which included body weight gain, food consumption, and survival, were unaffected by exposure to methenamine. Similarly, post-mortem analyses, which included organ weights, gross pathology and histopathology, were unchanged. The systemic NOAEL values for methenamine derived in several experimental animal species for different durations ranged between 60-2500 mg/kg bw/d.

There are a number of studies on health of workers in the steel foundry, tire and rubber industry repeatedly exposed

to methenamine. Due to deficiencies in conducting, reporting, inadequate methenamine exposure data and/or mixed exposure to other chemicals, the effects could not be attributed clearly to methenamine. No complications were observed in patients receiving methenamine or its salts as a urinary antibacterial-antiseptic at dose levels of 2 to 4 g/d for weeks (corresponding to a NOAEL of 57 mg/kg bw/d). A higher therapeutic dose of 8 g/d (114 mg/kg bw/d) for 3 to 4 weeks produced bladder irritation, painful and frequent micturition, albuminuria and hematuria.

Methenamine was weakly positive in bacterial gene mutation assays at extremely high concentrations (10000 µg/plate) and in an *in vitro* chromosomal aberration assay. The negative *in vivo* chromosomal aberration tests (2000/32/EC, B.11) and the negative dominant lethal test (87/302/EEC, part B) indicate that methenamine is unlikely to be genotoxic *in vivo*.

The carcinogenic potential of methenamine has been investigated in a number of old long-term/lifetime studies in a variety of strains of rats and mice, using the oral route. There was no indication of carcinogenic effects in rats and mice following prolonged exposure to high dosages up to and including 2.5 g/kg bw/d methenamine.

Results from retrospective and prospective epidemiology studies on workers in the steel foundry, tire and rubber industry did not show clearly the presence of a carcinogenic activity of methenamine in humans. The observed excess risks of skin, lung and bladder cancer reported in these studies could not be conclusively attributed to the exposure of methenamine because workers had also been exposed simultaneously to other chemicals. With respect to the extensive use of methenamine as a drug, there is no evidence for the formation of tumours in the urinary tract in humans.

In non-guideline fertility studies in Wistar rats administered high doses of methenamine in drinking water (1.5 - 2 g/kg bw/d for males and 2 - 2.5 g/kg bw/d for females), no adverse effects on fertility were observed. The dose of 1000 mg/kg bw/d is considered as the NOAEL for fertility.

In limited studies, methenamine induces developmental toxicity in experimental animals. In rats (at high gavage dosage of 1000 mg/kg bw/d) and in beagle dogs (30 mg/kg bw/d), effects were observed during the postnatal period of development in terms of pre-weaning mortality and postnatal growth retardation.

Human data on potentially adverse effects to development are available from investigations on women that had been treated with methenamine salts during pregnancy. No indications for a specific impairment of pregnancy outcome or of the development of the children were observed at therapeutic doses of 2 g methenamine hippurate or 4 g methenamine mandelate per day (corresponding to about 13 or 27 mg methenamine/kg bw/d, respectively).

Environment

At 20°C, methenamine is a white crystalline powder with a density of 1.33 g/cm³. At 230°C, the substance starts to sublime, and the melting temperature is > 270°C. The vapour pressure is 0.05 Pa at 20°C. The Henry's Law Constant was calculated to be 1.051×10⁻⁵ Pa m³ mol⁻¹. With a solubility of 667 g/l (25°C) the substance is highly soluble in water which is also the target compartment in the environment. The n-octanol water partition coefficient (log Kow) was calculated as -4.15 indicating a low bioaccumulation potential.

The information on environmental fate and behaviour indicates no tendency to volatilize into air or to be distributed into sediment. The target compartment is the water-phase of aqueous systems. Once released into air, methenamine will degrade rapidly by photo-oxidation. The half life estimated using the different models was 30 – 45 minutes. In water, methenamine is degraded hydrolytically to ammonium and formaldehyde, which is further degraded biologically (ready biodegradable). The extent of hydrolysis is dependent on the pH of the medium. At acidic pH-levels degradation within a few hours could be expected. At neutral and basic pH-levels the half life might increase to several days. In the studies on biological degradation, between 28% and > 100% was degraded. This can be explained by hydrolysis of methenamine to ammonia and formaldehyde followed by complete biological degradation.

The available ecotoxicological studies indicate that methenamine is non-toxic for aquatic organisms following short term exposure (tests performed at pH>7 ==> hydrolysis of methenamine was minimised). In a test on inhibition of microbial nitrification, no effects could be observed up to 100 mg/l. Using *Lepomis macrochirus*, a LC₅₀ (96 h) of 41 g/l, and using *Pimephales promelas* a LC₅₀ (96h) of 49.8 g/l were determined. The EC₅₀ (48 h) for *Daphnia magna* was 36 g/l and for the crustacean *Nitrocras spinipes*, the LC₅₀ (96 h) was 92.5 g/l. A 14 day algae test with *Selenastrum capricornutum* (formally not valid, but reliable) was used to estimate an ErC₅₀ of 3g/l from the growth

curve. The EC_{50} of a 96-h test with *Scenedesmus quadricauda* was $> 10\text{g/l}$. Since acute aquatic toxicity data for three trophic levels are available, the Predicted No Effect Concentration (PNECaqua) can be calculated with an assessment factor of 1000. Hence, the PNECaqua is 3 mg/l .

The information available for the main metabolite formaldehyde (CAS-No. 50-00-0) indicate that fish, invertebrates and algae are more than three orders of magnitude more susceptible to this metabolite than to methenamine (formaldehyde was assessed in the OECD HPV Chemicals Programme). However, it could be assumed that following hydrolysis of methenamine, formaldehyde is degraded rapidly by microbiological activity.

The other degradation product is ammonia (ammonia CAS No. 7664-41-7 was assessed in the OECD HPV Chemicals Programme as part of a category).

Reliable data about the effects of methenamine on terrestrial organisms were not available. However, according to the environmental fate and behaviour, no relevant exposure of the terrestrial compartment is to be expected. In addition to that the available information indicate that the substance is non-toxic and of low environmental concern.

Exposure

Methenamine is produced in several EU-Member states with a total amount of approximately 30,000 t in 2001. With 95 % of the total production, the main use (non-dispersive) is in the polymer and rubber industry to produce powdery or liquid preparations of phenolic resins, urea resins, and phenolic resins moulding compounds to which methenamine is added as a curing or a vulcanisation agent. Additional minor uses are as intermediate in nitration reactions (production of explosives) and as fuel tablets for camping stoves.

In general, methenamine is expected to be released into the environment during production, formulation and processing via waste water and exhaust dust. Due to the negligible sorption potential and the incineration of the sludge at the production sites, direct releases to the soil compartment via sludge application can be excluded. Residual contents in final phenolic resins and rubber products are not expected due to complete decomposition during processing. Since the fuel tablets are pressed in a dry process and burned without residues, no environmental releases are expected from this use.

The main route of potential consumer exposure is assumed to be via dermal contact. Exposure of consumers to methenamine results from the use of cosmetics containing the substance as a preservative (maximum allowed concentration 0.15%) and in addition, from the use of solid fuel tablets. Oral exposure may result from the intake of provolone cheese (according to the German law 25 mg methenamine/kg (calculated as formaldehyde) are allowed in provolone cheese. It is not allowed in other food).

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 sensitisation, repeated dose toxicity and developmental toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary, a risk assessment.

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

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-42-2
Chemical Name	2,2'-iminodiethanol (diethanolamine, DEA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

2,2'-Iminodiethanol (diethanolamine, DEA) is well absorbed following oral administration in rats (57%) and to a lower degree after dermal administration (3-16% in rats; 25 – 60% in mice). When applied dermally, DEA appears to facilitate its own absorption, as higher doses were more completely absorbed than lower doses. DEA (20 mg/cm²) applied to skin preparations *in vitro* showed penetration rates of 6.68% (mouse) > 2.81 % (rabbit) > 0.56% (rat) > 0.23% (human). Distribution to the tissues was similar via all routes examined. DEA is cleared from the tissues with a half-life of approximately 6 days. The highest concentrations are observed in liver and kidney. Metabolism after oral administration revealed non-metabolized DEA and smaller proportions of N-methyl-DEA (N-MDEA), N,N-dimethyl-DEA (N,N-DMDEA) and DEA-phosphates co-eluting with phosphatidyl ethanolamine and phosphatidyl choline. After digestion, 30% of the phospholipids were identified as ceramides and the remaining 70% as phosphoglycerides. DEA is excreted primarily in urine as the parent molecule (25-36%), with lesser amounts of O-phosphorylated and N-methylated metabolites. Accumulation of DEA at high levels in liver and kidney is assumed by a mechanism that normally conserves ethanolamine, a normal constituent of phospholipids. DEA is incorporated as the head group in phospholipids, presumably via the same enzymatic pathways that normally utilize ethanolamine.

DEA has a moderate acute oral toxicity, while it is considered low after inhalation or dermal exposure. Oral LD₅₀ values ranged from 780 -3,540 mg/kg bw in rats, from 3,300 – 4,570 mg/kg bw for mice and were reported as 2,200 mg/kg bw for rabbits and Guinea pigs. Inhalation risk test showed no mortality in rats after an 8 h exposure to an atmosphere enriched with vapour. A dermal LD₅₀ value of 13,000 mg/kg bw was reported for rabbits. DEA is a skin and severe eye irritant in rabbits and caused upper respiratory tract irritation in subchronic studies in rats. No information was available on the respiratory irritation in humans. DEA is not a skin sensitizer in animals and available information in humans suggests no such effects. A slightly higher incidence of skin sensitization in cutting fluid workers is of a secondary nature, due to conditions not attributable to DEA (wet skin, chronic solvent exposure). Nose-only exposure of rats to DEA aerosols for 3 months resulted in systemic effects such as anaemia, adaptive liver and kidney effects, damage of male reproductive organs and upper respiratory tract irritation. No functional or morphological evidence of neurotoxicity was observed. The NOAEC for systemic effects was 15 mg/m³ and the NOAEC for upper respiratory tract irritation was 3 mg/m³.

Repeated unoccluded dermal application of ethanolic DEA solutions in subacute and subchronic studies with rats and mice led to mortality at high dose levels (≥500 mg/kg bw in rats; ≥1000 mg/kg bw in mice). In rats, systemic signs of toxicity consisted predominantly of anaemia and nephropathy. In addition, liver weights were increased without a histopathological correlate. In mice, systemic effects occurred mainly in the form of liver and kidney damage. In both species, local skin irritation was observed. A NOAEL for

systemic effects or local skin irritation could not be achieved (LOAEL 32 mg/kg bw in rats; 80 mg/kg bw in mice). In rats, subchronic oral treatment via the drinking water caused mortality at the high dose in males (5000 ppm). Impaired body weight gains were observed at concentrations equal to or higher than 320 ppm in females and 630 ppm in males. Systemic effects consisted of anaemia, nephrotoxicity, cortical vacuolization of adrenal glands and demyelination of brain/spinal cord without any neurofunctional finding. In males, damage of reproductive organs in the form of testicular degeneration and associated weight changes and impaired spermatology was observed. Based on anaemia observed, a LOAEL of 25/14 mg/kg bw (equal to 320/160 ppm) was achieved in males/females.

In the subchronic oral study in mice, mortality was observed in males at ≥ 5000 ppm and in females at ≥ 2500 ppm. Body weight gain was decreased in both species at concentrations of 1250 ppm (females) or 2500 ppm (males) and higher. Systemic effects consisted of hepato- and nephrotoxicity and myocardial degeneration. The most sensitive effect was necrotic liver damage at all concentrations. A LOAEL of 104/142 mg/kg bw (equal to 630/630 ppm) was noted in males/females.

In subacute (14 days) oral screening examinations in rats and mice, DEA revealed some immunomodulating effects at dose levels with overt signs of systemic toxicity. The most sensitive parameter was red blood cell alteration with a LOAEL of 50/100 mg/kg bw in rats and mice, respectively, based on reduced numbers of reticulocytes.

DEA did not induce reverse mutations in *Salmonella typhimurium* or *Escherichia coli* and had no effect on gene conversion in *Saccharomyces cerevisiae*. In mammalian *in vitro* systems, DEA did not induce chromosomal aberrations in rat hepatocytes, gene mutation in mouse lymphoma cells, sister chromatid exchange or chromosomal aberrations in Chinese hamster ovary cells. DEA formulated in ethanol did not induce micronuclei *in vivo* in peripheral blood erythrocytes of mice after repeated unoccluded dermal application for 13 weeks at doses clearly showing systemic availability.

DEA formulated in ethanol showed no oncogenic potential in the rat after unoccluded daily dermal exposure for 2 years. In the dermal mouse carcinogenicity study using similar exposure techniques, there was an increased incidence of liver neoplasms in males and females at all doses tested and an increased incidence of renal tubule adenomas in males at the high dose level only. The liver tumours in mice were considered to be directly related to the observed increase in the cellular proliferation rate, which is due to the observed enzyme induction, weak peroxisome proliferation and choline depletion with subsequent disturbance of its metabolism. While nitrosamine formation has been highlighted as a matter of concern for DEA, and for this reason it has been banned for use in cosmetics in the EU, nitrosamine formation was ruled out under the conditions of this study. Benign kidney tumours (adenomas) were only observed in male mice at the high dose level at a low incidence, when using serial sections. Based on the increased S-phase synthesis observed in this organ, it is conceivable that a similar non-genotoxic mode of action involving choline deficiency is responsible for the renal tubular adenomas.

In short term tests on carcinogenicity, DEA was not carcinogenic, when tested in the Tg.Ac transgenic mouse model up to topical dose levels exceeding the MTD. Cell transformation in Syrian hamster embryo cells *in vitro* was observed predominantly in the range of cytotoxic concentrations but supplementation of choline completely inhibited this effect.

Various mechanistic *in vitro* and *in vivo* studies identified that DEA induced choline depletion is the key event in the toxic mode of action. DEA decreased gap junctional intracellular communication in primary cultured mouse and rat hepatocytes, but all these events were prevented with choline supplementation. DNA hypomethylation was observed in mouse hepatocytes as a further epigenetic mechanism involved in liver tumourigenesis.

DEA decreased phosphatidylcholine synthesis by blocking the cellular uptake of choline *in vitro*, but these events did not occur in the presence of excess choline.

DEA increased S-phase DNA synthesis in mouse hepatocytes but had no effect on apoptosis. No such effects were noted in human hepatocytes *in vitro*. Apparent differences in the susceptibility of two different mice strains (B6C3F1 > C57BL) were noted. B6C3F1 mice are extremely sensitive to non-genotoxic effects and are known to possess a relatively high incidence of spontaneous liver tumours.

Moreover, chronic stimulation and compensatory adaptive changes of hepatocyte hypertrophy and proliferation are able to enhance the incidence of common spontaneous liver tumours in the mouse by mechanisms not relevant to humans. Analysis of gene expressions in animal studies showed an increase in genes associated with cell proliferation, while a decrease in genetic processes relevant for apoptotic mechanisms was observed.

There was no specific reproduction toxicity and fertility study available but there was an influence on the male reproductive system at the high concentration in the 3-month inhalation study in rats. The NOAEC for male fertility parameters was 0.15 mg/l. When DEA was orally administered to rats via the drinking water for 13 weeks, decreases in testis and epididymis weights, testicular degeneration, atrophy of the seminal vesicles and prostate glands and associated effects on spermatology were observed. The NOAEL for fertility effects in males was 48 mg/kg bw. In all of these studies no histopathological effects were observed in female reproductive organs.

DEA exposure to an aerosol in a nose-only exposure system led to maternal toxicity at the highest concentration (0.2 mg/l) and induced at this dose level signs of embryo- or fetotoxicity in the form of an increased number of foetuses with skeletal variations. Malformations were not observed. The NOAEC for maternal and prenatal developmental toxicity was 0.05 mg/l.

Prenatal developmental toxicity of DEA following dermal application was investigated in rats and rabbits. In rats, maternal toxicity was substantiated by moderate to severe skin irritation, reduced maternal body weight gain, increased kidney weights and haematological effects including anaemia, abnormal red cell morphology and decreased platelet count. In the foetuses, increased incidences of skeletal variations were observed. The LOAEL for maternal toxicity was 150 mg/kg bw, while the NOAEL for prenatal developmental toxicity was 380 mg/kg bw. The NOAEL for teratogenicity was 1500 mg/kg bw. In rabbits, doses displayed marked skin irritation, reduced body weight gain and food consumption and discoloured kidneys. The NOAEL for maternal toxicity was 35 mg/kg bw, the NOAEL for prenatal developmental toxicity including teratogenicity was 350 mg/kg bw, the highest dose tested.

Orally applied DEA within a developmental toxicity study in rats caused maternal toxicity in the form of increased mortality at high dose levels. Reduced body weight/body weight gain and food consumption and increased kidney weight were observed. Developmental toxicity consisted of an increase in postimplantation mortality and early postnatal mortality as well as reduced pup body weight. The NOAEL for maternal and postnatal developmental toxicity was 50 mg/kg bw. Thus, pre- and postnatal developmental toxicity was only observed in the presence of clear maternal toxicity and at dose levels considered as high.

Environment

The colourless solid DEA is completely miscible with water at ambient temperature and has a negligible vapour pressure of 0.0028 hPa (25 °C). The measured log K_{OW} of -2.18 (25 °C) and the calculated BCF of 3.16 indicate a low potential for bioaccumulation. The Henry's law constant of 3.97×10^{-6} Pa·m³/mol (uncharged) is considered as an indication for low volatility. The calculated K_{oc} of uncharged DEA is 1 (corrected log K_{oc} = 0). Thus, the potential for adsorption to soil, sediment, and suspended solid may be low. However, binding of the substance to the matrix of soils (and sediments) with high capacities for cation exchange (e.g. clay) can not be excluded for the charged molecule. The measured pKa value of 8.92 (23 °C) indicates that at environmentally relevant conditions of pH 6 – 8, the molecule will predominantly occur in the charged (cationic) form. At pH values > 9, DEA will predominantly be present as the uncharged species.

According to Mackay Level I modelling, uncharged DEA will distribute almost completely into water (99.99 %). DEA is readily biodegradable according to OECD criteria. Potential for anaerobic degradation of DEA was also observed. In the atmosphere, it will be photodegraded by reactions with OH radicals (calculated half-life of the uncharged molecule for a 12-hour day and $1.5E06$ OH/cm³: 2.4 hours = 0.1 day; for a 24-h day and $0.5E06$ OH/cm³: 4.2 hours = 0.2 days). At environmental pH conditions hydrolysis is not expected to be a relevant degradation process due to the absence of hydrolysable groups. The lowest reliable acute toxicity values for aquatic species were as follows:

<i>Pimephales promelas</i> (fish)	96-h LC ₅₀ = 1370 mg/l (nominal)
<i>Daphnia magna</i> (invertebrates)	48-h EC ₅₀ = 55 mg/l (nominal)
<i>Pseudokirchneriella subcapitata</i>	96-h ErC ₅₀ = 2.2 mg/l (nominal)
<i>Pseudomonas</i> sp. (microorganisms)	16-h TTC = 16 mg/l (nominal)

In a chronic toxicity test on reproduction of the water flea *Daphnia magna*, the NOEC (21 days) was 0.78 mg/l (nominal, based on analytical verification).

Exposure

DEA belongs to the ethanolamines group that includes monoethanolamine (MEA), diethanolamine (DEA) and triethanolamine (TEA). Large-scale production of DEA is carried out by the reaction of ethylene oxide and excess ammonia, followed by fractionation of the three ethanolamines (mono-, di- and tri-ethanolamine).

The annual world production in 2005 for the ethanolamines was estimated at 1,510,000 tons, subdivided into 400,000 tons/a for Europe, 780,000 tons/a for North and South America, 30,000 tons/a for Middle East, and 300,000 tons/a for the Asia/Pacific region. Individual capacity data on DEA were not available.

Ethanolamines are used widely as intermediates in the production of anionic and non-ionic surfactants, which have become commercially important as detergents, textile and leather chemicals, and emulsifiers. Their uses range from drilling and cutting oils to medicinal soaps and high-quality toiletries. DEA is an important additive of corrosion inhibitors, particularly in coolants for automobile engines. DEA is also employed as an additive in lubricants and in cement/concrete production. Large amounts of DEA are used as such in closed systems for absorptive gas purification to remove weakly acidic components. In the production of detergents, cleaners, fabric softeners and metalworking fluids DEA is used for acid neutralization and to prevent soil deposition. DEA is also used as an intermediate in the production of morpholine, photographic chemicals and polyurethanes. In addition, DEA is used as a building block for agrochemicals.

The SPIN database for Substances in Preparations in Nordic Countries lists a wide variety of uses of DEA registered in Denmark (DK), Norway (N), Sweden (S), and Finland (FIN). In the most recent year reported (2004), 520 DEA-containing preparations accounting for a total volume of 19865.8 tons were registered in Denmark. In Norway, Sweden, and Finland 103 (856.8 t), 307 (459.0 t), and 75 (132.7 t) products were registered in 2004, respectively. Use categories included intermediates, cleaning/washing agents, paints, lacquers and varnishes, surface treatment, cutting fluids, pH-regulation agents, impregnation materials, surface-active agents, corrosion inhibitors, process regulators, colouring agents, reprographic agents, lubricants and additives. The use in consumer preparations was indicated for products registered in Norway and Sweden.

According to the Commission of the European Communities, general public use is known for cleaning/washing agents, disinfectants, colouring agents, construction materials additives, corrosion inhibitors, cutting oil, and others.

Some of the above mentioned applications may not be representative of, or comparable to current conditions. According to EU Council Directive 76/768 EEC, the use of DEA in cosmetics is prohibited in the European Union.

Releases of DEA into the environment may occur during manufacturing and processing in the industry.

DEA was not detected in a study carried out in 1978 in any of the 21 samples taken from surface water (limit of determination: 0.3 - 0.34 µg/l) in Japan.

DEA was detected in German surface waters of the rivers Elbe at 0.34 µg/l – 0.58 µg/l, Mulde at 2.54 µg/l - 4.6 µg/l, Neibe at 0.72 µg/l - 1.8 µg/l and Rhine at 0.30 µg/l - 0.59 µg/l.

With respect to Canada's National Pollutant Release Inventory, total on-site releases in Canada of DEA and its salts accounted for 32.6 tonnes in the reporting year 2005.

During production and internal processing at BASF AG, Ludwigshafen (Germany), less than 100 kg/a (threshold value for releases to air according to the German Emission Register) were emitted to the air in 2004. At the production site of INEOS Oxide (Lavera, France; Plaquemine, USA) the whole process is performed in a closed system. Only the vents of the distillation columns are emitting to air. The average mass loss is <0.01 kg C_xH_y/ton DEA produced.

Data regarding emission via waste water treatment effluent are not available from BASF AG production and processing sites. At the production site of INEOS, average production loss via the aqueous effluent resulting from the production is <0.001 ton TOC/ton DEA produced. The streams are treated in waste water treatment units.

Occupational exposure to DEA can occur during manufacture, distribution, and use. Due to the negligible vapour pressure of DEA, the potential for inhalation exposure is minimized, with dermal exposure the most likely route.

At BASF AG, Ludwigshafen site, DEA is produced in one production plant and is becoming further processed within 8 other operations and plants. During the time period between January 2001 and December 2006 an overall number of 53 workplace exposure data were collected, covering all operations by means of personal air sampling (PAS). The reported data are 8 hour shift average values (TWA). In Germany, there is no official work place exposure limit value. The DFG MAK-value is 1 mg/m³ (as an aerosol, inhalable fraction). For the production plant the highest recorded value was 0.026 mg/m³. At the filling stations the maximum value recorded was 0.062 mg/m³. The overall range of the measurement results (53 data) was < 0.019 to 0.062 mg/m³.

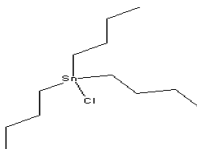
Direct consumer exposure to DEA is anticipated to be low based on recent use changes and regulations such as the Cosmetic Directive in Europe.

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 a hazard for human health (skin/eye/respiratory irritant, repeated-dose, reproductive/developmental 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: The chemical is currently of low priority for further work. The chemical has properties indicating a hazard for the environment (acute toxicity to green algae and *Daphnia magna*: EC₅₀ between 1 and 100 mg/l). However, the chemical is of low priority for further work because of its rapid biodegradation and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1461-22-9
Chemical Name	Tributyltin chloride (TBTC)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Based on the analytical methods currently available, only the alkyltin moiety, tributyltin (TBT), can be quantified. Information presented on the environmental levels of TBT is included with the caution that the source of TBT cannot be attributed to just TBTC alone. In many cases, when the identity of the specific chemical is not clear, the general term "TBT" is used. For toxicity and bioaccumulation data, however, specific data on TBTC is generally available.

Human Health

After oral ingestion by male albino mice at a dose of 180 μmol TBT/kg, TBTC was biotransformed to dibutyltin chloride, dibutyltin(3-carboxypropyl)tin chloride, monobutyltin species, and tributyltin species; a P450 enzyme pathway was involved. Oral administration of TBTC resulted in elevated levels of serum enzymatic activities and a depression of hepatic mitochondrial respiration in mice, but not in guinea pigs. IC₅₀s for the inhibition of succinate-linked State 3 mitochondrial respiration in TBTC-treated mice and guinea pigs were 8.9E-7 M and 9.1E-7 M, respectively. The primary metabolite in the hepatic mitochondria was DBTC in both mice and guinea pigs. In Wistar rats, after administration at dosages of 5, 25 or 125 ppm diet, TBTC and/or metabolites distributed to liver, brain, and fat (with concentrations highest in liver and lowest in fat). No information was available on the absorption potential of TBTC.

The acute oral LD₅₀ of TBTC is 122 mg/kg bw from a well reported study. Pathological findings at 62 mg/kg bw and above included focal pneumonia and focal to diffuse thickening of the cutaneous stomach mucosa in animals that were necropsied at the end of the 8-day observation period. One or more animals that died exhibited inflammation of the intestinal or gastric mucosa, pneumonia, gastric overload, thickening of the cutaneous mucosa of the stomach, bleeding, pulmonary emphysema, or hyperemia of the mesenteric vessels. There are no adequate data on acute inhalation or dermal toxicity, or sensitization of TBTC.

TBTC caused skin damage and irritation in rat studies. Irritation, dermatitis and skin burns have been reported in industry workers using TBTC. TBTC is corrosive to the skin.

In repeated-dose studies of TBTC, the critical target tissue was most often the thymus. Results of two 28-day studies, taken together, show a consistent dose-response effect with dietary administration and allow the derivation of NOAEL and LOAEL values for TBTC. Based on intake of TBT, the NOAEL for subchronic (28-day) toxicity for young adult rats is approximately 0.4–0.7 mg/kg/day and the LOAEL is approximately 1.5 mg/kg/day, based on observed thymic and splenic atrophy and lymphocyte depletion as well as bleeding in lymph nodes and reduced food consumption and body weights. The LOAEL for gavage administration to weanling rats which also received in utero and lactational exposure was 0.025 mg/kg/day based on decreased liver weights and increased serum GGT levels in females at 60 days of age. Decreased thymus weights were noted in the females administered 0.25 mg/kg/day. A NOAEL was not determined in a 14-day repeat dose dietary study of male rats; the LOAEL was established at 15 mg/kg diet (equivalent to ca. 0.75 mg/kg bw/day) based on decreased spleen weights and reddening in lymph nodes. Higher doses (50 and 150 mg/kg diet equivalent to about 2.5 and 7.5 mg/kg bw/day) also resulted in: decreased thymic cell counts, thymus weights, and iron in the spleen and increased liver weights. Reduced body and brain weights and food consumption were seen at the highest dose only.

TBTC was negative in a standard *in vitro* Ames assay conducted with and without metabolic activation, and in an SOS chromotest conducted without metabolic activation. TBTC was positive in a preincubation assay using only strain TA100 without metabolic activation and in a Rec-assay conducted without metabolic activation. Results (statistically significant but not biologically relevant increase in micronuclei) from a micronucleus assay indicate that TBTC is not genotoxic *in vivo*.

In a two generation reproduction study, the NOAEL for fertility (P) was 25 mg/kg diet (equivalent to ca. 2 mg/kg bw/day). Decreased live birth index and total numbers of pups per litter were reported at 125 mg/kg diet (LOAEL, ca. 10 mg/kg bw/day) indicating an effect on fertility. TBTC affected the male and female reproductive systems of offspring in this study. Testis and epididymis weights were decreased and spermatid/sperm counts were depressed, mainly at 125 mg/kg diet in the F1 and F2 generations (equivalent to ca. 9.75 mg/kg bw/day), with effects also observed at 25 mg/kg diet. The LOAEL for the F1 generation can be determined at 25 mg/kg diet. Effects were more severe in the F2 generation. An increase in female anogenital distance was found at and above 5 mg/kg diet (LOAEL ca. 0.4 mg/kg bw/day for the F2 generation), and a delay in vaginal opening and impaired estrous cycles were observed at 125 mg/kg diet.

In several oral studies, maternal exposure to TBTC during early pregnancy caused embryo-lethality and suppression of fetal body weights at maternally toxic doses in rats. Depending on the dose and period of exposure, a few studies resulted in malformations (generally cleft palate) in offspring. A NOAEL for maternal toxicity was established at 5 mg/kg bw/day in dams exposed on gestation days (GD) 7 - 15. In another study, the NOAEL for maternal toxicity was established at 8 mg/kg bw/day when dams were exposed on GD 0-7. The LOAEL for teratogenicity was determined to be 25 mg/kg bw/day in pups exposed during gestation days 13-15 due to increased incidence of cleft palate. The LOAEL for developmental effects in pups when dams were exposed from gestation days 7 to 15 was determined at 5 mg/kg bw/day based on a decreased number of ossified sternebrae (variation in TBTC had no significant effect on dam body weights, duration of gestation, litter size, or pup survival to weaning in rat dams administered up to 2.5 mg/kg bw/day by gavage from gestation day 8 through lactation although some immunological changes and thymus atrophy were seen at 0.025, 0.25, and/or 2.5 mg/kg bw/day). The maternal NOAEL was 0.025 mg/kg day based on heart and lung effects at 0.25 mg/kg/day.

Environment

The EPIWIN suite developed by Syracuse Research Corporation has not been validated for chemicals that contain metals 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.

TBTC has a labile ligand, the chloride anion (Cl^-). The nature of the anion, in any TBT compound influences the physico-chemical properties, particularly the relative solubility in water and non-polar solvents. At $\text{pH} < 6.51$ (pK_a of unspecified TBT compound), the predominant species in water is the TBT cation (TBT^+); at $\text{pH} > 6.51$, the neutral hydroxide, TBTOH predominates. TBTC predominates in waters with high concentrations of Cl^- , such as seawater. In water, the redox potential, pH, temperature, ionic strength, and concentration and composition of dissolved organic matter can influence the solubility and fate of tributyltin compounds. This information is important in understanding the behavior of TBTC in the environment.

TBTC is a colorless to pale yellow liquid at room temperature. The melting and boiling points of TBTC are -18°C and $264\text{--}275^\circ\text{C}$ at 1013.3 hPa, respectively, the relative density is 1.2 g/cm^3 at 20°C and the calculated vapor pressure is 0.016-0.028 hPa at 25°C . TBTC is slightly water soluble (ca. 6-10 mg/L) and has a measured octanol-water partition coefficient ($\log K_{ow}$) of 2.07 (EPIWIN calculated $\log K_{ow}$ is 4.7). Possible differences in the percentage of impurities may influence physicochemical property values. Based on the $\log K_{ow}$ value and measured $\log \text{BCFs}$ ranging from -1.40 to 5.96, TBTC is relatively lipid soluble and may bioaccumulate in the tissues of certain aquatic organisms, particularly bivalves. TBTC was not readily biodegradable in a standard OECD TG 301F test, but a microcosm study shows that it was susceptible to microbial degradation. TBTC would be expected to be photochemically degraded by hydroxyl radicals (calculated rate constant = $42.6 \times 10E^{-12} \text{ cm}^3/\text{molecule}\cdot\text{sec}$; estimated half life = 3 hours) and by UV radiation. The salt dissociates in water, depending on the pH; however, the hydrolysis of the TBT moiety in natural waters appears to be negligible, as the TBT moiety was stable in filtered water over 63 days at 20°C in the dark, at pH values of 2.9, 6.7, and 10.3. TBTC half-lives in the water column range from 5 to > 63 days, and TBTC is degraded by microbial debutylation to dibutyltin, with lesser amounts of monobutyltin and inorganic tin. TBT tends to be more persistent in sediments, with half-lives of 1-5 years reported in freshwater and marine sediments.

If released to the environment, TBTC is predicted to partition primarily to the soil (73%) and water (18%) compartments. Most of the TBT released to the environment (not specifically TBTC) is associated with ships, thus,

adsorption to particulate and sedimentation makes sediment a more important environmental compartment for TBT than soil. A calculated Henry's Law Constant of 1.67×10^{-3} atm-m³/mol predicts TBTC will volatilize from surface water; estimated half-lives from a model river and lake are 2.5 hours and 7.43 days, respectively.

TBTC has been shown to be toxic to aquatic life, particularly certain marine species. TBTC has been tested in a number of aquatic species using both measured and nominal concentrations. The 96-h LC₅₀ value for freshwater fish (*B. rerio*) was 7.9 µg TBTC/L (measured as total tin,). Saltwater fish had 96-h LC₅₀ values of 3 – 9 µg TBT/L (measured as TBT).

The 48-h EC₅₀ values for *D. magna* ranged from - 9.8µg TBT/L (nominal) to 18 µg TBTC/L (nominal). For the saltwater invertebrate, *M. bahia*, 96-h LC₅₀ values were 1 – 2 µg TBTC/L (measured as TBT).

EC/IC₅₀ values for algae ranged from 0.99µg TBTC/L (*S. costatum*, 72-h, growth rate) to 55 µg TBTC/L (*A. falcatus*, 24-h, primary productivity), based on nominal concentrations. Chronic (100-d) NOEC and LOEC values in rainbow trout (*O. mykiss* and/or *S. gairdneri*) were 0.04 – 0.2 µg/L (nominal), respectively.

TBTC was found to be moderately toxic to the microbial population in activated sewage sludge, with concentrations of 4.1 and 42.5mg/L (nominal, attributed to TBTC) causing a 50% reduction in the respiration rate. Additional studies in aquatic freshwater and saltwater species conducted using tributyltin chloride have found effects including disrupted hatching, reproductive failure, delayed development, imposex, decreased metabolism of nutrients, reduced photosynthesis, abnormal shell development, altered behavior, and increased respiration. However, the amount of data available precludes discussion of these studies here. TBT in the environment can be derived from precursors other than TBTC and chronic exposure to the TBT moiety has been reported to cause reproductive effects in marine and freshwater molluscs at concentrations < 0.001 µg/L.

Exposure

TBTC is used as an industrial intermediate in the production of other butyltin chemicals, including tributyltin oxide. In 2000, worldwide production of TBTC was estimated at 2,500 to 3,000 tonnes annually. There are no commercial applications for TBTC. Releases to the environment would therefore only occur as part of the production of this intermediate or its conversion to other organotin chemicals. Based on the virtual elimination of the production of TBT biocides, the production of TBTC has fallen far below the level of HPV in 2006 in the U.S. TBTC or other TBT compounds may be present as an impurity in butyltin stabilizers for PVC. These impurities are currently voluntarily controlled by the manufacturers to ≤ 0.67% as tin. Releases from production facilities have been documented; measurements of TBT released during a PVC extrusion operation showed approximately 0.006% of the TBT processed being released. Most tributyltin compounds manufactured using TBTC as an intermediate were used as biocides in antifouling paints applied to boat/ship hulls. When used as an antifouling agent, TBT is directly released to the environment by leaching during use or in the removal of TBT paints during hull maintenance. TBT (from TBTO) also may leach from treated wood used for piers and other materials. Antifoulant use has been banned for more than 15 years by many countries on boats less than 25 meters in length.

In the U.S., regulations ban the use of TBT on boats smaller than 25 meters in most cases. Registrations for all antifoulant applications of TBT compounds were voluntarily cancelled in the U.S. in 2004. In addition, notifications of TBT compounds used as biocides were withdrawn under the EU Biocides directive; therefore, as of September 2006 there will be no TBT biocides approved for use in the EU.

Occupational exposure to TBTC can occur via the inhalation and dermal routes. In the production of TBTC and in the use of TBTC as an intermediate; operations are usually sealed to prevent releases to the atmosphere. Exposure in the workplace is controlled through engineering and administrative controls such as the use of Personal Protective Equipment (PPE). Such controls include ventilation to reduce exposures below airborne exposure limits, use of chemical goggles to prevent eye contact, and the wearing of chemical-resistant clothing and gloves to prevent skin contact. If airborne exposure limits are expected to be exceeded, approved respiratory protection equipment is used.

Data from a biological surveillance program of 287 male workers at an organotin production facility found no chronic health problems associated with the occupational exposure of workers to organotins, and blood values were within normal limits.

In the U.S., the small percentage of TBTC that is transported from the manufacturing site is packaged in intermediate bulk containers (totes) that are returned through the tote manufacturer or the chemical supplier to designated facilities for treatment of residues and recycling of the container.

TBT may accumulate in fish from the presence of tributyltin compounds, including TBTC, in seawater. TBT

concentrations and estimated consumer exposures from fish have been evaluated in some studies. For example, in 11 samples of fish products collected in 1996 that are representative of the Japanese fish market, contamination levels in cultured fish products were higher than natural products. TBT (not specifically TBTC) concentrations in farmed products ranged from 0.81 ng TBT/g (minimum concentration in sea bream) to 273 ng TBT/g (maximum level in Pacific oysters). In natural marine products, levels ranged from not detected ($< \sim 0.5$ ng TBT/g) in four species to a maximum of 66 ng TBT/g in brown sole. The authors theorized that the lower levels in natural products resulted from legal controls enacted in 1990 in Japan. It should be noted that these studies cannot necessarily identify the actual tributyltin compound due to difficulty in measuring the labile ligands as well as reactions in water that result in changes to the parent compound. It is possible that the source is another TBT compound (e.g., tributyltin oxide, which has been used as an antifouling paint). However, because of available TBTC toxicity data, and because of the uncertainty in the source of the tributyltin compound found in these fish and marine species, these data may be relevant.

In Europe, several exposure assessments regarding tributyltin in fish and fishery products have been conducted and a risk assessment evaluated risks from use of tributyltin in antifouling paints. In addition to fish consumption, use of TBT-based products in foot spray and in insoles by adult consumers were identified as uses for which further control measures might be considered. For children, consumption of fish products was identified as an area that might warrant further consideration in terms of control measures.

Tributyltin was found in dust samples taken from vacuum bags from homes in seven U.S. states, with an average concentration of 0.080 μg TBT/g and was also detected in all pooled dust samples from homes and commercial buildings in the UK, with a mean of 0.563 μg TBT/g. Tributyltin concentrations in ear plugs were found to range from the limit of detection (0.002 mg TBT/kg) to 3.6 mg TBT/kg. However, in Japan, TBT was not found in 95 household commodities that included textiles, shoe polish, paint, wax, and adhesives. Similar to the concentrations in fish reported above, it is possible that the source of the tributyltin contamination measured is a tributyltin compound other than TBTC.

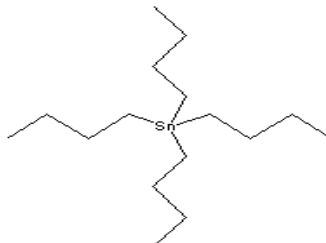
Industry will voluntarily withdraw TBT biocides from the market in accordance with the EU Biocides Directive, and with the ban on the application of TBT antifouling paints, existing levels of TBT in the environment will continue to decline. However, in some ports, harbors, and marinas where antifouling paints were historically applied and where boats larger than 25 meters dock, levels of TBT in the environment may continue to exceed some local or regional water quality criteria.

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

Human Health: This chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (acute and repeated-dose toxicity, immunotoxicity, reproduction and developmental toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: This chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (acute and chronic aquatic toxicity to fish, aquatic invertebrates, and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment. Countries may also desire to check the effectiveness of risk management measures already in place.

SIDS INITIAL ASSESSMENT PROFILE

CAS No. (Nos.)	1461-25-2
Chemical Name(s)	Tetrabutyltin (TTBT)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Tetrabutyltin (TTBT) was reported to be taken up primarily in the jejunum, liver and the duodenum of rats. Small amounts of absorbed TTBT (0.12-0.16% of dosed amount) were dealkylated in the body and the tributyltin cation (TBT⁺) metabolite was excreted in the urine and feces of rats. Lipid-soluble TTBT that was not dealkylated was excreted into bile and either further metabolized in the small intestine or reabsorbed there. Additionally, the percentage of an ingested butyltin dose appears to increase as the number of butyltin moieties increases, suggesting that more highly-butylated tin compounds may be absorbed to a greater extent.

The acute oral LD₅₀ of TTBT to rats was > 2000 mg/kg bw. Clinical signs included hunched posture, lethargy, ataxia, and piloerection that disappeared by 2 days post-exposure. At 2000 mg/kg, half of the animals showed thickening of the non-glandular region of the stomach. There are no data on acute dermal or acute inhalation toxicity, irritation, or sensitization.

The repeated-dose toxicity of TTBT (96.52% purity) was evaluated in a combined repeated-dose and reproduction/developmental toxicity screening test (OECD TG 422) conducted in rats at doses of 100, 300, and 2,000 mg/kg diet. At 300 mg/kg diet (equivalent to 16-24 mg/kg bw/day), decreased spleen weight and lymphoid depletion in the thymus were observed. At 2000 mg/kg diet (100-130 mg/kg bw/day), the following effects were observed: decreased body weights and food consumption; decreased spleen weights in males and decreased thymus weights (both sexes); increased thrombocytes and decreased prothrombin time; increased gamma glutamyl transferase, cholesterol, and phospholipids; blood in the lymph nodes; and lymphoid depletion. Based on the observed effects in the 300 mg/kg diet group, the NOAEL for sub-chronic toxicity was 100 mg/kg diet (equivalent to 5–8 mg/kg bw/day for both sexes), and the LOAEL was 300 mg/kg diet.

TTBT was negative in all tests for genotoxicity conducted with and/or without metabolic activation, including standard and modified Ames assays using single and multiple strains of *Salmonella typhimurium* and/or *Escherichia coli*, a SOS chromotest and a Rec-assay. TTBT was not clastogenic in an *in vivo* mouse micronucleus test.

In the reproductive/developmental segment of the OECD 422 study, adverse developmental/reproductive effects observed in the high-dose (2000 mg/kg diet) group (LOAEL; equivalent to 100-118 mg/kg bw/day for both sexes) included decreased number of pups, increased pup mortality, decreased pup body weight, increased number of runts, and increased post-implantation loss. The NOAEL for maternal and reproductive/developmental toxicity was 300 mg/kg diet (equivalent to 16-24 mg/kg bw/day). In a limited exposure gavage study in rats, TTBT resulted in malformations (i.e., cleft palate) at ≥ 229 mg/kg bw/day; significant only at 1833 mg/kg bw/day.

Environment

The EPIWIN suite developed by Syracuse Research Corporation, used to predict Henry's Law Constant and partitioning in the environment, has not been validated for chemicals that contain metals 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.

TTBT is a colorless liquid at room temperature. Based on experimental data, the freezing point of TTBT is $< -20^{\circ}\text{C}$, the boiling point is $196.9 @ 1013.3 \text{ hPa}$, the relative density is $1.05 \text{ g/m}^3 @ 20^{\circ}\text{C}$, and vapour pressure measurements are 0.0014 and $0.0026 \text{ hPa} @ 25^{\circ}\text{C}$. The most reliable measured water solubility value is $<0.1 \text{ mg/L}$ and the measured octanol-water partition coefficient ($\log K_{ow}$) is >5.07 (calculated $\log K_{ow}$ is 9.37). TTBT has a strong tendency to sorb to labware. Additionally, the low solubility of TTBT presents significant challenges to testing and analysis in aqueous solution.

TTBT is not readily biodegradable, but atmospherically degraded by reaction with photochemically produced hydroxyl radicals ($t_{1/2} = 4.5$ hours; rate constant of $56.9 \times 10^{-12} \text{ cm}^3/\text{molecule}\cdot\text{second}$). TTBT is hydrolytically stable, with an estimated half-life of >1 year at 25°C at both pH 7 and 9. A Henry's Law Constant of $0.0092 \text{ atm}\cdot\text{m}^3/\text{mol}$ was estimated. If released to the environment, TTBT is predicted to partition primarily to soil (68%); partitioning to water and sediment were nearly equal (17 and 14%, respectively). Measured bioconcentration factors of 38 to 97 ($\log \text{BCFs}$ of 1.8–2) using a concentration of 0.005 mg/L , and 127 to 310 ($\log \text{BCFs}$ of 2.1–2.5) using a concentration of 0.0005 mg/L were reported for carp (*Cyprinus carpio*) in flow-through tests. The calculated BCF is 3980 ($\log \text{BCF}$ of 3.6).

Typically the TTBT commercially produced is approximately 96% pure. TTBT contains technical impurities, including tributyltin chloride (TBTC) and dibutyltin dichloride (DBTC). Because of the high toxicity of TBTC and chronic toxicity of DBTC, the level of these impurities (and their degradation products) should be taken into account when assessing the ecotoxicological profile of commercial products.

The 96-h LC/EC_{50} was 0.045 mg/L (based on measured values) for fathead minnows (*Pimephales promelas*) in a flow-through exposure regime. A static study in *Pimephales promelas* using nominal concentrations resulted in a 96-hr LC_{50} of 0.19 mg/L . TTBT also reduced *Skeletonema costatum* growth (72-h $\text{EC}_{50} = 0.05 \text{ mg/L}$, based on nominal dilutions of a measured stock solution of TTBT).

The acute toxicity (EC_{50}) of TTBT to *Daphnia magna* is estimated to be approximately 0.2 mg/L (based on measured values) at 48 hours. The 21-day LC_{50} for parental survival of *D. magna* was 0.051 mg/L , and the overall LOEC and NOEC were 0.034 and 0.014 mg/L , respectively, based on time-weighted average measured concentrations. The 21-d EC_{50} for reproduction could not be determined; at the highest concentration not resulting in 100 percent parental mortality (0.034 mg/L), reproduction was affected in less than 50% of the surviving daphnids. TTBT was moderately stable (decrease of 10–30% of nominal) between media exchanges in the chronic daphnia reproduction study based on measured concentrations.

Exposure

In 2000, worldwide production of TTBT was estimated at 10,000 to 12,500 metric tonnes per year. TTBT is produced by companies in North America, Europe, and Asia-Pacific. TTBT is used by producers as an industrial intermediate in the production of butyltin chemicals or may be sold to other chemical/industrial manufacturers for conversion to other products.

Releases to the environment could occur as part of the production of this intermediate, or during its conversion to other butyltin chemicals.

Exposure to TTBT in an occupational setting can occur via inhalation and dermal contact. Exposure in the workplace is controlled through equipment design, the use of appropriate personal protective equipment, and regular air monitoring. In the production of TTBT, operations are usually sealed to prevent releases to the atmosphere. Worker exposure is expected to be confined to manual operations such as material addition, transfer, or sampling. For those operations that specifically involved manual handling of organotin stabilizers (not TTBT specifically), the measured exposure potential was 50% to just above the threshold limit value (TLV) of 0.1 mg/m^3 .

There are no direct consumer applications for TTBT as a product itself; however, consumers may be exposed to TTBT that may be present as an impurity in products containing other butyltin compounds (e.g. PVC articles) or may be released into the atmosphere during processing. TTBT was not detected ($<1 \text{ }\mu\text{g/kg}$) in dust samples collected from Parliament buildings in European countries, or in American private household dust samples. No TTBT was detected

(at a detection limit of 0.03 mg/kg) in a variety of Danish consumer products manufactured wholly or in part from PVC. A small sampling (n = 5) of PVC flooring from the UK contained TTBT at concentrations ranging 0.14 to 12.3 mg/kg.

TTBT was not detected (at 1.4 to 2.6 µg/kg tissue wet weight) in samples of oysters, clams, Dungeness crab, and mussels from Washington State in a screening level study.

In England and Wales, 0.5% of estuarine and coastal water samples had TTBT concentrations >0.1 µg/L, and marine water samples from the Northern Adriatic Sea had TTBT levels ranging from not detected to 6ng/L as Sn. In Germany, river sediments had TTBT concentrations ranging from <1µg/kg dry wt to 14mg Sn/kg, concentrations in zebra mussels (*Dreissena polymorpha*) ranged from <1 to 4µg Sn/kg round weight, and concentrations in brace (*Abramis brama*) muscle tissue ranged from <1 to 13µg Sn/kg round weight. TTBT was not detected in mussels (*Mytilus galloprovincialis*) collected in 2000 from 3 locations in the Adriatic Sea.

A multi-year national monitoring program in the U.S. measured TTBT in water, sediment, and bivalve tissue collected in and around US commercial harbors, shipyards/dry docks, marinas, and ecologically significant areas (ESAs). Across the various media collected, geometric mean TTBT concentrations ranged from not detected to a maximum of 543.4ng/g dry weight in subsurface sediments collected 1995-1996.

Organotins (not further specified) were found in air and water samples collected from current and former hazardous waste sites in the United States. No organotins were found in air or groundwater at these sites; however, organotins (concentrations not reported) were found in surface water at 1 of 8 sites, in sediment at 4 of the 8 sites, and in soil at one site.

Tin is not listed as a hazardous waste constituent by the U.S. EPA; therefore, its disposal is not restricted by federal land disposal restrictions. The preferred method of disposal for organotin compounds is incineration in an approved hazardous waste incinerator, which converts the organotin to inorganic tin.

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

Human Health: This chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (repeated-dose and reproduction/developmental toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

Environment: This chemical is a candidate for further work. The chemical possesses properties indicating a hazard for environment (acute and chronic aquatic toxicity). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2487-90-3
Chemical Name	Trimethoxysilane
Structural Formula	<chem>C[Si](H)(OC)OC</chem>

SUMMARY CONCLUSIONS OF THE SIAR

Reduced Testing Rationale

Trimethoxysilane undergoes rapid hydrolysis in water; the half life at pH 7 and 2°C is < 0.3 minutes. The hydrolysis product, methanol was measured in this study and based on trimethoxysilane's chemical structure, hydrolysis is expected to produce 3 moles of methanol and 1 mole of silanetriol. Depending on the pH and concentration of the substance, the silanetriols may condense to form oligomers and polymers. Because the material is hydrolytically unstable, water solubility, partition coefficient and biodegradation were not measured. Nonetheless, these endpoints provide valuable information on the behavior of the substance. Modelled values are provided for water solubility and partition coefficient for both trimethoxysilane and silanetriol. In aqueous solutions, exposures to trimethoxysilane are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products methanol, silanetriol, and possible oligomers formed from cross-linking of hydrolysis products. Data from the hydrolysis product methanol (CAS. 67-56-1) were assessed at SIAM. The information on biodegradation potential of methanol is available; both trimethoxysilane and silanetriol are not expected to be readily biodegradable.

No reproductive or developmental toxicity studies have been conducted with trimethoxysilane. Additional testing with this material is not warranted because on a global basis, trimethoxysilane is a site-limited intermediate and is produced and used in closed systems (hard piped). There is no off-site transport and there are no consumer applications of trimethoxysilane. All the trimethoxysilane that is manufactured is consumed on site, in closed systems, in the manufacture of organofunctional silanes that generally contain less than 0.001 %, but may contain up to 0.2% trimethoxysilane. There are no intentional releases to the environment.

Human Health

In rats, exposure to trimethoxysilane by oral gavage resulted in an LD₅₀ = 4.47 mL/kg bw (ca. 4291 mg/kg bw). Symptoms of toxicity noted at the two highest dose levels included depression, labored respiration, and ataxia. In an additional rat study, the oral gavage LD₅₀ was 2.46 mL/kg bw for males (ca. 2458 mg/kg bw) and 1.56 mL/kg bw in females (ca. 1498 mg/kg bw). Signs of toxicity, observed in some animals, included sluggishness, lacrimation, an unsteady gait, distended abdomens, head and body twitches, piloerection, prostration, moribund appearance, red crust around nose and eyes, diarrhea, unkempt appearance and emaciation. In a third gavage study, the LD₅₀ in male rats was 9.33 mL/kg (ca. 9857 mg/kg bw). The animals became sluggish soon after dosing and deaths occurred within the ensuing four-hour period at the highest dose level. The 4-hr inhalation LC₅₀ for trimethoxysilane in rats is 60 ppm (ca. 300 mg/m³). Observations on the day of exposure in the two highest concentration groups (166 or 71 ppm (ca. 830 or 355 mg/m³)) included involuntary blinking or spasm of eyelids, periocular wetness, mouth and abdominal breathing, decreased motor activity, ataxia, and a slow surface-righting reflex. In the 39 ppm (ca. 195 mg/m³) group, unkempt fur, periocular wetness, abnormal breathing and decreased motor activity were observed. No clinical signs of toxicity were observed in the low concentration group (19 ppm (ca. 95 mg/m³)). Additional 4-hr studies resulted in inhalation LC₅₀s

of $31.25 < LC_{50} < 62.5$ ppm (ca. $156 < LC_{50} < 312$ mg/m³) and 53 ppm (ca. 265 mg/m³; nose only). In the rabbit, one study resulted in dermal LD₅₀s of 7.46 mL/kg bw in males (ca. 7160 mg/kg bw) and 6.73 mL/kg bw in females (ca. 6460 mg/kg bw). Local skin effects in 1 or more animals included erythema, edema, necrosis, ecchymosis, fissuring, ulceration, desquamation, scabs and alopecia. Sluggishness, salivation, prostration, emaciation and a clear or red discharge around nose were among the signs of toxicity observed. Histopathology of the lungs included abscesses, congestion, hemorrhages, edema, alveolar histiocytosis, mononuclear cells and black deposits. In another study, trimethoxysilane was applied to the skin of male rabbits for 24 hours using a covered application; the animals were observed for 14 days. The dermal LD₅₀ from this study was 6.30 mL/kg bw (ca. 6050 mg/kg bw). Marked erythema of the skin was observed and gross necropsy findings included congested lungs, mottled livers, and bright mottled kidneys with prominent markings on the surface.

Trimethoxysilane has been shown to be corrosive to the skin and a moderate to severe eye irritant. Signs of respiratory tract irritation have been observed in workers and following repeated exposure to experimental animals. Trimethoxysilane is not a skin sensitizer.

Several inhalation repeated-dose studies of various durations have been conducted in rats and other mammals with trimethoxysilane. Groups of rats were exposed by inhalation at target concentrations of 10, 25, and 50 ppm (ca. 50, 125 or 250 mg/m³) trimethoxysilane for seven hours/day for five days; the LC₅₀ value was 13 ppm (ca. 65 mg/m³). Gross clinical observations indicated the respiratory system was the target organ of toxicity. Repeated (9 days) inhalation exposure of rats to trimethoxysilane resulted in lethality at 5 ppm (25 mg/m³), with death likely due to respiratory tract injury; the NOEC was 0.2 ppm (ca. 1 mg/m³) and the LOAEC was 1 ppm (ca. 5 mg/m³). No signs of systemic toxicity were observed and histopathological changes were seen only in the respiratory tract (the site of contact). Repeated inhalation exposure of rats to trimethoxysilane for 28 days at 5 and 10 ppm (ca. 25 or 50 mg/m³) was lethal, with death probably being a consequence of respiratory tract injury. Based on the body weight, organ weight, clinical pathology, histopathologic observations, and deaths, the NOAEC from this study appeared to be 0.5 ppm (ca. 2.4 mg/m³). In each of these repeated exposure studies, there were no other organs or tissues noted to have histopathological lesions even at the highest exposure concentration which produced severe effects in the respiratory tract and/or death. Exposure of rats to trimethoxysilane vapor (0.02, 0.1 or 0.5 ppm; ca. 0.1, 0.5 or 2.5 mg/m³) for 90 days, followed by a 4-week recovery period produced no exposure-related effects in the biologic parameters monitored during this study. The NOEC in this 90-day inhalation study with rats was determined to be at least 0.5 ppm (ca. 2.5 mg/m³). Groups of mice and hamsters were exposed by inhalation at target concentrations of 10, 25, and 50 ppm (ca. 50, 125 or 250 mg/m³) trimethoxysilane for seven hours/day for five days; the LC₅₀ values were 14 ppm (ca. 70 mg/m³; mouse) and 72 ppm (ca. 360 mg/m³; hamster). Gross clinical observations indicated the respiratory system was the target organ of toxicity.

Trimethoxysilane was not mutagenic *in vitro* in bacterial reverse mutation assays. Trimethoxysilane was negative for the induction of structural and numerical chromosome aberrations *in vitro* in the non-activated test system, but was positive in the S9-activated test system. Trimethoxysilane was not considered to be an inducer of micronuclei *in vivo*. The available information suggests that this substance is not likely to be genotoxic.

Exposure to trimethoxysilane up to 0.5 ppm (ca. 2.5 mg/m³) for 90 days or 5 ppm (ca. 25 mg/m³) for 9 days did not result in any signs of reproductive organ toxicity in rats. Developmental toxicity studies have not been conducted with trimethoxysilane. As noted above under **Reduced Testing Rationale**, no additional testing is needed because trimethoxysilane is a site-limited intermediate.

Environment

Trimethoxysilane is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions. At pH 7 and 2°C, the half-life is < 0.3 minutes. This hydrolysis is expected to produce 3 moles of methanol and 1 mole of silanetriol. Silanetriols (at concentrations greater than 500 ppm) can condense to form highly cross-linked, high molecular weight polymers, further reducing the potential for exposure. If trimethoxysilane is 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. The melting point of trimethoxysilane is -113.6°C and the boiling point is 84.4 °C at 1013 hPa. The vapor pressure is 75.11 hPa at 20°C. The estimated water solubility of trimethoxysilane is 1,000,000 mg/L; the estimated log K_{ow} is -1.22. The water solubility and log K_{ow} values may not be applicable because the chemical is hydrolytically unstable. The estimated water solubility of silanetriol is also 1,000,000 mg/L; the estimated log K_{ow} is -2.91.

The overall OH rate constant for trimethoxysilane and resulting half-life and rate constant due to indirect photolysis are estimated to be 2.5×10^{-12} cm³/molecule-sec and 6.4 days, respectively, using a hydroxyl radical concentration of 5.0×10^5 molecule/cm³. Photodegradation as a mode of removal is unlikely as trimethoxysilane is hydrolytically

unstable. It is assumed that reaction with water vapor is the predominant degradation process for trimethoxysilane in air. The products resulting from trimethoxysilane hydrolysis in the atmosphere are expected to further react with hydroxyl radicals. For the hydrolysis product, silanetriol, the half life due to the atmospheric oxidation from indirect photolysis was determined to be 1.6 days; the overall OH rate constant is $10.35 \times 10^{-12} \text{ cm}^3/\text{molecule-sec}$.

Level III Fugacity modeling, using loading rates of 1000 kg/h each for air, soil, and water, shows the following percent distribution of trimethoxysilane when it is released simultaneously to all three compartments: Air = 47.6%; Soil = 47.6%; Water = 4.8%; Sediment = 0%. However, because it is hydrolytically unstable, trimethoxysilane is unlikely to be found in the environment. Therefore, Level III Fugacity modeling for the hydrolysis product, silanetriol was conducted using loading rates of 1000 kg/h each for air, soil, and water. The model estimated the following percent distribution, when silanetriol is released simultaneously to all three compartments: Air = 1.07%; Soil = 56.7%, Water = 42.24%; and Sediment = 0.08 %. Modeling suggests trimethoxysilane is not readily biodegradable. Any expected biodegradation is likely reflective of the hydrolysis product, methanol, which is readily biodegradable. Silanetriol and condensed silanetriol materials are inorganic compounds and therefore standard biodegradation tests are not applicable. Bioaccumulation of the parent substance is not anticipated since this material is hydrolytically unstable. The bioaccumulation of silanetriol is also unlikely given its low Log K_{ow} value.

Due to the rapid hydrolysis of trimethoxysilane, observed aquatic toxicity is likely due primarily to the hydrolysis products. The 96-hour LC_{50} and LC_0 of trimethoxysilane in freshwater fish (*Oncorhynchus mykiss*) are $\geq 100 \text{ mg/L}$. The 48 hour EC_{50} of trimethoxysilane is $>100 \text{ mg/L}$ for the water flea (*Daphnia magna*) under static conditions. In an algae study with trimethoxysilane, the 72 hr E_bC_{50} values and NOEC for biomass were $> 100 \text{ mg/L}$ and $< 6.3 \text{ mg/L}$, respectively. The 72 hr E_rC_{50} values and NOEC for growth rate were $> 100 \text{ mg/L}$ and $< 6.3 \text{ mg/L}$, respectively.

Exposure

In the Sponsor Country, production volume in 2001 was 1702 tonnes. Trimethoxysilane is not imported in the Sponsor Country; on a global basis this material is a site limited intermediate and is not transported. In production, this material is handled in closed systems (hard piped). Trimethoxysilane is used as a key intermediate in the manufacture of other chemicals (organofunctional silanes). Final industrial products generally contain less than 0.001 %, but may contain up to 0.2% trimethoxysilane. The substance is reacted during use and loses its chemical identity.

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 trimethoxysilane. Due to known and expected reactions, some exposure to methanol, silanetriols, or highly cross-linked, high molecular weight polymers may occur.

Five plants in the Sponsor Country use/manufacture trimethoxysilane. The reactive nature of trimethoxysilane requires handling in closed systems that exclude moisture. Trimethoxysilane is produced in closed reactors that are fed directly to strippers. The stripper separates the lights (solvent) and recycles it back to the reactor; the crude trimethoxysilane is cooled and transferred by hard piping to storage tanks. The crude trimethoxysilane is transferred to a stripper by means of hard piping and then transferred to tanks following condensation. The "heavies" are removed from the bottom of the stripper, and piped directly to a "heavies" storage tank; this tank is hard piped to an incinerator. Trimethoxysilane is transferred by hard piping to a tank where it is intentionally reacted. There is no intentional exposure to trimethoxysilane during production. Trimethoxysilane is not sold in industrial consumer markets and is not shipped from the original point of manufacture.

There are no consumer applications that use trimethoxysilane; the substance is used as a key intermediate in the manufacture of other chemicals (organofunctional silanes). Trimethoxysilane is not sold in consumer markets.

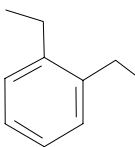
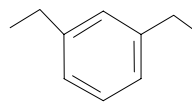
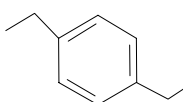
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (corrosivity to the skin, moderate to severe eye irritation, respiratory tract irritation and/or death due to respiratory failure in repeated-dose toxicity studies). Due to the rapid hydrolysis to methanol and the corresponding silanetriol and based on exposure data presented by the Sponsor country (closed system site limited intermediate with no transport globally) and relating to use pattern in one country, 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 based on its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	25340-17-4
Chemical Name	Diethylbenzene, mixed isomers (DEB mixed isomers)
Structural Formula	 1,2-DEB (4-5%)  1,3-DEB (60-65%)  1,4-DEB (27-30%)

SUMMARY CONCLUSIONS OF THE SIAR

Commercial Diethylbenzene (DEB) is available only as a mixture of DEB isomers: 1,2-DEB, 1,3-DEB, and 1,4-DEB, with a typical purity of >92.3% (v/v). The characteristic isomer distribution is as follows: 1,3-DEB (60-65%), 1,4-DEB (27-30%), and 1,2-DEB (4-5%). This SIDS initial assessment does not cover the production and uses of individual DEB isomers. However, selected data for the DEB isomers, e.g., physico-chemical properties and QSAR modeling results, is included in this dossier for the substance DEB mixed isomers to support the assessment of the substance.

Human Health

For DEB mixed isomers, limited toxicokinetic data are available only for the 1,2-DEB isomer. In mammals, 1,2-DEB is absorbed and metabolized rapidly after oral or i.v. exposure; the majority is excreted *via* urine or feces, after extensive enterohepatic recirculation. Oxidation of 1,2-DEB to the γ -diketone 1,2-diacetylbenzene and its subsequent urinary elimination have been demonstrated.

The acute oral LD₅₀ of DEB mixed isomers in rats is >2000 mg/kg bw (from 2050 to 6900 mg/kg bw). Generalized central nervous system depression was observed. For acute dermal toxicity (24-hour) the LD₅₀ is $\geq$ 2000 mg/kg bw. Skin irritation consisting of red, swollen and scabbed skin was noted. From a study with only limited information available, the LC₅₀ for inhalation toxicity (7-hr) in rats is >1400 ppm (7.7 mg/l; highest technically feasible dose). Clinical signs consisted of drowsiness observed at the end of exposure.

Based on tests with rabbits DEB mixed isomers has demonstrated a range of potential for skin irritation, from mild and reversible to severely irritating. DEB mixed isomers causes mild irritation when instilled directly into the eyes of rabbits. DEB mixed isomers did not induce sensitization in a Buehler test in Guinea pigs.

In a 13-week inhalation study in rats, repeated inhalation exposure to DEB mixed isomers (190, 610 and 1400 mg/m³; calculated equivalence of 34, 110, and 252 ppm) resulted in decreased mean body weights in the high-dose animals throughout most of the study and abnormal serum chemistry results in some high- and mid-dose animals that were considered treatment-related, as well as moderate decreases in total white cells and lymphocytes in mid and high dose males. Relative liver weights were slightly increased in male animals from all three treated groups, with no treatment-related changes observed microscopically. There were no obvious target organs from repeated inhalation exposure to DEB mixed isomers; the NOAEL value from this GLP study was 190 mg/m³ (34 ppm). Repeated oral exposure (~7 weeks, daily) to the 1,4-DEB isomer (30, 150 and 750 mg/kg) demonstrated enlarged liver and kidney (male mid and high dose), and corresponding liver histopathology and changes in clinical chemistry, likely due to effects on kidney and liver. The repeat dose NOAEL in rats for orally administered 1,4-DEB isomer was 30 mg/kg bw/day in males and 150 mg/kg bw/day in females (increased liver weight).

A series of subchronic studies, both oral (up to 10 weeks) and inhalation (18 weeks) administration, specifically investigated the neurotoxic potential of DEB mixed isomers and of the individual DEB isomers. Adverse clinical observations, and peripheral and central nervous system effects were noted for the 1,2-DEB isomer in repeated oral exposure to the lowest tested dose of 100 mg/kg bw/day, a dose that caused some mortality. These effects were observed as severe weakness or paralysis of hind limbs at high doses. The decrease in peak amplitude of the

BAEP (brainstem auditory evoked potentials) components was seen and it did not recover during the follow up. Similar data collected from rats treated with the individual isomers 1,3-DEB or 1,4-DEB were negative, with NOAEL values for those individual isomers of 500 mg/kg bw/day indicating that the observed neurotoxicity is due to the 1,2-DEB isomer. A NOAEL for the 1,2-DEB isomer was not demonstrated. However, in a 13-week inhalation study in rats, repeated inhalation exposure to DEB mixed isomers (190, 610 and 1400 mg/m³) reported clinical signs of neurotoxicity (head tilt and loss of balance) only in one high-dose male. A NOAEL for neurotoxicity signs of 610 mg/mg³ (calculated oral equivalent ~ 152 mg/kg bw/day) can be derived for DEB-mixed isomers based on this study.

DEB mixed isomers was not genotoxic or mutagenic in any tests conducted, including the following: negative for bacterial mutations, negative for chromosomal aberrations in CHO cells, and negative for induction of micronuclei in bone marrow erythrocytes from treated mice.

A dermal carcinogenicity study on DEB mixed isomers was conducted in mice. Doses of 25 μ l of a 10% DEB in acetone solutions were administered dermally to the backs of 40 C3H/HeJ mice/group, 3 days/week for the lifetime of the test animals, up to 72 weeks. During the dosing period, hyperkeratosis, epidermal hyperplasia, surface crusting, dermatitis, and dermal fibrosis were pronounced. There was no difference in mortality between treated and control animals. A fibrosarcoma and a lymphosarcoma were identified in two of the control mice. A single squamous cell carcinoma (1/40 mice) was identified in the 10% (v/v) DEB group, at the site of application. The authors considered this to be probably treatment-related, given the very low spontaneous incidence of squamous cell carcinoma in male C3H/HeJ mice. However, given the clear lack of *in vitro* or *in vivo* genotoxicity for DEB mixed isomer, the induction of epidermal hyperplasia and dermal fibrosis, and the single squamous carcinoma are all considered to be manifestations of a proliferative response at the application site due to prolonged, chronic irritation. Therefore, this finding does not reflect a carcinogenic potential for dermal exposure to DEB mixed isomers.

Repeated inhalation exposure up to 1400 mg/m³ of DEB mixed isomers for 13 weeks did not result in any histopathological effects in reproductive organs of male or female Sprague-Dawley rats. In a well-conducted prenatal developmental study in rats (20, 100, 200 mg/kg bw/d) oral gavage dosing of DEB mixed isomers did not produce any indication of developmental toxicity although there was a slight reduction noted in both fetal and maternal body weight (6%) noted at the highest dose (200 mg/kg bw/d). Overall the maternal and developmental NOAEL value is 100 mg/kg bw/d and DEB mixed isomers is not considered to be a developmental toxicant.

Environment

DEB mixed isomers is a liquid at 20°C, with an unpleasant, aromatic odor, and a melting point <-75°C. It is poorly soluble in water (15.7 mg/L at 20°C), has a high vapor pressure (310 Pa at 20°C) and an estimated log K_{ow} between 4 and 4.6. A log K_{oc} of 3.2 was estimated for each of the three DEB isomers which indicates a low mobility of DEB mixed isomers in soil. BCF values of 320-629 and 350-854 were measured for 1,4-DEB and 1,3-DEB, respectively, in fish. These measured values exhibit no apparent isomer specificity, and are supported by calculated BCF (EPIWIN version 3.12/BCFWIN version 2.15) values of 671 for 1,4-DEB and 659 for 1,3-DEB. There is a calculated BCF of 146 for 1,2-DEB (EPIWIN version 3.12/BCFWIN version 2.15). This indicates that DEB mixed isomers have a moderate potential for bioaccumulation.

There is no reliable measured data on biodegradation of DEB mixed isomers in aqueous media available. In a 35-d aerobic biodegradation study with activated sewage sludge according to EC Directive 92/69/EEC, C.4-C, Mixed DEB (contained > 85% diethylbenzenes) was not readily biodegradable. But the results of this study are not considered valid due to the fact that the test material was substantially volatilized from the medium during the test. The estimated potential for primary and ultimate biodegradation, using BIOWIN v4.01, indicates that DEB isomers are not readily biodegradable, but would ultimately biodegrade in a timeframe of weeks. The OASIS Catabol model (v5.099) predicts that 80-85% of theoretical oxygen demand (ThOD) as the DEB isomers would be consumed within a 28-day test according to OECD 301F. Collectively, these QSAR predictions, in addition to the well-established pathways for microbial degradation of substituted mono-aromatics, would suggest the DEB isomers to exhibit potential for inherent, ultimate biodegradability in the environment.

Based on Level I fugacity modeling (EQC Level I, version 3.00) for the individual DEB isomers, all three isomers exhibit a high potential to partition into air. These calculations result in 81 to 90% of all three DEB isomers being distributed to the air, assuming equilibrium conditions, no degradation and no advection processes occurring. In the atmosphere DEB mixed isomers are expected to be removed predominantly by indirect photodegradation, i.e., by reaction with hydroxyl radicals. The calculated half-life for the major constituents of commercial DEB mixed isomers (1,2-DEB, 1,3-DEB, 1,4-DEB) and for trimethylbenzenes and ethylbenzene as minor constituents is in the range of 3.7-18 hours (AOPWIN, version 1.9). The photochemical ozone formation potential of DEB mixed isomers was calculated based on the weighted average MIR value and was determined to be 6.2 g O₃/g, which indicates an intermediate potential. None of the DEB isomers contain a chlorine or bromine and therefore the mixture will have no stratospheric ozone depletion potential. The substance will adsorb to soil

and sediments, but will be removed by partitioning to air. The Level III fugacity model (EQC Level III, version 2.80) predicts that, when released continuously to air, all three isomers will primarily remain in air (>97%) with minimal transfer to soil, water and sediment. When released continuously into the water compartment, Level III fugacity modelling predicts that all three isomers will primarily remain in water (65-88%) with minor transfer to sediment (6-30%), air (3-6%) and soil (<0.1%). Under continuous equal loading of water, soil, and air in the Level III model, all three isomers will distribute mainly to soil (50-63%) and water (27-37%) and minor amounts being transferred to air (5-12%) and sediment (1.4-4.5%).

Based on acute toxicity test results, DEB mixed isomers is very toxic to fish, and toxic to daphnia and algae. Acute toxicity values of DEB mixed isomers for aquatic organisms have been determined according to OECD Test Guidelines:

Fish: 96-hr LC_{50} (*Oncorhynchus mykiss*) (Rainbow Trout) = 0.673 mg/L, based on measured concentrations;

Invertebrates: 48-hr EC_{50} (*Daphnia magna*) = 2.01 mg/L, based on measured concentrations;

Algae: based on growth rate, a 72-hr E_rC_{50} of 1.21 mg/L, and based on biomass, a 72-hr E_bC_{50} of 1.0 mg/L was determined based on measured concentrations for *Pseudokirchneriella subcapitata*; formerly *Selenastrum capricornutum*.

No data on chronic toxicity to aquatic organisms are available for DEB mixed isomers. In a 21-d chronic toxicity study of 1,4-DEB to aquatic invertebrates (*Daphnia*) a NOEC of 0.93 mg/l ($p < 0.05$) has been determined.

Exposure

Global production of DEB mixed isomers (CAS 25340-17-4) is not known. In the US, production of DEB mixed isomers, as reported in the 2002 Inventory Update Rule (IUR), was between 10,000,000 and 50,000,000 pounds (5,000 to 25,000 tonnes). Total emissions of DEB are <10,000 lbs (<4,500 kg)/yr, based on the major producer's data. The reported IUR volumes for DEB mixed isomers have declined from the 500,000,000 to 1 billion pounds (250,000 to 500,000 tonnes) reported in 1990. DEB mixed isomers is produced in closed systems as a by-product in the ethylbenzene process and may also be a by-product/impurity of other aromatic streams.

The primary uses for DEB mixed isomers are limited to specific industrial processes, i.e., as a raw material/chemical intermediate (95%) or as an industrial heat transfer fluid (<5%), where the material is contained in closed systems and the potential for releases to the environment are minimal. Only five industrial products that contain DEB mixed isomers are listed in the product register of the Sponsor Country. These are registered as heat transfer fluids (2 products, containing 97-100% of the substance), cross-linking agent for polymer manufacturing, ultraviolet light stabiliser for furniture, and additive/lubricant for Diesel engines (DEB mixed isomers contents of these three products between 0.001% and <1%). In the Nordic product register only three products with DEB mixed isomers, all of them registered as heat transfer agents, could be retrieved, amounting at a volume of 16 tonnes in 2004. DEB mixed isomers is neither used in pesticides that are registered in the Sponsor Country nor it is used in consumer products, according to the product registers in the Sponsor Country and the Nordic Countries.

However, individual DEB isomers (1,2-DEB; 1,3-DEB; and 1,4-DEB) are also present as minor constituents in crude oil and as a result of processing in various high volume petroleum products, e. g. gasoline. Exposure of humans and the environment that may occur from these DEB isomer-containing products and from incomplete combustion processes are not covered by this hazard assessment for DEB mixed isomers. Individual DEB isomers have been detected in urban and rural air at pptV to low ppbV concentrations. US-EPA reported for 2006 average/maximum ambient air concentrations of 0.142/3.59 ppbV for 1,3-DEB and 0.018/2.48 ppbV for 1,4-DEB. Exposure to the general population is possible through very low ambient air concentrations, primarily due to gasoline and automobile emissions.

The most likely route of occupational exposure is via inhalation, although DEB mixed isomers is handled using appropriate personal protective equipment to minimize exposure. The AIHA Workplace Environmental Exposure Level (WEEL) for DEB mixed isomers is 5 ppm. Measured personal monitoring data from production and use workplaces indicate that occupational exposures are <1 ppm.

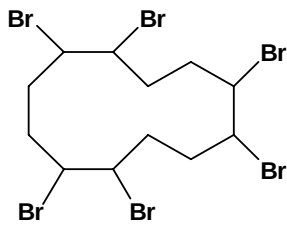
RECOMMENDATION, RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The substance is currently of low priority for further work. The substance possesses properties indicating a hazard for human health (mild eye irritation and skin irritation; effects on PNS and CNS due to the 1,2-DEB isomer, a minor constituent of the substance, may become evident at high doses of the substance). These hazards do not warrant further work as they are either related to reversible effects or effects that may become evident at high doses only. They should nevertheless be

noted by chemical safety professionals and users.

Environment: The substance is currently of low priority for further work. The substance possesses properties indicating a hazard for the environment (acute toxicity to aquatic organisms and a moderate potential for bioaccumulation). However, based on data presented by the Sponsor Country (which accounts for the major fraction of global production, situated in one OECD-country), the substance is used only in closed industrial systems and as a raw material/intermediate with application of adequate emission control and risk management measures. There are no known uses in consumer products. Therefore exposure of the environment is expected to be low. Countries may wish to investigate any exposure scenarios for the environment that were not presented by the Sponsor Country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	25637-99-4, 3194-55-6
Chemical Name	Hexabromocyclododecane (HBCDD)
Structural formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Available studies demonstrate that HBCDD can be absorbed from the gastro-intestinal tract. The highest concentrations are subsequently reached in adipose tissue and muscles followed by liver, and with much lower concentrations present in lung, kidney, blood, brain, and gonads. At long-term exposure, higher concentrations are achieved in females than in males, but the substance is bioaccumulating in both sexes. Of the three diastereoisomers constituting HBCDD, the α -form is much more accumulating than the others (the relative bioaccumulation factor is 99:11:1 for α , β and γ , respectively). The time to reach steady-state seems to be in the order of months. HBCDD can be metabolised, and three polar metabolites are identified. Elimination of HBCDD and its metabolites mainly occur via faeces with a minor part excreted in urine. The absorption, both after oral and inhalation exposure, is set to 100 %, whereas a value of 2 % (granules) or 4 % (powder) is set for the dermal absorption, depending on the size of the particles occurring at the exposure situation.

HBCDD has demonstrated a low acute toxicity. The minimal lethal dose is greater than 20 g/kg for both dermal and oral routes of administration, and greater than 200 mg/L at inhalation for 4 hours.

HBCDD is mildly irritating for the eyes, but not irritating to skin.

Two Magnusson-Kligman studies performed with HBCDD of unknown specification have given positive results. However, studies on HBCDD of known specification by the major producers of HBCDD, has shown negative results both in a Magnusson-Kligman test and in a Local Lymph Node assay. Overall, HBCDD is therefore not regarded as a skin sensitizer.

No repeated dose toxicity studies with inhalation or dermal exposure as route of administration are available.

A 28-day repeated dose toxicity study has been performed using a benchmark model design with oral administration of dissolved HBCDD. There were five dose groups, the highest dose group achieved 200 mg/kg bw/day. The result showed organ weight increase of the liver, the thyroid, and the pituitary. Enzyme induction in the liver was likely the cause of the effects, as hepatic enzyme induction leads to increased excretion of T4, compensatory activation of the pituitary, increased serum TSH concentration and thereby activation of the thyroid.

Other repeated dose toxicity studies, both 28- and 90 days with oral exposure of HBCDD particles, support the liver and thyroid being the main target organs. The NOAEL of 1000mg/kg bw/day from the 90 days study would normally be preferred, but the uncertainties introduced in the evaluation of this study by the dosing of HBCDD-particles to the animals, leads to the choice of a NOAEL from a 28-days study.

Overall, a NOAEL/BMD-L of 22.9 mg/kg/day for liver weight increase is decided for repeated dose toxicity.

HBCDD did not induce mutations in the Ames test, and was negative in both an *in vitro* chromosome aberration test and an *in vivo* micronucleus test. Therefore, it can be concluded that HBCDD lacks significant genotoxic potential *in vitro* as well as *in vivo*. Based on one available lifetime assay, it is not possible to assess the carcinogenic potential of HBCDD. However, the available database gives no

reason for further exploration of this endpoint.

Two developmental toxicity studies have failed to demonstrate any fetotoxicity, teratogenic potential, or adverse effects from HBCDD on development postpartum. A NOAEL of >1000mg/kg/day (highest dose tested) is decided for developmental toxicity.

A study on developmental neurotoxicity in adult mice exposed as pups at day 10 postpartum has been conducted. It indicates that HBCDD may cause statistically significant changes in spontaneous behaviour, learning, and memory defects at the dose 0.9 mg/kg/day. The study is published, but has not been performed according to OECD Test Guideline or GLP and thus would benefit from being confirmed by other laboratories. Overall, the study thus indicates that the substance is a possible developmental neurotoxicant.

Functional observation batteries and motor activity tests in the 28-day and 90-day studies showed no evidence of neurotoxicity.

The reproductive toxicity is not fully tested because there are no fertility studies available. However, the 90-day study included investigation on the reproductive organs including histopathological examination, semen analysis and estrous cycle monitoring. At the highest dose (1000 mg/kg/day) a statistically significant increase in absolute and relative prostate weight was observed, but no accompanying microscopical changes were detected. Females showed signs of inhibited oogenesis in most of the follicles and sparse ripening follicles in the ovaries at exposure to 4700 mg/kg/day in a 28-day study not conducted in accordance with present standards. The effect on the prostate and the oogenesis has not been confirmed in any other studies and the inhibited oogenesis occurred at a very high dose.

Environment

Technical grade HBCDD is generally produced from *cis trans*, *trans*-1,5,9-cyclododecatriene (CDT), one of four CDT isomers, (CAS No. 27070-59-3). The reaction, *trans*-addition of bromine to the double bounds of CDT, results in the three diastereomers α -, β - and γ -HBCDD. The final distribution of the diastereomers in technical HBCDD varies with a range of about 70-95 % γ -HBCDD and 5-30 % α - and β -HBCDD. The major impurities are tetrabromocyclododecene and isobutanol. HBCDD is a white odourless solid. The log n-octanol/water partition coefficient (log Kow) of HBCDD was determined to 5.6 at 25±0.05°C. The composite sample produced by mixing equal amounts of three commercial HBCDD technical products contained 8.5 % β -, 6.0 % α - and 79.1 % γ -HBCDD (total HBCDD 93.6%). There was no information on the identity and properties of the remaining 6.4%. A vapour pressure of 6.3·10⁻⁵ Pa at 21°C is used in the assessment. The melting point range varies from approximately 172-184 °C for a crude product to 201-205 °C for the highest melting version following crystallisation. Melting points for the individual diastereomers have been determined to 207-210°C for γ -HBCDD, 171-181 °C for α -HBCDD and 169-172 °C for β -HBCDD. The water solubility of technical HBCDD has been determined to 3.4µg/l at 20°C. However, this value mainly reflects the water solubility of γ -HBCDD. The different diastereomers have different water solubilities, 49 µg/l for α -HBCDD, 15µg/l for β -HBCDD and 2µg/l for γ -HBCDD. The value of 66µg/l, which is the sum of the water solubilities of the three diastereomers, is used for the technical HBCDD mix of diastereomers in the EUSES calculations as a worst case estimate.

The log Koc of HBCDD is calculated to be 4.66 thus, HBCDD is predicted to absorb strongly to organic carbon (i.e. soil and sediment). The substance has a low potential to evaporate from the aquatic surface and evaporation is therefore considered as a less important route of dispersion. Despite this two different studies have shown that HBCDD has a low long-range transport potential (LRTP). The distance was estimated to be in the range of 760-2550 km. The LRTP potential is confirmed by findings of HBCDD in biota in the arctic. Calculations (EUSES model) indicate that the overall removal of HBCDD in a sewage treatment plant is approximately 80%. The major part is expected to be adsorbed to the sludge.

The log Kow of HBCDD of 5.6 indicates a potential for accumulation in living organisms. Results from two studies on fish support each other. One of the studies gave a BCF value of 18100 for fathead minnow. The other study, where two different test concentrations were employed, gave BCF values of 8974 and 13085 in the high and low dose group, respectively. When estimated with kinetic modelling the BCF-values from the study were calculated to be 16450 and 21940, in the two dose groups respectively. An overall BCF of 18,100 is chosen as representative from these studies. One existing study on earthworms (*Eisenia fetida*) shows that HBCDD is taken up in the worm tissue. Although not valid for making conclusions about the magnitude of bioconcentration of HBCDD in earthworms it shows that the uptake of α -HBCDD (BAF: 0.3-0.8) was more than one order of magnitude higher than for γ -HBCDD (BAF: 0.005—0.02). This is in line with what has been observed also for other biota e.g. mammals and fish where α -HBCDD is the dominating diastereomer despite constituting only 6% of the technical product and in most cases having the lowest concentrations in the abiotic environment i.e. sediment.

There are lots of monitoring studies showing uptake of HBCDD in biota. Data exists from freshwater invertebrates, freshwater fish, plants and birds, where the concentrations range between 0.025-28, 0.03-9432, 1.5-11114 and 0.002-160 µg/kg ww, respectively. Moreover, there are data from brackish and marine biota including invertebrates (0-329 µg/kg ww), fish (0.001-89 µg/kg ww), and marine birds mainly eggs (0-100 µg/kg ww). The highest concentrations of HBCDD in marine biota are measured in marine mammals with concentrations ranging from 0.5-6404 mg/kg ww. This is a strong indication that HBCDD biomagnifies in the marine food chain. Monitoring data also indicate that the concentrations of HBCDD are increasing. The mean concentrations measured in Atlantic puffin, Herring gull and Kittiwake in the North of Norway have increased with a factor of about 5-8 over 20 years. The mean concentrations measured in eggs from Guillemot from St. Karlsö in the Baltic Sea has approximately doubled from 8 µg HBCDD/kg ww in the early 1970-ties to about 16 µg HBCDD/kg ww in the late 1990's. The increase has levelled out since the mid 1990's. Also for marine mammals the data indicate increasing tissue concentrations. The median concentrations in the blubber of harbour porpoises stranded or dying due to physical trauma in the UK increased from below 100 µg/kg lw in the mid 1990's to 9400 µg/kg lw in 2003. HBCDD has also been detected in adipose tissue of polar bears from Svalbard in concentrations 5-45 µg HBCDD/kg ww.

The hydrolysis of HBCDD has not been studied. Hydrolysis should however, not be considered as a significant route of environmental degradation for this substance due to the low water solubility and high partitioning to organic carbon. Furthermore, the dissipation of HBCDD in abiotic aerobic water sediment studies was very slow. No studies on abiotic degradation of HBCDD in air, i.e. photodegradation exist. The route is however considered to have low environmental significance because of low vapour pressure of HBCDD.

Standard ready and inherent biodegradation tests show no biodegradation over a 28d test period under aerobic conditions. Several studies on biodegradation of HBCDD in sediment and soil are available giving different results. Two of these are considered reliable. In the first study the HBCDD concentrations ranged between 34-89 µg/kg sediment dw (which is comparable to the mean concentrations of HBCDD in sediment if sediments affected by point sources are excluded) and 25 µg/kg dw in soil. Due to the low concentrations only the degradation of the γ -diastereomer could be followed. The half life for γ -HBCDD in aerobic sediment was 11 and 32 days in two different sediments and approximately 1 day in anaerobic sediment at 20 °C. The half life for γ -HBCDD in aerobic and anaerobic soil at 20 °C was 63 days and 7 days, respectively. No degradation products were detected neither in sediment nor soil. In the second study the HBCDD concentration was 4.3 – 4.7 mg/kg dw in sediment (which is comparable to levels in sediment measured close to some point sources) and 3 mg/kg dw in soil. In soil no degradation was observed whereas in sediment the half-life of total HBCDD at 20°C was 101 days under aerobic conditions and 66 days under anaerobic conditions. α - and γ -HBCDD had similar half lives under aerobic conditions but γ -HBCDD disappeared with a half life of 66 days compared to 113 days for α -HBCDD under anaerobic conditions, indicating that α -HBCDD may be more stable than γ -HBCDD. Results from degradation studies in sewage sludge support this indication where α -HBCDD degraded more slowly than γ -HBCDD in two studies out of three. The transformation pathway of HBCDD was identified as being a step-wise dehalogenation, via tetrabromocyclododecene and dibromocyclododecadiene to 1,5,9-cyclododecatriene. The degradation of the transformation product 1,5,9-cyclododecatriene has been studied in a modified ready biodegradation test. The test substance was coated on silica gel and incubated for up to 77 days. During this period significant amounts of CO₂ (70%) of were formed indicating that the substance is biodegradable.

Five studies on the toxicity of HBCDD for algae are available. The 72h-EC₅₀ value of 52 µg/l is considered as the most realistic and reliable result. From corresponding experiments on invertebrates (2 studies) and fishes (3 studies), a 48h-EC₅₀ of >3.2 µg/l for a crustacean (*Daphnia magna*) and a 96h-EC₅₀ value of ≥2.5 µg/l for rainbow trout (*Oncorhynchus mykiss*) was determined respectively. The toxicity of HBCDD to aquatic organisms has also been obtained with QSAR for *Daphnia magna*. The result show a 48h-EC₅₀=140 µg/l, which is far above the water solubility of HBCDD. Two long term tests are available for HBCDD. The first study, a reproduction test (21d) on *Daphnia magna* reports a NOEC of 3.1 µg/l. In the other study, a fish early life stage test on *Oncorhynchus mykiss*, no effects were seen at the highest tested concentration, which was 3.7 µg/l. Two studies on sediment dwelling organisms are available, both considered reliable. The lowest NOEC value is 3.1 mg/kg dw sediment for the reduction of total numbers of worms (*Lumbriculus variegatus*).

There are three studies available on terrestrial organisms from three trophic levels, soil micro-organisms, plants, and soil dwelling organisms. No effects on soil micro-organisms (nitrification) were seen in any treatment giving a NOEC >1000 mg HBCDD/kg dw soil. No effects could be determined for the plants in the highest concentration tested 6200 µg HBCDD/kg soil. The test species were corn (*Zea mays*), cucumber (*Cucumis sativa*), onion (*Allium cepa*), ryegrass, (*Lolium perenne*), soybean (*Glycine max*), and tomato (*Lycopersicon esculentum*). A NOEC value of 128 mg HBCDD/kg dry soil for reproduction

of earthworms (*Esenia fetida*) (56d) is concluded for the terrestrial environment.

Exposure

HBCDD was in 2006 only produced at one site in EU15¹, located in the Netherlands. The total annual (2005) EU15 production of HBCDD is around 6 000 tonnes. No information on export of HBCDD from the EU has been provided. Countries outside the EU15 known to produce HBCDD are the USA and Japan. HBCDD is imported to the EU15 from the USA (around 5 000 tonnes per year). Data from Japan indicate that the consumption of HBCDD in Japan is about 2 000 tonnes per year.

The main uses of HBCDD are in the polymer and textile industries. HBCDD can be used on its own or in combination with other flame retardants e.g. antimony trioxide and decabromodiphenyl ether. HBCDD is used in four principal product types, which are Expandable Polystyrene (EPS), Extruded Polystyrene (XPS), High Impact Polystyrene (HIPS) and Polymer dispersion for textiles.

According to industry information, the main use (90%) of HBCDD is in polystyrene (PS). The predominant use of PS is in rigid insulation panels/boards for building and construction (EPS and XPS). About 2 % of the total use of HBCDD is in "high impact polystyrene" (HIPS). Most of the flame retarded HIPS-products are used in electrical and electronic appliances e.g. audio visual equipment cabinets (video and stereo equipment), distribution boxes for electrical lines in the construction sector, refrigerator lining.

Textiles with back-coating containing HBCDD can be used for e.g. flat and pile upholstered furniture (residential and commercial furniture), upholstery seatings in transportation, draperies, and wall coverings, bed mattress ticking, interior textiles e.g. roller blinds, automobile interior textiles and car cushions.

Humans may be exposed to HBCDD at the workplace, from use of consumer products, and indirectly from the environment via food, soil, water and air. The highest exposures undoubtedly occur in the workplace environment. Still, there are no occupational exposure limits for HBCDD. The available information about releases of HBCDD from waste and waste management is limited. Possible routes of release are as dust particles from demolition of buildings, leakage from landfilled material and from waste remained in the environment. The emission today are assumed to be limited, due to that HBCDD has only been used in the last decades, but may increase in the future depending on how the waste will be handled.

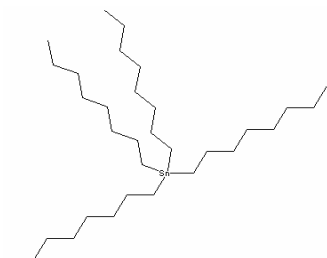
RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health with regard to repeated dose toxicity and possible developmental neurotoxicity. Therefore, member countries are invited to perform an exposure assessment and if then indicated a risk assessment. Note: A risk assessment performed in the EU in the context of the EU Existing Chemicals Regulation is in progress.

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (acute aquatic toxicity to algae, chronic toxicity to *Daphnia*, high bioaccumulation potential). Therefore, member countries are invited to perform an exposure assessment and if indicated a risk assessment. Note: A risk assessment performed in the EU in the context of the EU Existing Chemicals Regulation is in progress.

¹ Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxemburg, Netherlands, Portugal, Sweden, Spain, United Kingdom

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3590-84-9
Chemical Name	Tetraoctyltin (TTOT)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute oral LD₅₀ of tetraoctyltin (TTOT) to rats was >2000 mg/kg bw. There are no data on acute dermal or inhalation toxicity, irritation, or sensitization.

The repeated-dose toxicity of TTOT (90.8% purity) to rats was evaluated in a combined repeated-dose and reproduction/developmental toxicity screening test (OECD TG 422). Based on the observed effects in the 7500 mg TTOT/kg diet group (decreased thymus weight, as well as thymic lymphoid depletion and macrophage accumulation), the NOAEL for sub-chronic toxicity was 1500 mg TTOT/kg diet (equivalent to 86–99 mg/kg bw/day for males and 80–141 mg/kg bw/day for females) and the LOAEL was 7500 mg TTOT/kg diet (445–480 mg/kg bw/day for males and 426–624 mg/kg bw/day for females).

TTOT was negative in a standard *in vitro* Ames assay using multiple strains of *Salmonella typhimurium* and with *Escherichia coli*, conducted with and without metabolic activation. TTOT was also negative in a standard *in vivo* mouse micronucleus test.

No adverse effects on fertility or reproductive performance and development were observed in the reproduction/developmental toxicity segment of the OECD 422 study, even at the highest (maternally toxic) dose tested of 7500 mg TTOT/kg diet. Based on the lack of observed effects, the NOAEL for reproductive and developmental toxicity of TTOT was 7500 mg TTOT/kg diet (445–480 mg/kg bw/day for males and 426–624 mg/kg bw/day for females).

Environment

Because of the insolubility of TTOT and strong adsorption of TTOT to labware, several physicochemical properties could not be readily measured and thus are based on modeled data. Estimated values derived from the current EPIWIN models developed by Syracuse Research Corporation should be used with caution, as the current versions have not been validated for estimating endpoints for chemicals that contain metals in their molecular structure. TTOT is a colorless to slightly yellow turbid liquid, with a measured freezing point of -102°C and a boiling point of 414–425°C at 1013.25 hPa (760 mm Hg). TTOT has a calculated vapour pressure of 9.4×10^{-6} hPa at 25°C, a relative density of 0.96–0.98 g/cm³ at 20°C, and a calculated log K_{ow} of 17.2. TTOT is only sparingly soluble in water with an estimated water solubility of 1.3×10^{-12} mg/L using a Log K_{ow} of 17.2. An additional estimation of the water solubility of TTOT was performed using an estimated log K_{ow} of 8.0, which is widely accepted as a realistic maximum value for this parameter; the resulting water solubility was 9.5×10^{-4} mg/L. Possible higher solubility suggested by the aquatic toxicity studies, where total tin was measured, may be due to differences in the percentage of impurities present (e.g., tin tetrachloride, trioctyltin chloride, and dioctyltin dichloride) that may either be more soluble or may hydrolyze to more soluble tin compounds. Measured vapour pressures present similar difficulties in that impurities may volatilize more readily than pure TTOT.

TTOT is stable in water due to a lack of hydrolyzable functional groups, and it is not readily biodegradable. Releases of TTOT to air are not expected to be significant due to its low vapour pressure. Vapour-phase TTOT would be expected to be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals, with a calculated rate constant of 79.5×10^{-12} cm³/molecule*sec and an estimated half life of 3.2 hours.

Based on a Level III fugacity model assuming emissions of 1000 kg/hr to soil, air, and water, TTOT is predicted to partition primarily to sediment and soil (68% and 28%, respectively, based on a log K_{ow} of 17.2; 84.5% and 10.5%, respectively, based on a log K_{ow} of 8.0). A calculated Henry's Law Constant of 562 atm.m³/mol predicts that TTOT will volatilize from water; half-lives from a model river and lake are estimated at 2.4 hours and 9.5 days, respectively. Calculated BCFs of 100 (based on a log K_{ow} of 17.2) and 2188 (log K_{ow} of 8.0) were determined using BCFWIN. These values are considered representative based on comparison with measured BCF values experimentally determined for a related material, tetrabutyltin, which had BCF values ranging from 38 - 310.

Aquatic toxicity studies were conducted in accordance with OECD Test Guidelines and exposure concentrations were measured on the basis of total tin, then converted to and reported as the named substance. All of the measured tin (including contributions from more water-soluble tin compounds, impurities, or hydrolysis products) was attributed to the named substance, TTOT. A 100% Water Accommodated Fraction (WAF), prepared at a loading rate of 100 mg TTOT/L, induced no visible effects in zebra fish (*Brachydanio rerio*) (96-h LC_{50} > 0.52 mg TTOT/L). A filtered, saturated solution immobilized *Daphnia magna* in all concentrations tested (24-h EC_{50} < 0.13 mg TTOT/L). A 100% WAF, prepared at a loading rate of 100 mg TTOT/L, induced no treatment-related deaths or adverse effects on growth or reproduction of *D. magna* (21-day EC_{50} [reproduction] > 0.068 mg TTOT/L; overall LOEC > 0.068 mg TTOT/L; and overall NOEC ≥ 0.068 mg TTOT/L). A filtered, saturated solution of TTOT showed no to only very slight (7%) growth inhibition to the green alga *Scenedesmus subspicatus* (72-h EC_{50} > 0.21 mg TTOT/L). A possible explanation for the disparity between the chronic and acute toxicity may be attributed to the tendency for this material to adsorb to surfaces and cause immobilization due to a physical rather than toxicological mechanism. The reason for this may be the difference in WAF preparations of the two studies. In addition, the possibility of water soluble impurities present at the lowest concentration tested causing the observed toxicity can also not be ruled out.

Exposure

In 2000, worldwide production of TTOT was estimated at 2,500 to 7,500 tonnes. TTOT is produced in North America, Europe, and Asia-Pacific, and is only used as an industrial intermediate in the synthesis of other octyltin compounds. In individual dioctyltin and monoctyltin compounds, or in mixtures used as stabilizers, TTOT may be present at levels < 0.1 percent. TTOT may be present at levels up to 5% in trioctyltin chloride which is used as an intermediate in the production of other trioctyltin compounds. TTOT may be transported to the other organotin producers; however, all produced TTOT is consumed during its conversion to other compounds. There are no commercial applications for TTOT. Releases to the environment could occur via losses during the production of this intermediate, or during its conversion to other octyltin chemicals.

In the production of TTOT, the operations are usually sealed to prevent releases to the atmosphere. No information is available on the release of organotin compounds from the Toxics Release Inventory in the U.S. because manufacturers are not required to report releases under Section 313 of the Emergency Planning and Community Right-to-Know Act. The recommended method of disposal is incineration in an approved hazardous waste incinerator, which converts the organotin to inorganic tin.

The most prominent routes of potential exposure to TTOT in an occupational setting are inhalation and dermal contact. Exposure in the workplace is controlled through equipment design (engineering controls) and regular air monitoring. Engineering controls, such as local mechanical exhaust ventilation at sources of air contamination can be utilized to provide ventilation to control exposure levels below airborne exposure limits. Also, the use of personal protective equipment (PPE), such as chemical-resistant goggles, rubber gloves, and approved respirators is routinely advised. Worker exposure is confined to manual operations such as material addition, transfer, or sampling. For operations that specifically involve manual handling of organotin compounds (not TTOT specifically), recently measured exposure potentials were 50% to just greater than the threshold limit value (TLV) of 0.1 mg/m³.

Additionally, in the U.S. the small percentage of TTOT that is transported from the manufacturing site would be packaged in intermediate bulk containers (totes) which are returned through the tote manufacturer or the chemical supplier to designated facilities for treatment of residues and recycling of the container. The use of bulk shipments minimizes exposure to workers.

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

Human Health: The chemical is currently of low priority for further work. This chemical possesses properties indicating a hazard to human health (repeated-dose toxicity). Based on data presented by the Sponsor country

(relating to production in one country which accounts for unknown fraction of global production) and relating to the 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 countries.

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to aquatic invertebrates). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	51000-52-3
Chemical Name	Neodecanoic acid ethenyl ester, vinyl neodecanoate
Structural Formula	$\text{CH}_2=\text{CH}-\text{O}-\text{CO}-\text{C}(\text{CH}_3)(\text{R}^1)(\text{R}^2)$ where R^1 and R^2 contain seven alkyl carbons in total

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There are no standard toxicokinetic studies on neodecanoic acid ethenyl ester. However, it is evident that the chemical is absorbed and distributed because there were specific organ effects in kidneys and liver following oral and inhalation dosing. Although it appears to be a very stable monomer that is not degraded, at least to a significant extent, by crude liver homogenates of rats *in vitro*. The acute toxicity tests indicate low toxicity by inhalation, dermal, and oral routes of exposure to rodents. In rats, the oral and dermal LD₅₀ were > 8850 mg/kg bw and > 3540 mg/kg bw, respectively, and the 4-h LC₅₀ was > 2.6 mg/L. With regards to irritation in animals, there is evidence of limited (minimal to non-irritating) potential to eyes and skin. However, the substance is not a sensitizer. Repeated dosing of neodecanoic acid ethenyl ester has shown a low degree of toxicity in rats by inhalation (0.25, 0.5 and 1.0 g/m³ for 6hr/day, 5d/wk, 13 weeks) or oral exposure (100, 250, 1000 mg/kg/d, for 28 d). The NOAEL for a 28-d oral exposure was 250 mg/kg bw/d based on specific kidney effects (so called male rat nephropathy) seen at 1000 mg/kg bw/d. The 13-week NOAEC for inhalation was 0.50 g/m³ or 61.7 ppm based on increased liver and kidney, and reduced body weights.

The mutagenic/genotoxic assays which were broadly consistent with modern guidelines show that neodecanoic acid ethenyl ester is not mutagenic or genotoxic *in vitro* (bacterial, yeast and mammalian cell gene mutation and rat liver chromosomal aberration) or *in vivo* (rat liver DNA integrity). No information is available for carcinogenicity. Results from a rat combined repeated dose toxicity study, including reproductive and developmental screening tests (OECD 422) show that neodecanoic acid ethenyl ester (1000, 250, and 100 mg/kg bw/d) is not toxic to reproductive functions such as fertility and there was no evidence of skeletal or visceral malformations or variations. There was a minor, not statistically significant decrease of about 5% in mean day 1 pup weights at the limit dose of 1000 mg/kg/d. The limited effects at the 1000 mg/kg/d limit dose indicate the chemical is not a specific developmental toxicant.

Environment

Neodecanoic acid ethenyl ester is a commercial mixture of isomers used mainly in the synthesis of polymers to make them more hydrolytically and UV-stable. It is a light viscous liquid, moderately volatile (Henry's Law Constant 1295.3 Pa.m³/mol (1.3 x 10⁻² atm.m³/mol), measured boiling point 212°C and vapour pressure 0.386 hPa at 25 °C), of low water solubility (5.9 mg/L, measured), and with a moderate affinity towards organic matter (predicted Log K_{oc} 2.75). While the measured octanol-water partition coefficient (Log K_{ow} or Log P) is 4.9, the bioaccumulation potential from a fish study in which the substance was dosed via the feed indicates that the compound is rapidly eliminated (95% clearance in 14 days depuration, biomagnification factor 0.09). The assimilation efficiency of the hexachlorobenzene control was 47% (indicating high assimilation and in agreement with historical data), and 18% for neodecanoic acid ethenyl ester. The data were also used to derive a bioconcentration factor from an equation validated for compounds tested in aqueous-dosed bioaccumulation studies (BCF 1100 - 1390). However given that neodecanoic acid ethenyl ester is poorly soluble in water this range is likely to be a protective estimate. As stated earlier, the tertiary (neo-) carbon bonding and alkyl chain structure confers a high degree of stability to the molecule, thus it is expected to be strongly resistant to UV light and hydrolytic degradation. When modelling for its environmental distribution (Mackay Fugacity Level III) with

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equal release to air, water and soil, it is predicted that the bulk transport should be to soil and sediment compartments (~78 and 14%, respectively), with very little to air and water (0.5 and 7.6%). This chemical was neither readily nor inherently biodegradable (OECD 301D, 14 – 17% degradation after 28 days; OECD 302C, 3 – 5% after 28 days). Microbial toxicity results show no adverse effects up to forced solubility limits ($IC_{50} > 100$ mg/L).

Neodecanoic acid ethenyl ester has been tested for its acute toxicity to fish, invertebrates and algae. No chronic studies have been conducted. Aquatic toxicity testing has been problematic due to its low water solubility and its likely adherence to glassware. The substance is acutely toxic to aquatic organisms: the lowest GLP results are fish LC_{50} 0.84 mg/L, invertebrates (marine copepod) EC_{50} 0.3 mg/L, and algae EC_{50} 3.4 mg/L and $ErC_{50} > 4.8$ mg/L. As indicated above this chemical exhibited a low biomagnification factor, but according to OECD GHS criteria by its derived BCF would be considered to bioconcentrate since the derived BCF >500.

Exposure

Neodecanoic acid ethenyl ester is used exclusively in polymerization as a monomer to make the resulting products more hydrolytically and UV-stable. It is not meant to be used as an unreacted substance in any application. The primary uses include vinyl acetate latex polymers where the principal application is paints and coatings (65%), and adhesives i.e. re-dispersible powders (35%).

Four potential sources of environmental exposure have been identified: (1) Production; (2) Processing (monomer polymerization); (3) Formulation of the polymer into a coating; and, (4) Use by consumers and professional users. Production of neodecanoic acid ethenyl ester (or vinyl neodecanoate) takes place at one site in the Netherlands, and is performed in a continuous closed system as a “dry” process for 365 days/year. Releases from production are expected to be minimal. The total global production volume ranges from 46,000 to 230,000 tonnes/yr.

Exposure from processing is deemed as negligible as the chemical is non-dispersive and carried out in a closed system. Engineering controls are in place to minimize emissions, and transport from storage into a reactor tank is done in a completely closed environment. Any minimal waste water generated in the process would be fed to a waste water treatment plant (WWTP), and since neodecanoic acid ethenyl ester is normally directed to the oil phase in the oil / water separator before the WWTP it is treated as chemical waste, and hence incinerated.

Exposure from formulation of the polymer into a coating (i.e. paint) estimates a very small amount of unreacted residual neodecanoic acid ethenyl ester in the end product (0.006% max). It is assumed that dedicated equipment with very little cleaning is used for formulation, given the high quantities of product needed.

Exposures from uses (application) are more difficult to estimate. Based on the amount of unreacted residual monomer in an end-product such as paint (0.006%), an estimate of 350-600 kT paint containing residual neodecanoic acid ethenyl ester could be on the European market. The coating film is required to be stable for at least 3 years.

The circumstances of manufacture and use of neodecanoic acid ethenyl ester allow for a continuous control of human and environmental exposure, which are done in closed systems and under strict norms of safety. Occupational, consumer, and even environmental exposure are anticipated to be low, if not negligible. Despite the high toxicity seen in aquatic testing, exposure to the environment is anticipated to be low. In the event of an accidental spill there are mitigation plans in place to minimize exposure and potential hazards.

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

Human Health: The chemical is a low priority for further work due to its low hazard profile.

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to fish and aquatic

invertebrates). Member countries are invited to perform an exposure assessment for the environment and if necessary a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-12-7
Chemical Name	Formamide
Structural Formula	$\begin{array}{c} \text{H} \quad \text{O} \\ \quad \parallel \\ \text{C} \\ \quad \\ \text{NH}_2 \end{array}$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Toxicokinetic and other toxicity studies show that formamide is readily absorbed after inhalation, oral and dermal application. Maximum plasma levels are reached within 1 – 2 hours in rats and mice. Elimination half-life from plasma is approx. 15 hours in rats and only 4 - 6 hours in mice. Approx. 30% of the dose is excreted unchanged in urine within 72 hours, a high fraction is excreted as CO² (rats about 30%, mice about 50%), and only minor quantities are excreted with the feces (1 – 3%). Protein binding increased with time in both species. The metabolism depended on the activity of microsomal enzymes, specifically CYP2E1, and in analogy to methylformamide it was proposed that formamide is oxidized to isocyanic acid, which reacts with nucleophils and decomposes in the presence of water to ammonia and CO². The formation of carbon monoxide during metabolism is unlikely. Toxicokinetic studies indicate presence of a first pass effect.

No signs of toxicity and mortality were noted in a rat Inhalation Hazard Test (8 hours, saturated atmosphere, 20°C). Clinical signs of toxicity (irritation of mucous membranes, dyspnea, apathy, and loss of weight) and mortality (one of 12 rats) were seen after an 8-hour exposure when the saturated formamide atmosphere was generated at 150°C. Clinical signs were also seen in all rat groups when very high test substance concentrations were generated either at elevated temperature (100 to 210°C) or using a nebulizer (body weight losses, lethargy, hunched posture, clear or red ocular discharges, red nasal discharge, partially closed eyes, diarrhea, and brown-stained perineum). The inhalation LC₅₀ is > 21 mg/L (4 hr, in the atmosphere generated using an evaporator heated to 100-210°C). The acute dermal LD₅₀ in rats is estimated to be > 3000 mg/kg bw, based on two independent OECD TG 411 90-day repeated dose rat studies. Mortalities were 1/20 and 3/20, respectively, in the groups receiving 3000 mg/kg bw/day. The oral rat LD₅₀ was approx. 5325 mg/kg bw in a pre-guideline study that was conducted similar to the method described in OECD TG 401; a LD₅₀ of 3200 mg/kg bw was calculated in a less robust acute oral rat study.

There was no valid skin irritation study. Formamide was slightly irritating to the rabbit's eye in a test performed corresponding to OECD TG 405. The effects were described as reversible. No valid sensitization study was known to exist.

In a 4-week oral gavage rat study similar to OECD TG 407 male and female rats received 34, 113, 340, and 1130 mg/kg bw/day. No effects were noted at the lowest dose level, whereas 340 and 1130 mg/kg bw/day caused 50% and 100% mortality, respectively. Animals at 113 mg/kg bw/day and higher showed loss of appetite, body weight loss (7 – 11% at 113 mg/kg bw/day and 44 - 51% at 340 mg/kg bw/day), and failure of reflexes. Along with prostration, general organ atrophy and tissue damage (especially of the gastrointestinal tract, testes, adrenal gland and kidney) were noted. Changes in hematological parameters were also observed at 113 mg/kg bw/d. Most of these effects were reversible as the effects were less frequent and almost completely absent in the 14-day recovery group at

113 mg/kg bw/day. Histopathological findings were prominent at the dose of 340 mg/kg bw/day and above where a poor state of nutrition was observed combined with general organ atrophy, gastric ulcerations, intestinal hyperemia, indication of lipid depletion of the adrenal glands including necrotic areas in the cortex and dilation of blood vessels, renal changes, fibrosis of spleen and thymus, and testes degeneration. The NOAEL was 34 mg/kg bw/day; the LOAEL was 113 mg/kg bw/day.

In a 14 day rat inhalation study (similar to OECD TG 412; measured concentrations 0, 190, 930, and 2800 mg/m³), the high dose caused 30% mortality, significantly decreased body weight and body weight gain, and clinical signs of toxicity, weakness and hunched posture. No signs of toxicity or mortality were seen in the other dose groups. Hematology revealed mild thrombocytopenia in the mid and high dose group both during exposure and during recovery, and lymphopenia and hypocholesterolemia in the high dose group. Histopathology showed degeneration/ necrosis of the kidney and testicular degeneration in high dose rats. Based on the hematological findings the NOAEC was set at 190 mg/m³; the LOAEC was 930 mg/m³.

Two 90-day dermal rat studies were available. In the first study (OECD TG 411; applications of 0, 300, 1000, and 3000 mg/kg bw/day), hematological changes in all exposed groups (increased erythrocyte counts and hemoglobin) prevented to derive a NOAEL. Clinical signs (erythema, reduced general condition, apathy, reduced food consumption, decreased body weight) and pathological findings (decreased absolute weights of liver, kidney, spleen, adrenal glands and testes; increased relative weights of liver and kidneys) and an increased incidence of bilateral testicular tubular atrophy were limited to the high dose level. A follow-up study was conducted at lower dose levels (0, 30, 100, 3000 mg/kg bw/day). No substance related effect was seen in the groups at 30 and 100 mg/kg bw/day. Therefore, the NOAEL was 100 mg/kg bw/day based on the described adverse effects at higher doses.

Formamide was not mutagenic in a valid Ames Test (*S. typhimurium* TA100, TA97, TA 98, TA1535, and TA1537) both with and without metabolic activation up to 10000 µg/plate. Formamide did not induce micronuclei in the peripheral blood of male and female mice after oral doses of up to 160 mg/kg bw for 3 months. However, it gave positive results in a micronucleus test using mouse bone marrow (OECD TG 474) following intraperitoneal dosing with 900 mg/kg bw or more. Formamide at 412 mg/kg bw was negative in a Dominant Lethal assay using male mice (OECD TG 478). In conclusion; formamide was not mutagenic *in vitro*, but showed clastogenicity *in vivo* at least at higher doses after intraperitoneal injection.

There are different results from *in vitro* cell transformation assays. Formamide was negative in a cell transformation assay using rat embryo cells at test concentrations of 0.01 to 100 µg/ml whereas a statistically significant and dose-related increase in the number of transformed colonies was obtained with Syrian hamster embryo cells which were exposed to formamide in the range 200 to 550 µg/ml without metabolic activation.

Oral rat and mouse carcinogenicity studies are in progress.

In a continuous breeding study in mice with formamide in drinking water at concentrations of 0, 100, 350, and 750 ppm, reproductive toxicity was observed at 750 ppm (144-226 mg/kg bw/day) in the parental and offspring generation, mainly a decrease in fertility rate and reduction in live litter size. In a crossover experiment, this was shown to be mainly due to impairment of reproduction in females. At 750 ppm (approx. 210 mg/kg/day) a prolongation of the time to litter from 22 to 26 days was seen. The estrous cycle of F1 mice at 750 ppm was extended (6.5 vs. 4.8 days in controls), and the high-dose group tended to be in estrous for a shorter time than controls, and to be longer in diestrous. At necropsy, histopathological examinations revealed no treatment related effect on the non-reproductive tissues. In the reproductive tissues, a significant increase in relative corpus and caput epididymis weight and relative testis weight were noted, along with a decrease in relative seminal vesicle weight at the high dose level. The evaluation of sperm parameters (sperm concentration, motility, morphology, spermatid head count) revealed no treatment-related changes. The absolute and relative ovarian weight was reduced at the mid- and high-dose level. The NOAEL for generalized toxicity was 144 to 226 mg/kg bw/day for the F0 generation. The NOAEL for reproductive toxicity was 48 - 110 mg/kg bw/day for both generations.

Formamide was found to be embryotoxic and teratogenic in several guideline-conform oral gavage studies using rabbits, rats, and mice. The NOAEL values for maternal toxicity, embryo toxicity, and teratogenicity were 70, 70, and 140 mg/kg bw/day, respectively, in a recent rabbit study. In rats NOAELs ranged from 100-529 mg/kg bw/d for maternal toxicity, 50 - 529 mg/kg bw/d for embryo/fetotoxicity and 177 mg/kg bw/d or above for malformations. In mice treated during gestation, embryotoxicity and teratogenicity were seen in the absence of maternal toxicity. The NOAELs were 198 mg/kg bw/day for maternal toxicity and 133 mg/kg bw/day for embryotoxicity and teratogenicity. Mechanistic studies identified susceptible stages during gestation in both rats and mice.

Environment

The colorless to yellowish liquid formamide is slightly viscous, odorless, and hygroscopic. It has a nearly unlimited solubility in water (1000 g/l at 25°C) and a vapor pressure of 0.08 hPa at 20°C. The measured log K_{OW} of -0.82 (25°C) and the calculated BCF of 3.16 do not indicate a potential for bioaccumulation. At 25°C, the estimated K_{oc} is 8.5 and the Henry's Law Constant was calculated to be 0.0016 Pa·m³/mol. According to Mackay Level I modelling, formamide will distribute almost completely into water (99.99%). Formamide is readily biodegradable according to OECD criteria. In the atmosphere, it will be photodegraded by reactions with OH radicals (calculated half-lives: 8.0 days for a 24 hour day with 5.0E05 OH/m³ and 5.4 days for a 12-hour day with 1.5E06 OH/m³).

The rate constant (k) for reaction with photochemically-produced OH radicals in water was measured to be 5.0E+08 l/mol·sec at pH 5.5. Based on best and worst case conditions of OH-radical concentrations in water as measured in a natural lake in Switzerland, half-lives of 64.2 days and 14.7 years, respectively, can be calculated for the aquatic photolysis. Hydrolysis is expected to be slow at neutral conditions. A water rate constant (k_w) of 1.1E-10 s⁻¹ ($t_{1/2}$ = 199 years) at 25°C was estimated. Acidic and basic conditions as well as elevated temperatures accelerate the hydrolysis. The pK_a of -0.48 at 20 °C indicates that at environmentally relevant pH of 6 – 9, the molecule will be present as uncharged species.

Results on acute aquatic toxicity were available for fish (*Leuciscus idus*; 96-h LC_{50} : 6569 mg/l), invertebrates (*Daphnia magna*; 48-h EC_{50} : > 500 mg/l), and algae (*Scenedesmus subspicatus*; renamed to *Desmodesmus subspicatus* 96-h ErC_{50} : > 500 mg/l). Based on the acute toxicity studies, formamide is considered of low acute toxicity to aquatic organisms. In a test with embryos of *Danio rerio*, a 96-h LC_{50} of 9135 mg/l and a 96-h NOEC of 1080 mg/l were determined. Effect concentrations were based on nominal values because none of the tests were supported by analytical monitoring. According to the EU risk assessment procedure, a PNECaqua of 0.50 mg/l was obtained by applying an assessment factor of 1000 on the lowest endpoint.

Ion leakage resulting from membrane damage due to formamide exposure was examined in the aquatic plant *Lemna minor* and in the algae *Desmodesmus subspicatus*. The 24-h EC_{50} was 81.2 mg/l for *Lemna minor* and > 2000 mg/l for *Desmodesmus subspicatus*.

The pooled 96-h LC_{50}/EC_{50} values for mortality and malformation in the embryos of the South African clawed frog *Xenopus laevis*, corresponded to 11400 mg/l and 12800 mg/l, respectively. Multiple malformations like cephalic abnormalities, ocular abnormalities, gut abnormalities, and reduction or lack of pigmentation at exposure concentration $\geq$ 5870 mg/l were observed. Abnormal swimming behavior was observed at concentrations > 5870 mg/l. Growth retardation (reduced length) was observed at concentrations $\geq$ 8500 mg/l.

In a 30 min respiration inhibition test with activated sludge from a laboratory waste water plant treating municipal sewage, a 30-min EC_{50} of > 1000 mg/l was determined. In a 17-h cell growth inhibition test with *Pseudomonas putida*, the 17-h EC_{50} was > 10000 mg/l.

The nitrogen fixation of *Azotobacter sp.* was reduced by 75 - 100% after 21 days of incubation with 500 mg/l formamide.

Exposure

In the sponsor country, formamide is manufactured in a two stage process in which carbon monoxide

and methanol are reacted in the presence of catalytic sodium methoxide to form methyl formate, which is then reacted with ammonia to yield formamide.

The annual world production capacity in 2004 for formamide was estimated at 70,000 - 110,000 tons, subdivided into 50,000 - 80,000 for the sponsor country, 60,000 - 90,000 tons for Europe, 10,000 - 20,000 tons for Asia/Pacific.

In the sponsor country most of the produced formamide is internally converted to hydrogen cyanide (captive use approx. 80%). In addition formamide is used as a starting material in the synthesis of agrichemical and pharmaceutical products and as a solvent in the manufacture of synthetic leather in China.

Formamide is generally known to be used as an intermediate in the chemical industry to produce heterocyclic compounds, copolymers, pharmaceuticals, and crop protection agents such as fungicides as well as many other chemicals. Further, it is applied as softener in the production of pastes and paper and has a wide range of solvent applications. Formamide can also be used as an additive in lube oil or hydraulic fluid, as a component of deicing fluids for airport runways, a curing agent for epoxy resins, a plasticizer, an affinity enhancer for dyes, and a component of liquid fertilizers.

Some of the above mentioned applications were already published a couple of years ago and may not be representative of, or comparable to, current conditions. In the European Union, formamide is classified as Category 2 for reproductive toxicity (may cause harm to the unborn child). As a consequence, formamide or preparations containing it in concentrations equal to or higher than 0.5% may not be placed on the EU market for sale to the general public.

The Swiss Product Register of 2001 has listed two formamide-containing products, both for industrial usage. According to the SPIN database extract for 2004, 8 preparations with a total volume of 2.0 tons are registered in Denmark and 3 preparations in Sweden with a total volume < 0.1 tons. Finland reported that formamide preparations are registered in the national industrial use categories. Consumer preparations containing formamide are not mentioned in the database.

At the production sites, it is technically ensured that exposure of workers to formamide is minimized. Significant exposure is normally not expected during production, transportation, and sampling, because these processes are largely enclosed. Occupational exposure is limited to situations of maintenance and accidental spills. Due to the low vapor pressure of formamide, the potential for inhalation exposure is minimized, with dermal exposure to be the most likely route.

Between 1 Jan 2003 and 31 Dec 2005, 31 workplace measurements were carried out by personal air sampling at BASF AG in Ludwigshafen/Germany. Twenty-five of the 31 measurements were time-weighted averages of 8-hour work shifts. The measurements took place at six locations for production, processing, bottling, shipping, storing and chemical analysis of formamide. All measured values were below the limit of quantification. A significant worker exposure due to inhalation could therefore not be demonstrated.

Natural occurrence of formamide is not known. It may be emitted to the environment as a result of its manufacture and use as an intermediate and solvent. For example, formamide was detected at 2.0 mg/l in condensate retort water of an oil-shale retort, but was not detected in the process retort water. It was also detected in wastewater from a polyamide production plant as well as in the waste streams from an acrylonitrile plant as a result of a detoxification process for cyanide-containing wastewaters. Formamide may also be detected in waste streams due to chemical hydrolysis of cyanide.

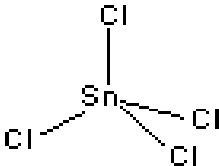
According to the data reported to the German Emission Register 2004, during production and processing at BASF AG in Ludwigshafen/Germany, less than 1 kg of formamide was emitted to air in 2004. Data regarding emission via wastewater treatment effluent are not available from BASF AG production and processing sites.

**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 (genotoxicity, toxicity to reproduction and developmental toxicity). Based on data presented by the sponsor country (related to production by one producer in the sponsor country), exposure to humans is anticipated to be low and adequate risk management measures are in place. 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 has a low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No. (Nos.)	7646-78-8
Chemical Name(s)	Tin Tetrachloride (SnCl ₄)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

In aqueous media, tin tetrachloride rapidly hydrolyzes to form hydrochloric acid (hydrogen chloride, HCl) and inorganic tin (IV) oxide or hydroxides; the oxide and hydroxides are insoluble and form precipitates. HCl (CAS.7647-01-0), the other biologically active hydrolysis product of tin tetrachloride, has already been through the OECD SIDS evaluation process. HCl rapidly dissociates and its effects are thought to be a result of pH change rather than effects of hydrogen chloride/hydrochloric acid. Thus ecotoxicity and mammalian toxicity data for HCl is considered representative of the toxicity to tin tetrachloride.

Human Health

Toxicokinetic studies show that inorganic tin (IV) is poorly absorbed and does not cross the placenta in pregnant rats. Absorption of Sn (IV) via the oral route (i.e., the gastrointestinal tract) has been shown to range from <1% to ca. 8%. Ingested tin is largely unabsorbed and excreted mainly in the faeces, with the absorbed fraction eliminated slowly in the urine. Inorganic tin typically distributes mainly to bone, but also to the liver and kidneys.

For tin tetrachloride, the inhalation LC₅₀ was determined to be 1.35 mg/L for male rats exposed to vapors in humidified air. For HCl, acute oral LD₅₀ values were determined to be 238–277 mg/kg bw for female; inhalation LC₅₀ values were determined to be 23.7–60.9 mg/L/5min, 5.7–7.0 mg/L/30min, and 4.2–4.7 mg/L/60min for rats, and 20.9 mg/L/5min, 3.9 mg/L/30min, and 1.7 mg/L/60min for mice, depending on the exposure period.

Tin tetrachloride is a severe eye irritant and may cause necrosis of the skin. If ingested, tin tetrachloride can cause severe burns of the mouth, throat, and stomach. HCl is corrosive to the skin and severe effects can be expected from exposure to the eyes. Tin tetrachloride did not cause sensitization in rats following mucosal elicitation and is not expected to be a skin sensitizer. HCl is not a skin sensitizer.

A 28-day gavage study of tin tetrachloride administered in milk+Tween 80 at a dose of 798 mg/kg/day produced no mortality and no treatment-related changes in body weight to male and female rats, although these data are limited (i.e., dosing was done in young animals and only a single dose was used). Additional supporting information for tetravalent inorganic tin (a primary hydrolysis product of SnCl₄ at neutral pH) shows that rats fed inorganic tin(IV)oxide at 0, 0.03, 0.10, 0.30, and 1.00% of the diet (~ 0, 23.7, 79, 237 and 790 mg Sn/kg-bw) for 28 days did not show any adverse effects at dietary levels up to 7900 ppm tin (1.0%) in overall weight gain, absolute and relative organ weights, and the gross and microscopic appearance of the liver, heart, kidneys and spleen. For HCl, a NOAEL of 10 ppm was determined for rats and mice in 90-day repeat dose inhalation studies. Liver weight changes (male mice) and histopathological inflammatory changes were seen at higher doses.

Tin tetrachloride was negative in standard and modified Ames tests, and positive in two *in vitro* chromosomal aberration tests. HCl was negative in a standard Ames test. Chromosomal aberration tests of HCl yielded both positive and negative results; however, the positive effect was considered an artifact of low pH. Overall, tin tetrachloride is not considered to be genotoxic.

For HCl, no evidence of treatment-related carcinogenicity was observed in animal studies performed by inhalation, oral, or dermal administration.

No information was available for tin tetrachloride regarding reproduction or developmental toxicity. In reliable 90-day inhalation studies, no effects were observed in the reproductive organs of rats and mice exposed to HCl

up to 50 ppm. Although no information is available on tin (IV) oxide for reproductive and developmental toxicity, available data for other endpoints show that the compound generally has low toxicity and is not expected to be a reproductive or developmental toxicant.

Environment

Tin tetrachloride is a colorless to pale yellow liquid with a melting/freezing point of -33°C and a boiling point of 114°C. The vapor pressure of tin tetrachloride is 24 hPa at 20°C. Tin tetrachloride is violently water reactive and rapidly undergoes chemical change to form tin (IV) oxide or hydrated tin (IV) oxide, hydrochloric acid (HCl), and heat. Stannic chloride pentahydrate is the commercially-available form and is chemically stable under normal conditions of use and storage. Similarly to tin tetrachloride, stannic chloride pentahydrate also will decompose upon exposure to water or to moist air.

The physical/chemical properties of tin tetrachloride make it impossible to maintain tin tetrachloride in preparations to be used for dosing in mammalian or aquatic studies as it rapidly hydrolyzes in water. Tin tetrachloride was not toxic to zebra fish (*B. rerio*) in a limit test (96-h LC₅₀ > 1000 mg/L), and primary productivity was only slightly inhibited in various algal species (IC₅₀ values range from > 11 mg/L to > 110 mg/L). For the ecotoxicity tests with tin tetrachloride, pH adjustment was conducted to stabilize the pH of the tested media. For HCl, a 96-h LC₅₀ of pH 4.3 (equivalent to 4.92 mg/L as test material) was reported for *Cyprinus carpio*, the 48-h EC₅₀ for immobilization of *D. magna* was determined to be pH 5.3 (0.492 mg/L), and the 72-h EC₅₀ and NOEC based on growth rate of the green alga *Pseudokirchneriella subcapitata* were determined to be pH 5.3 (0.492 mg/L) and pH 6.0 (0.097 mg/L), respectively. Tin tetrachloride is not toxic to aerobic bacteria in activated sludge.

The degree to which aquatic ecosystems can resist a change in pH depends on its buffering capacity, and aquatic organisms have different optimum pH conditions. HCl released into the environment is distributed both into water (as ions) and into the air, since HCl exists as a gaseous form at normal temperature and pressure and is very soluble in water. Considering its dissociation properties, HCl is not expected to accumulate in living organisms due to its high solubility. Further, the pH of effluents is frequently measured to maintain the water quality because pH is a key parameter in water quality and can be adapted easily in the aquatic ecosystem. Significant increase of the pH of the receiving water, therefore, is not expected.

Research on stability constants indicates generally stronger affinity of the Sn (IV) ion with oxides/hydroxides than with other anions, such as fluorides and chlorides. Tin (IV) oxide is insoluble in water and is expected to partition primarily to the soil and the sediment. Inorganic tin is relatively immobile and nonvolatile, and bioavailability to organisms tends to be low. Release of inorganic tin from benthic sediments is unlikely, except under highly anoxic conditions.

Exposure

In 2000, worldwide production of tin tetrachloride was estimated at 20,000 to 25,000 tonnes. There is not expected to be any direct consumer exposure to tin tetrachloride in any appreciable amounts. The majority of tin tetrachloride produced is used as a chemical intermediate in the manufacture of other tin compounds, for example, organotin compounds used as PVC stabilizers. Other uses include glass bottle coatings and specialty catalyst applications, including elastomer processing. Analysis shows that in most cases, tin tetrachloride was found at levels less than 0.1% in organotin stabilizers; one exception noted was the presence of ca. 5% tin tetrachloride in monomethyltin trichloride. When used as a chemical intermediate, closed systems control worker exposure and releases. The glass coating applications utilize local control of process vapor, with hoods and exhaust ventilation in the application area. The controlled nature of the applications limits potential for exposure to tin tetrachloride.

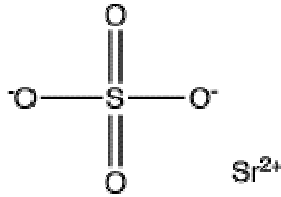
Releases to the environment are expected to only occur as part of the production of this intermediate or its conversion to other organotin chemicals. In the presence of air, tin tetrachloride reacts to generate tin oxide fume and chlorine gas, which may be released during production. Tin (IV) oxide has long been used in industry and is insoluble and nonvolatile. HCl occurs naturally and may be released to the environment from production and user sites. Increasing of the concentration of HCl in water decreases the pH in the aquatic ecosystem; however, generally, there is a buffer capacity to maintain the pH in the aquatic ecosystem.

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

Human Health: This chemical is a low priority for further work. The hydrolysis product of the chemical (HCl) possesses corrosive properties indicating a hazard for human health (acute and repeated-dose toxicity via inhalation and corrosivity to eyes and skin) at relatively low levels during professional use. 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 a low priority for further work. The hydrolysis product of the chemical (HCl) possesses properties indicating a hazard for the environment (acute toxicity to fish, invertebrates and algae due to the acidity of the test solution). This hazard does not warrant further work as it is related to pH effect which may become evident only at high exposure levels. They should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7759-02-6
Chemical Name	Strontium sulfate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There are no specific toxicokinetics data for strontium sulfate.

The acute oral toxicity study [OECD TG 423] and acute dermal toxicity study [OECD TG 402] of strontium sulfate in rats showed that this chemical did not cause any significant changes in body weights at 2,000 mg/kg bw-treated rats. No clinical effects were observed by strontium sulfate after 14 days. Therefore, the acute oral and dermal LD₅₀ values in rats were greater than 2,000 mg/kg bw.

There are no reliable data available for skin/eye irritation and skin sensitization of strontium sulfate.

In a repeated dose oral toxicity study in rats [OECD TG 422], strontium sulfate was administered by gavage to male for 42 days and female rats for 40 to 54 days at doses of 0, 500, 1,000 and 2,000 mg/kg bw/day. No deaths and clinical signs were observed in either sex. However, the high dose exposure of female rats resulted in reduction of reticulocyte and aspartate aminotransferase (AST) values. There were significant decreases of the spleen weights in all treated female groups (approximately 20% in all dose levels). However, this toxicological significant effect is uncertain as no dose response was observed and no histopathological findings were reported. In male rats, a significant increase in the testis weights was seen at dose of 2000 mg/kg bw/day, the NOAEL for this effect was 1,000 mg/kg bw/day. A NOAEL for repeated dose toxicity was not achieved in this study due to reduction of the spleen weight in female rats.

A bacterial reverse mutation assay [OECD TG 471] on strontium sulfate (39-1,250 µg/plate without S-9 mix and 156.3-5,000 µg/plate with S-9 mix) was negative with and without metabolic activation in *Escherichia coli* WP2 uvrA and *Salmonella typhimurium* TA1535, TA100, TA98, TA 1537. An *in vitro* chromosome aberration test using CHL/IU cells [OECD TG 473] was also negative with and without metabolic activation. Therefore strontium sulfate was not genotoxic *in vitro*. There is no data for *in vivo* genotoxicity.

There are no data regarding the carcinogenic potential of strontium sulfate.

In a reproductive/developmental toxicity screening test in rats [OECD TG 422], strontium sulfate was administered by gavage at doses of 0, 500, 1,000 and 2,000 mg/kg bw/day to males for 42 days and females from 14 days before mating to day 4 of lactation. No effect of strontium sulfate was observed on any reproductive performance (fertility, mating rate, birth rate and sex ratio and gestation period etc.) and developmental effects (malformation, etc.) up to 2,000 mg/kg bw/day. The NOAEL for reproductive /developmental toxicity was considered to be 2,000 mg/kg bw/day in rats.

Environment

Strontium sulfate is an odorless white inorganic solid. It occurs in nature as the mineral celestite or celestine. Celestite (SrSO₄) is the most common strontium mineral consisting of strontium sulfate. It is slightly soluble in water (135mg/L at 25 °C), slightly soluble in concentrated acids, insoluble in alcohol and dilute sulphuric acid. It

has a density of 3.96 g/cm³.

Vapour pressure and partition coefficient in n-octanol/water, photodegradation and biodegradation are not applicable due to inorganic properties. This chemical is stable in water and the soluble fraction dissociates in the aquatic environment to strontium and sulfate ions. In acidic to near-neutral pH solutions, dissolution rate of strontium sulfate is fast.

The following studies for aquatic organisms are available:

Fish (*Oryzias latipes*) : LC₅₀ (96 h) > 100 mg/L

Invertebrates (*Daphnia magna*) : EC₅₀ (48 h) > 100 mg/L

Green algae (*Pseudokirchneriella subcapitata*): E_rC₅₀ (72 h) > 100 mg/L (growth rate),
E_bC₅₀ (72 h) > 100 mg/L (biomass)

Exposure

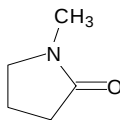
In Korea the imported volumes of strontium sulfate were 63,993, 61,727, and 60,158 tons in 2003, 2004, and 2005, respectively. World production volume of celestite, in the early 1990s, was estimated at ca. 250,000-300,000 tonnes per year. It has been reported that the production figures of celestite (tons) in 1991, Spain, Turkey, United Kingdom, China, Mexico, Iran, and Morocco are 70,000, 65,000, 2,000, 25,000, 90,000, 20,000, and 4,000, respectively. In Korea this chemical was used as major raw material for production of strontium carbonate (SrCO₃). Strontium sulfate is also employed in ceramics and pyrotechnics industry and manufacturing of paints, lacquers, vanishes, glass and paper. The environmental exposure due to dust emission is low resulting from employing bag filters and vent scrubbers to collect particles released during processing. Occupational exposure is maintained low resulting from wearing PPE (person protective equipments) required in all facilities.

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

Human Health: The chemical is of a low priority for further work. The chemical possesses a hazard for human health (repeated dose oral for female). Based on the data presented by the sponsor country (relating to the use pattern and no production in the Sponsor country), exposure to humans is anticipated low. Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	872-50-4
Chemical Name	1-methyl-2-pyrrolidone
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1-methyl-2-pyrrolidone (NMP; N-methylpyrrolidone) is rapidly and well absorbed following inhalation (40% - 60%), oral (~100%) and dermal ($\leq 100\%$ depending on conditions) routes of exposure. In rats, NMP is distributed throughout the organism and eliminated after hydroxylation to polar compounds *via* the urine. About 80% of the administered dose is excreted as NMP and NMP metabolites within 24 hours. The major metabolite is 5-hydroxy-N-methyl-2-pyrrolidone (5HNMP). Studies in humans show that NMP is rapidly biotransformed to 5HNMP, which is further oxidized to N-methylsuccinimide (MSI); this intermediate is further hydroxylated to 2-hydroxy-N-methylsuccinimide (2HMSI). The excreted amounts of NMP metabolites in the urine after inhalation or oral intake represented about 100% and 65% of the administered doses, respectively. Excretion of 5HNMP is useful as a biological marker for NMP exposure.

Dermal penetration through human skin has been shown to be very rapid and the absorption rate is in the range of 1 - 2 mg/cm²/h, which is 2 to 3-fold lower than those observed in the rat. Prolonged exposures to neat NMP was shown to increase the permeability of the skin. Water inhibits dermal absorption while organic solvents (*e.g.*, d-limonene) can increase it. The dermal penetration of 10% NMP in water is 100-fold lower than that of neat NMP, while dilution of NMP with d-limonene can increase the absorption of NMP by as much as 10-fold. The dermal absorption of neat NMP indicated that dermal absorption 1 hour post-exposure was greatest under unoccluded (69%), followed by semi-occluded (57%) and occluded (50%) conditions.

Oral LD₅₀ values range from 3605 - 7725 mg/kg bw in rats and mice and dermal LD₅₀ values range from 5000 - 7000 mg/kg in rats. Reliable inhalation exposure studies were generally conducted with vapor/aerosol mixtures. The representative LC₅₀ was >5.1 mg/l/4h in rats.

NMP is a mild skin and eye irritant in rabbits. In humans, NMP is not irritating to the eyes and upper respiratory tract but is a skin irritant. No valid animal data on skin sensitization exist. Experience at the workplace does not indicate such an effect. In rats, repeated exposure to aerosols under whole body conditions causes severe toxic effects (lethargy, respiratory effects and mortality at high exposures) as a consequence of mixed oral (grooming), dermal and inhalation exposure.

However, after 90-day head-nose aerosol exposures of NMP in rats, only high concentrations caused systemic effects including testicular damage and local respiratory tract irritation. The no observed adverse effect concentration (NOAEC) was 0.5 mg/l. Repeated dermal exposure to rabbits led to mortality at high dose levels without other signs of systemic toxicity. The no observed adverse effect level (NOAEL) was 826 mg/kg bw, while 413 mg/kg bw was the lowest observed adverse effect level (LOAEL) for local irritation. Repeated oral administration did not lead to the identification of a target

organ for systemic toxicity, although systemic effects were observed (decreased body weight, testicular atrophy, thymic atrophy, swelling of distal kidney tubuli). In all species tested, urine discoloration was the only indicator of systemic availability of NMP. In a 4 week feeding study in rats, unspecific signs and adaptive liver effects were observed. The NOAEL was 6000/18000 ppm (429/1548 mg/kg bw, males/females). In a 90-day oral study in rats, the liver and kidney weights were increased and hepatocellular hypertrophy in females was the only histopathological finding. Males exhibited slight and reversible neurological alterations in a few parameters (increase in foot splay, higher incidence in low arousal and slight light palpebral closure) mainly suggestive of a mild sedative effect, which is not considered an indication for specific neurotoxicity. The NOAEL was 3000 ppm for both sexes (169/217 mg/kg bw, males/females). In a 4 week dietary oral study in mice, renal impairment was observed. The NOAEL was 2500 ppm for both sexes (820 mg/kg bw). In a 90-day feeding study in mice, adaptive liver effects in the form of increased weight and histopathological findings were observed. The NOAEL was 1000 ppm (about 229/324 mg/kg bw, males/females). In dogs, no substance-related findings were observed. The NOAEL was the highest dose level tested (250 mg/kg bw).

NMP showed no mutagenic/genotoxic potential in several bacterial and mammalian test systems *in vitro*, covering different genetic endpoints (point mutations, DNA damage and repair). *In vivo* no clastogenic or aneugenic potentials of NMP were reported for somatic or germ cells. NMP showed no oncogenic potential in the rat after long-term exposure *via* inhalation or dietary administration. However, in mice, NMP revealed an oncogenic potential (liver tumors) at very high oral dose levels exceeding 1,000 mg/kg bw.

Two oral reproduction toxicity studies in Sprague-Dawley and Wistar rats caused pup mortality at parental toxic dose levels (350 mg/kg bw and higher). No effects on fertility parameters were noted including histopathological examinations of the male/female reproductive systems. The NOAEL for reproduction was 350 mg/kg bw and the NOAEL for developmental toxicity was 160 mg/kg bw. In an inhalation reproduction toxicity study there was no effect on reproductive performance or fertility to rats exposed to 116 ppm. The NOAEC was 116 ppm for reproductive toxicity and 50 ppm for maternal and developmental toxicity (decreased fetal weight). NMP, but not its metabolites, was embryotoxic (whole embryo culture test) *in vitro* and *in vivo* (oral rat). Several studies addressed prenatal developmental toxicity *via* the inhalation, dermal and oral exposure routes in rats and rabbits. No adverse effects were observed at the highest achievable vapor concentration of 120 ppm. When administered *via* the dermal route, malformations in rats but not rabbits were observed at high dose levels (NOAEL 235 mg/kg bw). *Via* the oral route, embryotoxicity and malformations were noted with NOAELs of 125 mg/kg bw in rats and 175 mg/kg bw in rabbits in the presence of maternal toxicity. However, the developmental effects are not considered secondary to maternal toxicity.

Environment

The colorless liquid 1-methyl-2-pyrrolidone (NMP) has a melting point of -23.5 °C, a boiling point of 204.1-204.4 °C at 1013 hPa and a vapor pressure of 0.32 hPa at 20 °C. The solubility of NMP in water is 1,000 g/l. The measured log P_{ow} of -0.46 (25 °C) and the calculated BCF of 3.16 do not indicate a potential for bioaccumulation. The estimated Koc is 20.94. The Henry's law constant of $3.2 \cdot 10^{-4}$ Pa·m³/mol was measured at 20 °C and indicates low volatility from water. The SPARC-calculated pKa of 0.93 indicates that at environmentally relevant conditions, the molecule will occur almost entirely as uncharged species. According to Mackay Level I modeling, NMP will distribute almost completely into water (99.9 %). With Mackay Level III modeling using equal distribution to all compartments, NMP partitions to soil (56.4 %), water (43.2 %) and air (0.4%). NMP is readily biodegradable according to OECD criteria. In the atmosphere, it will be photodegraded by reactions with OH radicals (calculated half-life for a 12-hour day and $1.5 \cdot 10^6$ OH/cm³: 5.8 hours; for a 24-hour day and $0.5 \cdot 10^6$ OH/cm³: 17.5 hours). Hydrolysis in water is not expected to occur due to the lack of hydrolyzable functional groups.

Results on acute aquatic toxicity were available for fish (*Oncorhynchus mykiss*; LC₅₀ (96 hours) > 500 mg/l, nominal, based on analytical verification), invertebrates (*Daphnia magna*; EC₅₀ (24 hours) > 1,000 mg/l, nominal), and algae (*Scenedesmus subspicatus*; EC₅₀ (72 hours, nominal) > 500 mg/l). In a chronic toxicity test on reproduction of the water flea *Daphnia magna*, the NOEC (21 days) was 12.5 mg/l (nominal, based on analytical verification).

Exposure

Large-scale production of NMP is predominantly carried out in a continuous process by reaction of gamma-butyrolactone with methylamine. The annual world production capacity of NMP in 2003 was estimated at 100,000 to 150,000 tons, subdivided into 30,000 – 50,000 tons/year for Europe (3 production sites), 60,000 – 80,000 tons/year for USA (3 production sites), and 10,000 – 20,000 tons/year for Asia/Pacific (4 production sites). During 2005, the European production capacity was reduced to about 20,000 – 30,000 tons. NMP is used as an intermediate and as a solvent by a wide variety of industries such as petrochemical processing, producers of electronics, cleaners, coatings, pharmaceuticals, agricultural and photographic chemicals. Most of the NMP-containing consumer products are household and car cleaning agents, paints, adhesives and sealants, paint removers, and coated fabrics. The NMP content varies from 1 – 100 %.

The Swedish Product Register of 2003 quantifies the total number of registered NMP-containing products with 471, resulting in a total volume of 1,264 tons NMP/a. The total number of consumer products is given with 73. The Danish Product Register of 2004 includes 809 products with a total quantity of 609 tons NMP per year. The Swiss Product Register from 2005 states 2018 registered NMP-containing products for industry and 414 products for consumer use.

Environmental release of NMP occurs from industries such as textile, paper, furniture, printing, chemicals, plastics, and leather. Depending on the industrial leachate site, NMP was found in waste water concentrations ranging from 0.001 to 5 mg/l. Due to the ready biodegradability, NMP is quickly eliminated from water. This is confirmed by measurements of NMP levels in the influent and effluent of the waste water treatment plant of BASF AG (Ludwigshafen, Germany). Results from the year 2000 showed NMP levels in the effluent that were always below the limit of quantification. The elimination was calculated to be > 95 %. During production and internal processing at BASF AG (Ludwigshafen, Germany), 112 kg/a were emitted into the air in 2004. According to the information in the U.S. Environmental Protection Agency (USEPA) Toxics Release Inventory database for 2004, the total reported emissions of NMP were 6,311,272 lbs (2,862 tons). In the United States, NMP is registered as a pesticide inert and exempt from the requirement of tolerance by the USEPA, as described by 40 C.F.R. 180.920. NMP is also regulated by Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) and Section 6607 of the Toxic Chemicals and the Pollution Prevention Act.

Occupational exposure to NMP is most likely via the dermal route of exposure. However, manufacturing and distribution processes utilize closed system engineering practices to eliminate/reduce potential exposure to NMP. In addition, adequate ventilation and chemical-specific personal protective equipment (PPE) is utilized for additional protection. Depending on the type of industry and work place, breathing zone samples showed airborne NMP concentrations in the range 0.01 – 25 ppm with peak concentrations of up to 70 ppm. The American Industrial Hygiene Association (AIHA) has established a Workplace Environmental Exposure Level (WEEL) 8-hr time-weighted average (TWA) of 10 ppm for skin exposure.

In the United States, consumer exposure to NMP may result from the use of products containing NMP. However, NMP use in consumer products in the European Union is under review. In the European Union, NMP is classified as Category 2 for reproductive toxicity (may cause harm to the unborn child). Consumers may be exposed to NMP from tobacco smoke or other NMP emitting sources like floor varnish, sealants and wall paints. Consumer exposure to NMP containing products has been evaluated by the USEPA, and its use as a pesticide inert is regulated. Private and public indoor air sample analyses revealed NMP concentrations of up to 0.3 mg/m³. In Berlin, Germany, the arithmetic mean of 744 indoor air samples was 0.015 mg/m³. The median of < 0.002 mg/m³ indicated that NMP was often not found in indoor air samples above the limit of detection.

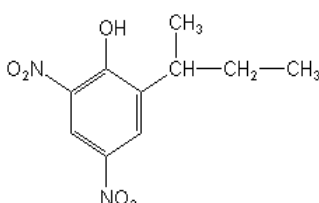
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical possesses a hazard for human health (skin/eye/respiratory irritation, repeated dose toxicity and reproductive/developmental effects). 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.	88-85-7
Chemical Name	2-sec-butyl-4,6-dinitrophenol (Dinoseb)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In young and adult female Fischer 344 rats, dermal absorption appeared to be biphasic. In six hours young and adult rats absorbed about 44% of the dose, while at 120 hours 75.9% was absorbed in young and 92.5% in adults. Adults excreted about 70% of the total recovered dose in urine, 16% in faeces and retained 7% in the body at 120 hours. HPLC analysis of urine collected at 24 hours from adults showed extensive metabolism of the parent compound. Blood had the highest concentration of 2-sec-butyl-4,6-dinitrophenol-derived radioactivity of the tissues examined.

In pregnant Swiss Webster mice, dosed by either intraperitoneal injection or gavage on gestation day 11, [¹⁴C]-2-sec-butyl-4,6-dinitrophenol crossed the placenta and reached the embryo although a barrier to transfer was present as embryonic levels never exceeded 2.5% of maternal plasma levels. Peak embryonic levels of radioactivity were similar but reached much earlier after intraperitoneal than oral administration. In maternal animals, radioactivity reached all tissues. The elimination rate constant was 0.02/hr after gavage and 0.09/hr after intraperitoneal injection. Between 67 and 78% of the administered dose was recovered in urine and faeces within 64 hours of the administration of a single dose of the test substance, regardless of the route of administration.

The inhalation LC₅₀ is 35-130 mg/m³ for 4-hr exposure in rats, and laboured breathing and decreased activity were observed. The dermal LD₅₀ is 40-146 mg/kg bw in rabbits, and decreased activity, salivation, nasal discharge, increased respiratory rate and ataxia were found. The oral LD₅₀ is 5-50 mg/kg bw in rats, and prone position, bradypnea, diarrheal stool and decreased motor activity were noted.

No valid information is available concerning skin irritation. 2-sec-Butyl-4,6-dinitrophenol is highly irritating to the eye in rabbits. No information is available regarding sensitization.

In a combined repeated dose toxicity study with reproduction/developmental toxicity screening test, conducted according to OECD TG 422, Crj:CD(SD)IGS rats were given 2-sec-butyl-4,6-dinitrophenol by gavage at 0 (vehicle), 0.78, 2.33 or 7 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. In males, no deaths were observed in any of the groups. At 7 mg/kg bw/day, seven females died on gestation day 19 and one on gestation day 21 and one animal was moribund on each of gestation days 19 and 20. The LOAEL for males and NOAEL for females were 0.78 mg/kg bw/day, based on increases in hematocrit in males at 0.78 mg/kg bw/day and decreased extramedullary hematopoiesis of the spleen in females at 2.33 mg/kg bw/day.

In a developmental toxicity study conducted according to EPA guidelines, New Zealand White rabbits were dermally applied with 2-sec-butyl-4,6-dinitrophenol at 0, 1, 3, 9 or 18 mg/kg bw/day for six hours per day on gestation days 7 through 19. The NOEL for dermal toxicity was 1 mg/kg bw/day for females, based on maternal

mortality and hyperthermia.

2-sec-Butyl-4,6-dinitrophenol was not mutagenic in bacteria [OECD TG 471 and 472] and did not induce chromosomal aberrations in mammalian cells *in vitro* [OECD TG 473] either with or without metabolic activation.

Limited carcinogenicity studies are available in rats and mice. Based on the data available there is no indication of carcinogenic effect.

In above mentioned OECD TG 422 study in rats, sperm analysis in males at the end of the administration showed that there were no significant changes at 0.78 and 2.33 mg/kg bw/day in any of the sperm tests. At 7.0 mg/kg bw/day, motile sperm rate, progressive sperm rate, path velocity and viability rate were significantly increased, and the amplitude of lateral head displacement, abnormal sperm rate and abnormal tail rate were significantly decreased. In addition, the survivability rate and abnormal head rate tended to be higher without significant difference. At completion of the recovery period, there were no significant changes in any of the sperm tests at 0.78 and 2.33 mg/kg bw/day. At 7.0 mg/kg bw/day, the viability rate and survivability rate were significantly decreased and the abnormal sperm rate and abnormal head rate were significantly increased. In females, the gestation index was lowered at 7 mg/kg bw/day (8.3% compared with 100% in controls). No changes attributable to the chemical were noted in the number of estrous cases, copulation index, number of conceiving days, number of pregnant females, fertility index, gestation length, delivery or nursing conditions, number of corpora lutea, number of implantation sites or the implantation rate. In offspring, no changes attributable to the chemical were noted in the total number of births, number of stillbirths, number of live neonates, sex ratio, delivery index, birth index, live birth index, general condition, number of live neonates on day 4 and viability index on day 4, external anomalies, body weight and autopsy of offspring at 0.78 and 2.33 mg/kg bw/day. The NOEL for reproductive and developmental toxicity was 2.33 mg/kg bw/day based on sperm mortality and morphology in males and gestation index in females.

In a developmental toxicity study, DC rats were dosed by gavage 2-sec-butyl-4,6-dinitrophenol at 0, 2.5, 5, 10 or 15 mg/kg bw/day or were fed a diet containing this substance at 200 ppm (approximately 15 mg/kg bw/day) on gestation days 6 to 15. Maternal body weight gain was reduced at 10 and 15 mg/kg bw/day by gavage and 200 ppm by feeding. A significantly lowered weight and delayed ossification in fetuses at 15 mg/kg bw/day and increased incidence of fetuses with skeletal variations at 10 and 15 mg/kg bw/day were found after gavage. A significantly lowered fetal weight and increased incidence of fetuses with microphthalmia were noted after feeding. The NOAEL for maternal and developmental toxicity was 5 mg/kg bw/day based on decreased maternal body weight gain and fetal skeletal variations.

In an EPA guideline study, New Zealand White rabbits were dermally applied with 2-sec-butyl-4,6-dinitrophenol at 0, 1, 3, 9 or 18 mg/kg bw/day for six hours per day on gestation days 7 through 19. Maternal mortality and hyperthermia were found at 3 mg/kg bw/day and higher. The number of live fetuses was reduced at 9 mg/kg bw/day. Significantly increased incidences of fetuses with cleft palate, microcephaly, hydrocephaly, microphthalmia and anophthalmia were noted at 9 mg/kg bw/day. Hydrocephaly and anophthalmia were also present in the fetuses at 3 mg/kg bw/day. The NOEL for maternal and developmental toxicity was 1 mg/kg bw/day based on maternal mortality and hyperthermia and fetal hydrocephaly and anophthalmia.

Based on the studies described above, this chemical is a reproductive and developmental toxicant.

Environment

2-sec-Butyl-4,6-dinitrophenol is a solid at room temperature. Melting point, boiling point and vapour pressure are 40.6 °C, > 300 °C, 9.77×10^{-3} Pa (25 °C) respectively. Partition coefficient (Log P_{ow}) and water solubility are 3.57 (neutral form) and 34.5 mg/L at 20 °C respectively. Hydrolysis test according to TG111 shows no hydrolysis at pH4, pH7 and pH9 at 50 °C for 5 days. As the acid dissociation constant (pKa) is 4.47, 2-sec-butyl-4,6-dinitrophenol mainly exists in its dissociated form at environmentally relevant pH values. Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life of 31.82 hours. Half-lives of 22 h and >30 h for direct photolysis in aqueous solution are calculated based on measured first order rate constant for the neutral and dissociated species respectively. 2-sec-butyl-4,6-dinitrophenol is not readily biodegradable under aerobic conditions (BOD = 0 %). 2-sec-Butyl-4,6-dinitrophenol does not have a bioaccumulation potential based on the results of bioaccumulation tests (BCF: <0.3 - 1.0 at exposure level of 10 µg/l, <2.5 at exposure level of 1.0 µg/l). Fugacity modelling is based on the assumption that the substance is present in its neutral form in the aqueous compartments. Fugacity Model Mackay level III calculations indicate that 2-sec-butyl-4,6-dinitrophenol

will be distributed mainly to soil (59.8 %), air (29.9 %) and water (9.51 %) compartments if released to air. If released to water, 2-sec-butyl-4,6-dinitrophenol will distribute mainly to water (91.6 %) and sediment (7.8 %). If released to soil, 2-sec-butyl-4,6-dinitrophenol will be distributed almost exclusively to the soil compartment (99.6 %). If released simultaneously to air, soil and water, 2-sec-butyl-4,6-dinitrophenol will be distributed mainly to soil (79.8 %) and water (17.4 %) compartment. Henry's Law constant is 4.43×10^{-6} atm.m³/mole at 20 °C.

Acute toxicities of 2-sec-butyl-4,6-dinitrophenol to aquatic organisms available from reliable tests are:

Fish (8 species)	48 h or 96 h -LC ₅₀	= 0.032 - 0.54 mg/L
Daphnids (<i>Daphnia magna</i>)	48 h EC ₅₀	= 0.24- 0.74 mg/L
Invertebrate (Scud)	96 h- L(E)C ₅₀	= 1.8 mg/L
Algae (<i>Pseudokirchneriella subcapitata</i>)	72 h E _r C ₅₀	= 0.49-1.4 mg/L, 72 h E _b C ₅₀ = 0.81 mg/L

The chronic toxicities aquatic organisms are:

Lake trout	NOEC (fry weight)	< 0.0005 mg/L
Fathead minnow	NOEC (fry weight, mortality)	= 0.0145 mg/L
Daphnids (<i>Daphnia magna</i>),	21-d EC50 (reproduction)	= 0.17 mg/L
	21-d NOEC (reproduction)	= 0.062 mg/L.

Algae(*Pseudokirchneriella subcapitata*) NOECb (72h) = 0.19 mg/L , NOECr (72h) = 0.36 mg/L.

The terrestrial toxicities to higher plants and birds are shown in below. However results from efficacy field trials are difficult to interpret for the assessment of the toxicity of 2-sec-butyl-4,6-dinitrophenol to crop and target species because the exposure concentrations in the soil cannot be reliably determined from treatments expressed in units of kg/ha:

Higher plants (3 spp.)	emergence after a 24hr aqueous exposure	EC ₅₀ = 3.1-4.0 mg/L
Higher plants(7 crop spp)	10-18 d-EC ₅₀	= 3.8 - 25 kg/ha (at high temperature)
	10-18 d-EC ₅₀	= 9.1 - 43 kg/ha (at low temperature)
Higher plant (4 target spp)	42 d EC ₅₀	< 0.56 - 1.12 kg/ha
Higher plants (3 spp.)	the inhibition rates of 0 to 53 %	= 0.01 – 0.06 kg/ha.
Birds (3spp.) dietary acute	8 d LC ₅₀	= 410 - >540 ppm.

Exposure

The volume of 2-sec-butyl-4,6-dinitrophenol imported into Japan were estimated at 215 tons in 2004 and 110 tons in 2005. No 2-sec-butyl-4,6-dinitrophenol seems to be produced in Japan. In Japan, 2-sec-butyl-4,6-dinitrophenol is used as a polymerization inhibitor. This chemical was used as a pesticide in the past, but this use is not allowed now in the sponsor country. Although the pesticide use is not allowed in many OECD member countries for long time, the residue of 2-sec-butyl-4,6-dinitrophenol in the environment might remain as this chemical is not readily biodegradable. No consumer use is known for 2-sec-butyl-4,6-dinitrophenol.

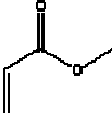
According to the Japanese PRTR (Pollutant Release and Transfer Register) system, the released amount to the environment or transferred amount to off site of 2-sec-butyl-4,6-dinitrophenol should be reported to the authority. However, there were no reported releases or transfers of 2-sec-butyl-4,6-dinitrophenol from users or manufactures in Japan in 2002, 2003 and 2004. Use of 2-sec-butyl-4,6-dinitrophenol as a polymerization inhibitor may result in its release to the environment through waste water streams. However, 2-sec-butyl-4,6-dinitrophenol is processed in a closed system. According to these information, it is concluded that significant environmental exposure of this chemical is not expected in the sponsor country.

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 hazards for human health (acute toxicity, irritation, repeated dose toxicity, reproductive and developmental toxicity). Based on data presented by the Sponsor country (relating to use and no production in the Sponsor country, global production is unknown) and relating to the use pattern in the Sponsor country, 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 a candidate for further work. The chemical possesses properties indicating a hazard to the environment (acute toxicity in the environment, chronic toxicity in fish and daphnids, acute toxicity in terrestrial higher plant, not readily biodegradable). Therefore, member countries are invited to perform an exposure assessment, a terrestrial (invertebrates e.g. earth worm) hazard assessment and, if necessary, a risk assessment for the environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	96-33-3
Chemical Name	Methyl Acrylate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Methyl acrylate is readily absorbed by all exposure routes and rapidly hydrolyzed by carboxyesterases to acrylic acid and methanol. Greater than 90% is excreted within 72 hours, primarily via the lungs (> 50%) as CO₂, and kidneys (40-50%) as products of glutathione conjugation.

The acute toxicity of methyl acrylate is moderate by the oral, dermal and inhalation routes: LD₅₀ rat (oral): 765 mg/kg bw; symptoms: staggering, apathy, labored breathing; LC₅₀ rat (inhalation, vapor): 5.7 mg/L/4h; symptoms: respiratory tract and eye irritation; LD₅₀ rabbit (dermal): 1250 mg/kg bw; symptoms: not reported. Methyl acrylate is highly irritating to the skin, eyes, and mucous membranes of animals and humans. It may cause serious damage to eyes. Methyl acrylate was shown to induce contact sensitivity in animals and humans. Cross-reactivity to other acrylates and methacrylates is known to occur.

In repeated-dose studies, the main effects observed following inhalation exposure were irritation of the respiratory tract and mucous membranes. Systemic effects were mainly associated with changes in body weights and organ weights. In a two-year bioassay, rats were exposed via inhalation to methyl acrylate at 15, 45, 135 ppm (0.058, 0.173, 0.519 mg/L) in which a concentration-dependent opacity and neovascularization in the rat cornea, and degeneration of the olfactory epithelium were observed. The only systemic effects observed were a slight and reversible delay in body weight gains along with changes in organ weights without histological correlation (mainly in the highest dose group.) The LOAEC for nasal (slight degeneration of the olfactory epithelium) and ocular effects was 15 ppm (0.058 mg/L).

In a sub-chronic inhalation study (12 weeks) with rats exposed to 23, 124, 242, 626 ppm (0.082, 0.44, 0.86 2.23 mg/L), reduced body weight gain was seen to be treatment related in the 124-626 ppm groups (0.440 –2.23 mg/L). Increased relative lung and relative liver weights were observed in the 242 ppm group, and in the females of the 124 ppm group without detectable microscopic changes in these organs. Absolute organ weights of heart, liver, kidney and spleen were decreased in males of the 242 ppm dose group; absolute spleen weight of males was also reduced in the 124 ppm group. The NOEC was 23 ppm (0.082 mg/L). The LOEC was 124 ppm (0.44 mg/L) (reduced body weight, reduced organ weights.) The NOEL following a 3-month oral administration to rats in drinking water was 5 mg/kg bw. At 20 mg/kg bw/d an increased incidence of a renal disease was observed together with an increase in the mean relative kidney weights.

In vitro, methyl acrylate was negative in a variety of studies for point mutation both in the presence (Ames test only) and in the absence of metabolic activation, but induced chromosome aberrations in Chinese hamster cells in the absence of metabolic activation. Reliable animal mutagenicity studies do not suggest a clastogenic potential under *in vivo* conditions.

Methyl acrylate was not carcinogenic in a 2-year inhalation study in Sprague-Dawley rats up to the highest tested dose of 135 ppm (0.519 mg/L).

Although no reproductive toxicity studies were available, methyl acrylate showed no adverse effects on reproductive organs in well-performed repeated-dose inhalation and oral studies. Inhaled methyl acrylate was not toxic to the embryo or fetus, except at concentrations that produced overt maternal toxicity in a developmental toxicity study in rats. The NOEL for maternal toxicity was 25 ppm (0.089 mg/L), the NOEL for developmental effects (fetotoxicity) was 50 ppm (0.179 mg/L), and the NOEL for developmental effects (teratogenicity) was 100 ppm (0.358 mg/L) (highest dose tested).

Environment

The water solubility of methyl acrylate is 52 g/L (25 °C) and specific gravity is 0.956 g/cm³ at 20 °C. The measured log K_{ow} is 0.74. The vapor pressure is 89.2 hPa at 20 °C. The melting point is - 75°C and the boiling point is 80 °C. Methyl acrylate is highly flammable and has explosive properties. Methyl acrylate is photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 13.6 hours (calculated). The hydrolysis rate of methyl acrylate is low. At pH 7, the half-life is > 28 days. Distribution modeling using Mackay Level I indicates that the main target compartment will be air (83.58 %) with smaller amounts partitioning into water (16.4 %) soil (0.1 %) and sediment (0.1 %). Fugacity model Level III, using US EPA TRI data for realistic release percentages, shows similar results: 92.2 % (air), 7.25 % (water), 0.56 % (soil) and 0.0127 % (sediment). A BCF of 3.162 was determined, based on a log K_{ow} of 0.74, indicating a low bioaccumulation potential. Methyl acrylate attained 59.8% biodegradation within 28 days in a closed bottle test according to OECD 301 D. In a CO₂-Headspace test according to ISO 14593 (identical to OECD Test Guideline 310), methyl acrylate was readily biodegradable (99. % TIC of ThIC after 28 days).

Methyl acrylate is reported to have acute toxicity to aquatic organisms based on measured concentrations. The most sensitive fish species reported was sheepshead minnow (*Cyprinodon variegatus*) with a 96-h LC₅₀ value of 1.1 mg/L. In aquatic invertebrates, the 48-h EC₅₀ for *Daphnia magna* was 2.6 mg/L. In algae, (*Selenastrum capricornutum*) the 72-hr EC₅₀ for growth rate and biomass were 3.55 and 2.02 mg/L, respectively. The 96-hr EC₅₀ for growth rate and biomass were 4.75 mg/L and 1.99 mg/L, respectively. In activated sludge, the inhibition of respiration for microorganisms was reported as a 5-d EC₅₀ value >100 mg/L.

Exposure

Methyl acrylate is manufactured as a chemical intermediate in a closed system. Its primary use is as a co-monomer in the preparation of polyacrylic fibers, in the manufacture of plastics, coatings, dispersions, flocculants and varnishes and in organic synthesis.

The worldwide annual production volume of methyl acrylate is between 100,000 and 200,000 tonnes. In 2000, three sites in Europe were reported to have produced a total of 50,000 to 100,000 tonnes and two sites in the NAFTA region were reported to have produced a total of 50,000 to 100,000 tonnes. In the US, six companies were reported to have produced a total of 45,000 to 127,000 tonnes in 1998. In 2000, US TRI reporting indicates that the majority of methyl acrylate was released to the air compartment (95%, 320,278 pounds). However, a small percentage was released to the water compartment (0.09%, 294 pounds).

In Western Europe, emissions from the production of methyl acrylate averaged 70 g/tonne (to water) and 30g/tonne (to air) produced. From polymer production plants using methyl acrylate, emissions were up to 1 g/tonne (to water) and around 5 g/tonne (to air). Negligible releases to the water compartment from residues in polymers are expected. Impact on the environment is expected to be low due to photolysis and biodegradative properties of methyl acrylate. Extensive occupational exposure monitoring records are available which indicate that 8 hr TWAs for a variety of operations were generally below the regulatory/guideline values. However, peak exposures were reported that in some circumstances exceeded the NIOSH REL of 10 ppm (TWA) during sampling, cleaning, filter cleaning and inhibitor preparation. Records indicate that personnel performing these tasks wear the appropriate personal protective equipment and therefore, exposures to personnel are estimated to be lower depending upon protection factors of the personal protective equipment. End use consumer products contain only trace levels of acrylic acid and esters (as a result of polymerization). Residual monomer concentrations in consumer polymer products are very low and releases are negligible. Therefore, consumer exposure to acrylate monomers is likely to be low.

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

The chemical possesses properties indicating a hazard for human health (skin sensitization, skin, and eye irritation) and the environment. Based on data presented by the Sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently a low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

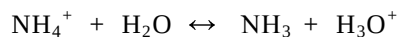
CAS Nos.	7664-41-7; 1336-21-6; 7783-18-8; 12593-60-1
Chemical Names	<u>Ammonia category</u> : ammonia, aqueous ammonia, ammonium thiosulfate, ammonium phosphate sulfate
Structural Formula	NH ₃ ; NH ₄ OH; (NH ₄) ₂ S ₂ O ₃ ; (NH ₄) ₂ H ₂ PO ₄ HSO ₄

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The ammonia category includes anhydrous ammonia, aqueous ammonia, ammonium thiosulfate and ammonium phosphate sulfate. In biological fluids and in aquatic environments, every substance of the category will dissociate to yield, respectively; ammonium ion (NH₄⁺), hydroxide ion (OH⁻), thiosulfate ion (S₂O₃²⁻), phosphate ion (H₂PO₄⁻) and sulfate ion (SO₄²⁻). Each of the compounds of the category contains the ammonia/ammonium ion functional group. The sulfate, thiosulfate and phosphate ions are normal constituents of the blood, and when in excess, are excreted via the urine. Among these compounds, *un-ionized* ammonia is considered the most toxic and is the basis for read-across for the category members.

The category is based on the dissociation of all the category members into the ammonium ion (NH₄⁺) and the corresponding anions in aqueous environments, where the ammonia/ammonium ion will exist in equilibrium between NH₃ and NH₄⁺, depending on the pH. At ambient environmental conditions, the category members are stable substances that show normal acid/base chemical activity with the following equilibria:



Thus for many environmental conditions (pH =5 to 8), the predominant form will be NH₄⁺. At pH =9 the ratio of ammonia to ammonium ion (NH₃/ NH₄⁺) should approach unity; at higher pHs the proportion of ammonia (NH₃) should increase. As inorganic salts that ionize in the aquatic environment, the category members can be considered chemically and structurally similar for the purposes of this category evaluation. As pH decreases, the concentration of ammonium ion increases with respect to decreases of unionized ammonia concentrations. However, the toxicity of the unionized ammonia is considered several orders of magnitude greater than the more abundant ammonium ion. The ammonium ion toxicity is considered to contribute to the overall toxicity.

Analog Rationale

Data for ammonium sulfate (SIAM 19; CAS No. 7783-20-2), sodium sulfate (SIAM 20; CAS No. 7757-82-6), ammonium chloride (SIAM 17; CAS No. 12125-02-9), sodium thiosulfate (CAS No.

7772-98-7) and di-ammonium phosphate (SIAM 24; CAS No. 7783-28-0) are used to fill the data gaps for SIDS endpoints. These substances all dissociate to their respective cations and anions at physiological pH, whose data are used to support the respective cations or anions of the category members.

Human Health

After uptake into a biological system the salts in the ammonia category will dissociate directly into ammonium ion and the corresponding anions, i.e. phosphate, thiosulfate and sulfate. The anions will enter the body electrolyte pool, and are not expected to play a significant toxicological role at low doses. After intestinal absorption, ammonium ions are converted to urea in the liver, and subsequently excreted in urine (within 6 hours). The ratio of ammonium ion to neutral ammonia is about 100 in blood of normal pH range.

The acute oral LD₅₀ values range from 1,950 to >2,000 mg/kg bw in rats for the ammonium salts. Aqueous ammonia has a higher oral toxicity (LD₅₀ of 350 mg/kg bw in rat) than the other compounds in the group. Clinical signs include sedation, staggering, abnormal posture, convulsions, tremors, ataxia, prostration, ptosis, exophthalmus, chromodacryorrhea, unilateral ocular opacity, salivation, labored and irregular breathing and diarrhea. Acute dermal LD₅₀ values are >2,000 mg/kg bw for ammonium sulfate and diammonium phosphate (DAP). The inhalation LC₅₀ values range from >900 mg/m³ for ammonium sulfate (guinea pig) to 13,770 mg/m³ for ammonia (rat). Clinical signs observed after inhalation include eye irritation, labored breathing and nasal discharge, pulmonary hemorrhages. Ammonia concentrations of 348-6953 mg/m³ may lead to death in humans. The LD₅₀ and LC₅₀ values are taken from studies whose reliability rating is a 4 (unassignable) and whose data are used on a weight of evidence basis.

Aqueous ammonia is corrosive to skin and eyes in animal studies and humans due to the high pH. The ammonium salts are slightly irritating to skin and moderately irritating to eyes in animal studies. In humans, slight respiratory irritation was observed at 50 mg/m³ ammonia and at 1 mg/m³ concentrations of ammonium sulfate, pulmonary function was affected. No data are available on the sensitization potential of the category members. However, human data suggest that DAP may be sensitizing to the respiratory tract. In repeated-dose inhalation studies, with ammonia (rats) and aqueous ammonia (rats, rabbits, guinea pigs and dogs), the main effects observed are irritation, and inflammation of the respiratory tract at 105 mg/m³ and above. For ammonia, the NOAEL of 6.4 mg/m³ was determined based on an occupational study and the lack of evidence of decreased pulmonary function or changes in subjective symptoms. No LOAEL was established. In rats, the LOAEL was determined to be 17.4 mg/m³ based on increased severity of rhinitis and pneumonia with respiratory lesions. A NOAEL was not established.

For ammonium sulfate, inhalation studies in rats showed respiratory effects (enlarged alveoli, alveolar ducts and sacs) at 1 mg/m³. In a semi-chronic study [input exposure duration], enhanced bronchiolar cell hyperplasia and fibrosis were reported at 0.5 mg/m³. In a sub-chronic inhalation study with rats, exposure to 26.8 mg/m³ of ammonium thiosulfate resulted in systemic effects such as growth reduction, increased levels of acid and alkaline phosphatase, effects on calcium, CNS effects and cardiovascular changes.

In a 13 week repeated-dose feeding study in rats given ammonium sulfate up to 1,975 mg/kg bw/day, no effects were observed on body weight, food consumption or hematological and clinical parameters. However, increased kidney weights (in males and females) and increased liver weights (females) were observed at the highest dose without histopathological changes. The NOAEL was 1,975 mg/kg bw/day for females and 886 mg/kg bw/day for males (diarrhea). In a combined repeated-dose/reproduction/developmental oral gavage screening study in rats exposed to 0, 250, 750 and 1,500 mg/kg bw DAP for 35 days, a NOAEL of 250 mg/kg bw was derived based on increased alkaline phosphatase and decreased total protein in blood.

Ammonia, ammonium thiosulfate and the analogues ammonium sulfate and DAP did not induce effects in tests on gene mutations and chromosomal aberrations. Ammonium sulfate was negative, *in vivo*, when tested for chromosomal effects. Ammonia is not carcinogenic when administered to rats in the drinking water. However, ammonia did have promoting effects in gastric cancer induced by N-methyl-N'-nitro-N-nitrosoguanidine (MMNG). Ammonium sulfate showed no promoting effect.

No histopathological changes to the reproductive organs were found in repeated-dose toxicity studies with ammonium sulfate. No effects on reproduction and development were found in studies with ammonia (at 24.3 mg/m³). In a reproduction/developmental toxicity screening test (similar to OECD 422) rats (5 males and 10 females/group) were administered DAP by oral gavage at doses of 0, 250, 750 and 1,500 mg/kg bw/day. Animals were exposed two weeks prior to mating, during mating (both sexes) and for an additional three and a half weeks through gestation until lactation day 4 (females). No effects on reproduction were reported up to 1,500 mg/kg bw/day. No developmental effects were observed up to 1,500 mg/kg bw/day. The NOAEL for reproductive and developmental toxicity for DAP was 1,500 mg/kg bw.

Environment

The melting points for ammonia, aqueous ammonia, ammonium thiosulfate, and ammonium phosphate sulfate are -78°C, -77°C, 150°C, and 235°C, respectively. The boiling points are -33°C, 36°C, for ammonia and aqueous ammonia, respectively, while ammonium thiosulfate and ammonium phosphate sulfate decompose at 150°C and >235°C, respectively. The vapor pressure for ammonia is 8611hPa at 20°C; aqueous ammonia, 2878hPa at 25°C; ammonium thiosulfate, 18 mm Hg at 70°F (21.1°C), and ammonium phosphate sulfate – (not applicable). The water solubility for the category substances is in the range of 430 to > 1000 g/L at 20°C. The pH for ammonia is 10.6-11.6 (0.01-1%) at 25°C and aqueous ammonia is expected to be similar. The pKa for ammonia is 9.25. Ammonium thiosulfate (200 g/L at 20°C) and ammonium phosphate sulfate (10% solution in water) pH values are in the range of 6.5-7.2 and 4.5-5.5°C, respectively.

All substances from the ammonia category are very soluble in water and dissociate upon release into water. Anhydrous and aqueous ammonia are volatile. Ammonia toxicity depends on the pH and temperature of the media, as well as the amount of ammonia already present. Increasing pH, and temperature to a lesser degree, results in the presence of more un-ionized ammonia (percentage of total ammonia present as NH₃ in aqueous solutions at 20 °C is 0.039% at pH 6 and 3.82% at pH 8).

Upon application of ammonium fertilizers, ammonium can be taken up by plants or adsorbed onto clay particles in the soil. Leaching or run-off may occur via cation exchange dependent on soil texture, clay content, pH and ionic strength of the irrigation water. Soil bacteria may convert ammonium to nitrate. Nitrate can be taken up by plants or denitrified again to yield nitrogen and nitrous oxide gas. Ammonia may also directly volatilize from the soil. Transport via the atmosphere will mainly be due to diffusion and air concentrations will decrease quickly with increasing distance from the source. Ammonium ion and the anions from the substances of the ammonia category are all subject to nitrification. The fate and behaviour of the substances, such as bioaccumulation, are also closely related to nitrogen cycles in air, soil and water. In anaerobic environments, sulfate is biologically reduced to (hydrogen) sulfide by sulfate reducing bacteria, or incorporated into living organisms as a source of sulfur, and thereby included in the sulfur cycle. In acidic aqueous environments, thiosulfate is similarly expected to dissociate to sulfur and sulfur dioxide and enter the sulfur cycle and/or the atmosphere. Phosphate salts released into the environment will be distributed between water and soil. Land-applied phosphate and ammonium are adsorbed to soil particles. In water the phosphate salts may result in eutrophication (caused by ammonium and phosphate ions), which may lead to increased algal growth. Decomposition of the algae may in turn result in lower dissolved oxygen concentrations. If dissolved oxygen concentrations are lowered significantly, suffocation of other aquatic organisms may occur.

LC₅₀ values for fish toxicity range between 6.9 and 175 mg total NH₃/L for the ammonium substances dependent on pH and temperature during the test. Long-term exposure of fish to ammonium compounds may induce reproductive changes starting at 100 mg/L. EC₅₀ values for invertebrates range from 21.8 mg total NH₃/L for ammonium chloride to > 25.7 mg total NH₃/L for ammonium sulfate. Long-term studies with invertebrates showed slightly lower NOEC values of 3.1-3.47 mg total NH₃/L. The algae *Chlorella vulgaris* EC₅₀ (biomass; 0-5d) was 1300mg/L using ammonium chloride). In a 21-day test with *Chlorella vulgaris* and ammonium sulfate, an EC₅₀ of 25,476 mg/L (2700 mg N/L) was established from exponential growth on day 11-18. Ammonia that is unionized is toxic to aquatic organisms at concentrations below 1 mg/L.

Exposure

For the year 2004 the global market for the ammonia category was estimated to be ca. 65,000 ktonnes. For the United States (Sponsor country) production was estimated at 9 ktonnes. The substances are mainly used as intermediates in the production of fertilizers, fibers and plastics, explosives, solvents and household cleaning products. Environmental exposure occurs through naturally occurring mechanisms whereby microorganisms break down organic nitrogen products such as urea and proteins found in manure as well as via the use of fertilisers and household cleaning

products. According to the information in the USEPA Toxics Release Inventory database for 2004, the total reported emissions of ammonia were 171,179,218 lbs (77,647 tonnes).

Occupational exposure may occur during the production, transportation and processing of ammonia containing compounds. Field exposure to workers is possible during use as fertilizers via both the dermal and inhalation routes of exposure. A generic Threshold Limit Value (TLV) of 10 mg/m³, as a nuisance dust, exists for the solids of the ammonia category. The Occupational Safety and Health Administration (OSHA) has set a Permissible Exposure Limit (PEL) of 50 ppm (35 mg/m³) averaged over 8 hours for ammonia and 15 mg/m³ for sodium thiosulfate. The National Institute for Occupational Safety and Health (NIOSH) has recommended an airborne exposure limit of 25 ppm (18 mg/m³) averaged over a 10 hour period and not to exceed 35 ppm (27 mg/m³) during any 15 minute work period for ammonia. Similarly, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a 25 ppm (18 mg/m³) airborne exposure limit averaged over 8 hours with a short term exposure limit (STEL) of 35 (27 mg/m³) ppm.

Consumer exposure can occur during the use of cleaning products and fertilizers.

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

Human Health: The chemicals are currently of low priority for further work. The chemicals possess hazards for human health (irritant to corrosive, acute 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. In the environment, ammonia degrades to nitrite. It is recommended that the use of the chemicals as fertilizers be taken into account when assessing the exposure of nitrite and nitrate to humans through drinking water.

Environment: The chemicals are currently of low priority for further work. The chemicals possess properties indicating a hazard to the environment (acute aquatic EC/LC₅₀ values between 1 and 100 mg/L). Unionized ammonia toxicity to aquatic organisms is reported at < 1 mg/L. The pH and temperature of water bodies can affect the EC/LC₅₀ values. The chemicals are of low priority for further work for the environment because of their rapid nitrification. Ammonia has indirect and long-term effects on ecosystems, e.g. eutrophication, groundwater pollution and soil acidification due to the nitrification of ammonia.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	Ferric chloride: 7705-08-0 Ferric sulfate: 10028-22-5 Ferrous sulfate: 7720-78-7 Ferric chloride hexahydrate: 10025-77-1 Ferric sulfate nonahydrate: 13520-56-4 Ferrous sulfate monohydrate: 17375-41-6 Ferrous sulfate heptahydrate: 7782-63-0 Ferric chloride hydrate, unspecified: 24290-40-2 Ferric sulfate hydrate, unspecified: 15244-10-7 Ferrous sulfate hydrate, unspecified: 13463-43-9
Chemical Name	Iron Salts Category
Structural Formula	FeCl_3 , $\text{Fe}_2(\text{SO}_4)_3$, FeSO_4 , $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{Fe}_2(\text{SO}_4)_3 \cdot 9\text{H}_2\text{O}$, $\text{FeSO}_4 \cdot \text{H}_2\text{O}$, $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, $\text{FeCl}_3 \cdot x\text{H}_2\text{O}$, $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$, $\text{FeSO}_4 \cdot x\text{H}_2\text{O}$

SUMMARY CONCLUSIONS OF THE SIAR

Iron is the fourth most common element in the natural environment, comprising about 5 % of the Earth's crust. It is abundant in minerals, soils, sediments and natural waters. Iron is biologically an essential element for micro-organisms, plants and higher animals. They have adapted to naturally occurring high environmental levels of iron, and have active intake mechanisms for it.

Rationale for iron salts category

Structural similarities of the inorganic iron ions, which will dissociate immediately in aqueous based media to the respective anions and cations, and form common reaction products via environmental and physiological processes. Iron dichloride (CAS No. 7758-94-3) was reviewed at SIAM 19 and the data from the SIAP and Dossier are published on the UNEP website.

Human Health

Toxicokinetics: Iron is an essential element in humans. Iron salts are absorbed from the GI-tract to varying degree. Before absorption ferrous iron is oxidised to ferric form, which is then transferred into the mucosal lining of the small intestine with the aid of various chelates such as ascorbate and citrate. Tannins and plant phytates inhibit the absorption. Diet may have a significant effect on iron absorption. Iron absorption in the rat is higher and the dietary intake is about 100 times greater than that of humans. Percutaneous absorption of iron in non-chelated form has not been reported. No data is available on respiratory iron absorption. Following absorption the majority of iron is bound to transferrin and transported to the bone marrow where it is incorporated into haemoglobin. Any remaining iron is contained within the storage forms, ferritin or haemosiderin, or as myoglobin, with smaller amounts occurring in haem-containing enzymes or in plasma bound to transferrin. About 1-2 mg of iron is lost daily.

Acute toxicity: In rats, the oral LD₅₀ was 300-2000 mg/kg (132-881 mgFe/kg) for ferrous chloride. For ferric sulfate, the oral LD₅₀ for iron is 500-2000 mg/kg (139 to 558 mg Fe/kg) in females. Ferrous sulfate heptahydrate did not show acute toxicity in rats up to 2000 mg/kg (400 mgFe/kg). The following acute toxic doses of ferrous sulfate have been considered to apply in humans: infants (<6 y) 20 mg/kg (7 mgFe/kg) (for gastrointestinal irritation only), children 200-300 mg/kg (74-111 mgFe/kg), adults 1400 mg/kg (516 mgFe/kg). The dermal LD₅₀ for dry ferrous chloride in rats was >2000 mg/kg (881 mgFe/kg). No relevant data were available for inhalation.

Irritation and sensitisation: Ferrous sulfate solids were irritating to skin. Ferrous chloride solid was weakly irritating, ferric sulfate solid and ferrous sulfate solutions were non-irritating in OECD 404. Ferric chloride was found irritating to respiratory tract in rats.

Ferrous chloride was corrosive, ferric chloride was irritating and ferrous sulfate heptahydrate solution was not irritating to the eye. Ferric solutions are acidic, whereas ferrous ones are not until they oxidise to ferric. The pattern of results is therefore somewhat inconsistent.

Although mixed results have been obtained from sensitisation tests, there is no convincing or reliable evidence of iron sensitisation.

Repeated dose toxicity: In a 13-week study with 0.12, 0.25, 0.5, 1.0 and 2.0% w/v ferric chloride in drinking water, a NOAEL of 0.5% approximately 277 mg/kg bw/day in males, and 314 mg/kg bw /day in females was found. Ferrous sulfate heptahydrate was assessed in oral (gavage) toxicity in rats in an OECD combined repeated dose and reproductive/developmental toxicity screening test under GLP at doses of 0, 30, 100, 300, and 1000 mg/kg/day. Based on extramedullary hematopoiesis of the spleen in the males at 300 mg/kg and increased levels of inorganic phosphate in females at 300 mg/kg, the oral NOAEL for repeated dose toxicity was considered to be 100 mg/kg/day, equivalent to 20 mgFe/kg bw/day for both sexes. In an OECD TG422 study, 0, 125, 250 or 500 mg/kg/day ferrous chloride was administered to rats for up to 42 days in males or 42-54 days in females using oral gavage, deaths were noted at 500 mg/kg. The NOAEL was concluded to be 125 mg/kg/day for males and females, equivalent to 55 mg Fe/kg. These results are applicable across the category.

Mutagenicity and Carcinogenicity: Most Ames tests conducted with iron salts are negative. In an *in vitro* mouse lymphoma test ferric chloride produced a positive and dose-related response in presence of S9 with a marked increase of cytotoxicity. Ferrous sulfate heptahydrate produced chromosomal aberrations in CHL/IU cells after short term treatment with and without S9. *In vivo*, iron has not produced positive responses in the five studies available. Overall iron category substances are not mutagenic *in vivo*.

No increase in tumour incidence was reported for rats ingesting ferric chloride in drinking water at received doses of up to 320-340 mg/kg body weight/day (110-117 mg Fe/kg body weight/day) for two years. Epidemiological investigations have not provided evidence of an increased cancer risk in human populations with increased iron intakes arising from food or clinical supplementation. The Scientific Panel on Dietetic Products, Nutrition and Allergies of the European Commission has concluded that some results indicate the possibility of a role of luminal exposure to excessive iron in the development of colon carcinoma, but the evidence is limited and not convincing.

Reproductive toxicity: In an OECD 422 study rats received 0, 125, 250 and 500 mg/kg/day of ferrous chloride by the oral route (gavage) for 42 days in males or 42 - 54 days in females with treatments continuing through a 14 day pre-mating period. A NOAEL of 500 mg/kg body weight/day was obtained, based on no significant difference in mating data and pre-and post-implantation loss rate. In another OECD 422 study rats received ferrous sulfate heptahydrate orally at doses of 0, 30, 100, 300, and 1000 mg/kg/day. The NOEL for reproductive performance from this study was considered to be 1000 mg/kg/day for both parental animals and pups. For developmental effects, the OECD 422 screening study with ferrous chloride found a NOAEL of 500 mg/kg (220 mg/kg iron). The study with ferrous sulfate heptahydrate using the same protocol found a development NOAEL of 1000 mg/kg, (200 mg/kg iron). These results are applicable across the category.

Environment

Environmental fate: Fe (II/III) category salts are non-volatile solid substances which are very soluble in water and have an acidic reaction with water (Fe(III) species being moderately strong acids). Fe(II) species are unstable in oxygenated water with a half-life under favourable conditions of minutes – hours, and oxidises easily to the Fe(III) state. Under conditions of high light intensity Fe (III) can be photo-reduced to Fe (II). Fe (III) species are soluble and stable in aqueous solution only at very low pH conditions. Normally they react with water to form colloidal and insoluble $\text{Fe}(\text{OH})_3$ which in typical aquatic environmental condition precipitates to sediments. Other metals and organic matter may be strongly adsorbed to Fe precipitates. Fe may also typically form precipitates with phosphate. Iron ions, especially Fe(II) ions may be also adsorbed to dissolved organic material and some dissolved iron in natural waters may be present as soluble organic-complexes. Physical effects arising from the presence of precipitated or colloidal $\text{Fe}(\text{OH})_3$ may be responsible for the effects observed in the tests that are summarised below.

Bioconcentration: Bioconcentration of iron to species is relatively low. Iron is an essential element for most living species and may be actively regulated in organisms.

Ecotoxicity: In general, Fe(II) seems to exhibit higher toxicity to aquatic species compared to Fe(III) ions. However, precipitating and colloidal $\text{Fe}(\text{OH})_3$ may have lethal effects through clogging and causing inflammation in respiratory organs of invertebrates and fish. It is difficult to separate these physico-chemical effects from the true ecotoxic effects even in the standard laboratory tests, other than on the reasonable chemical basis of knowledge of the solubility properties.

Acutely toxic levels of the iron salts to aquatic organisms are observed in nominal exposure concentrations in the range equivalent to 1 – 1000 mg/l salt, with the majority of the results being in the 10 – 100 mg/l range. Chronic effects on aquatic organisms are also observed at nominal concentrations in the range 1 – 1000 mg/l for each individual salt with the majority of the results being >10 mg/l. Summary acute results expressed, for consistency of comparison, relative to concentrations of Fe are:

Green algae (<i>Pseudokirchneriella subcapitata</i>)	ErC_{50} (72 h) = 18 mg/l (growth rate)
Invertebrates (<i>Daphnia magna</i> , 4 results):	EC_{50} (48 h) = 1 - 10 mg/l
Fish (various fish species):	LC_{50} (96 h) = 0.41 - >28 mg/l
Micro-organisms (<i>Vibrio fischeri</i>)	EC_{50} (15 min) = 40 mg/l

It is not possible to differentiate physical and direct toxic effect mechanisms as the cause of effects observed in the tests.

Ferric(III): it is unlikely that ferric iron salts will have direct toxic effects in aquatic environments because the rapid conversion to ferric hydroxide will result in very low concentrations of dissolved iron even under conditions of low pH.

Ferrous(II): it is possible that ferrous iron could have true toxic effects in circumstances where pH is low (<5), oxygen content is low and iron concentration is high (of the order of the apparent $\text{E(L)}\text{C}_{50}$ values).

Physical effects are a genuine hazard expressed via the concentrations reported above, but these are not an indication of a significant chronic hazard.

Exposure: Environmental exposure assessment takes into account exposure arising from intentional use of the specific iron salts in the Sponsor Country. It is important to note that Fe-ion discharges and environmental impact from other (potentially high) exposure sources like production of ferro metals and titanium dioxide, mining and mineralogy are outside the scope of this exposure assessment.

It is noted also that these Fe-category substances typically contain impurities such as Cd and Zn; however, their normal use does not give rise to concentrations exceeding international standards for surface waters.

In 1999 the annual production of these iron salts was 3,44 million tonnes for the European member companies of Inorganic Coagulants Producers Association (Incopa). The main application (ca. 45 % by volume) of the substances in the iron salt category is water treatment: they are used as flocculating and

precipitating agents in mechanical and biological wastewater treatment plants and paper mills as well as treatment of potable water. It has been estimated that about 30% of world iron coagulants are produced in Europe, about 40% in Asia Pacific and about 20% in North America.

Other applications include use as fertilizers, plant protection products, as raw material in synthesis, etching of copper and stainless steel, corrosion inhibition, colouring agent in cosmetics, laboratory and textiles, cement additive to prevent chromium(VI) dermatitis, and production of pharmaceuticals.

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

Human Health: The chemicals in this category are low priority for further work. They do possess properties indicating a hazard for human health, namely, acute toxicity (ferrous chloride, ferric sulfate), skin irritation (ferrous sulfate), eye irritation (ferric chloride) and eye corrosivity (ferrous chloride). These hazards do not warrant further work as they are related to acute toxicity which may become apparent only at high exposure levels. 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 members of the category are currently of low priority for further work. The hazard profile of iron salts is dependent on the environmental conditions and the necessary conditions for harmful effects to be expressed are very specific (low pH and low dissolved oxygen) and are, in themselves, intrinsically unfavourable to many aquatic species.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	-
Chemical Name	<i>N</i>-(2-Octadecanoylaminoethyl)octadecanamide - Commercial Grade. A mixture of approximately 40% w/w <i>N</i>-(2-Octadecanoylaminoethyl)octadecanamide (CAS No. 110-30-5), 40% w/w <i>N</i>-(2-Octadecanoylaminoethyl)hexadecanamide (CAS No. 5136-44-7) and 13% w/w <i>N</i>-(2-Hexadecanoylaminoethyl)hexadecanamide (CAS No. 5518-18-3)
Structural Formula	$\text{CH}_3(\text{CH}_2)_x\text{CONHCH}_2\text{CH}_2\text{NHCO}(\text{CH}_2)_y\text{CH}_3$ x & $y = 16$: <i>N</i>-(2-Octadecanoylaminoethyl)octadecanamidex = 16, $y = 14$: <i>N</i>-(2-Octadecanoylaminoethyl)hexadecanamidex & $y = 14$: <i>N</i>-(2-Hexadecanoylaminoethyl)hexadecanamide

SUMMARY CONCLUSIONS OF THE SIAR

This assessment has been performed for the commercial grade of *N*-(2-Octadecanoylaminoethyl)octadecanamide, which is a mixture of three homologues, as described below. Where data are available for pure *N*-(2-Octadecanoylaminoethyl)octadecanamide, they have also been incorporated into the assessment.

Commercially, *N*-(2-Octadecanoylaminoethyl)octadecanamide is manufactured from the reaction between octadecanoic acid and ethylenediamine. Industrially-produced octadecanoic acid is obtained by extraction from animal fat or from hydrogenation of vegetable oils and is actually a mixture of octadecanoic acid and hexadecanoic acid. In turn, commercial grades of *N*-(2-Octadecanoylaminoethyl)octadecanamide do not contain the pure substance alone, but are a mix of *N*-(2-Octadecanoylaminoethyl)octadecanamide (CAS No. 110-30-5, approximately 40% w/w), *N*-(2-Octadecanoylaminoethyl)hexadecanamide (CAS No. 5136-44-7, approximately 40% w/w) and *N*-(2-Hexadecanoylaminoethyl)hexadecanamide (CAS No. 5518-18-3, approximately 13% w/w) with other fatty acid amides and residual fatty acids making up the remainder of the mixture.

Human Health

No information on toxicokinetics or metabolism is available.

The inhalation LC_{50} is $> 112 \text{ mg/m}^3$ for 6-hr exposure in rats. The oral LD_{50} (rat) is $> 2000 \text{ mg/kg bw}$. For pure *N*-(2-Octadecanoylaminoethyl)octadecanamide (99.7% w/w) the oral LD_{50} (rat) is $> 2000 \text{ mg/kg bw}$. A dermal LD_{50} (rabbit) of $> 2000 \text{ mg/kg}$ is reported in the secondary literature.

Based on information available in the secondary literature, the mixture is reported to be slightly irritating to the rabbit eye and skin in several studies. The majority of studies, however, do not indicate an irritant potential. Based on a weight of evidence approach, the mixture is considered to be non-irritant. No information is available concerning sensitisation in animals.

In a 28-day repeated dose toxicity study [OECD TG 407], rats were administered the mixture by gavage at a dose of 0 (vehicle), 100, 300 or 1000 mg/kg bw/day. No treatment-related effects were

observed in males or females in any of the dose groups. The NOAEL was 1000 mg/kg bw/day for both male and female rats in this study. In a similar study [Japanese Guideline] rats were administered pure *N*-(2-Octadecanoylaminoethyl)octadecanamide (99.7% w/w) by gavage at a dose of 0 (vehicle), 100, 300 or 1000 mg/kg bw/day. No treatment-related effects were observed in males or females in any of the dose groups. The NOAEL was 1000 mg/kg bw/day for both male and female rats in this study.

The mixture was not mutagenic in bacteria [OECD TG 471] and did not induce chromosomal aberrations in mammalian cells *in vitro* [OECD TG 473] either with or without metabolic activation. Pure *N*-(2-Octadecanoylaminoethyl)octadecanamide (99.7% w/w) was also not mutagenic in bacteria [OECD TG 471] and did not induce chromosomal aberrations in mammalian cells *in vitro* [OECD TG 473] either with or without metabolic activation.

No information is available for carcinogenicity.

In a reproduction/developmental toxicity screening test [OECD TG 421] rats were administered the mixture by gavage at a dose of 0 (vehicle), 100, 300 or 1000 mg/kg bw/day. 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 4 of lactation (42-52 days). No treatment-related general toxicity effects were observed in males or females in any of the dose groups. The NOAEL was 1000 mg/kg bw/day for both male and female rats in this study. In parental males, there were no significant changes in the absolute and relative weights of the testes and epididymides in any dose group. In parental females, no changes attributable to the mixture were noted in estrous cycle, copulation index, pairing days until copulation, fertility index, number of corpora lutea and implantation sites, implantation index, gestation length and index or in delivery and lactation states in any of the dose groups. In offspring, no changes attributable to the mixture were noted in the numbers of pups born and pups alive per litter, delivery index, live birth index, sex ratio, body weight of live pups on day 0 or day 4 of lactation, viability index, general condition or autopsy in any of the dose groups. The NOAEL for reproductive/developmental toxicity was 1000 mg/kg bw/day in this study. Overall *N*-(2-octadecanoylamidoethyl)octadecanamide is not considered to be a reproductive or developmental toxicant.

Environment

The mixture is a solid at room temperature. Melting point is 140-141°C (pure *N*-(2-Octadecanoylaminoethyl)octadecanamide). Decomposition occurs at 260°C prior to boiling. Vapour pressure is 1.68E-15 - 2.95E-14 hPa (25°C, MPBPWIN v1.41) and log Kow is anticipated to be >6. Measured water solubility is < 0.0049 mg/L. The mixture is not expected to be hydrolyzed under normal environmental conditions. Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life of 1.82 – 1.98 hours (AOPWIN v1.91). The mixture is not readily biodegradable under aerobic conditions (BOD = 1.1%). The estimated BCF is 263 (BCFWIN v2.15) indicating low potential for bioaccumulation. This result should be treated with caution as it is based on a limit value for log Kow. Fugacity Model Mackay level III calculations indicate that the mixture will be distributed mainly to the soil (82.2%) and sediment (15.6%) compartments if released to air. If released to water, the mixture will distribute mainly to sediment (93.6%). If released to soil, the mixture will be distributed almost exclusively to the soil compartment (99.9%). If released simultaneously to air, soil and water, the mixture will be distributed mainly to sediment (58.3%) and soil (37.7%) compartments. These results should be treated with caution as they are based on a limit value for log Kow. Henry's Law constant is 1.49E-07 - 8.47E-08 (HENRYWIN v3.10) atm.m³/mole.

Acute toxicity to fish (*Oryzias latipes*)(96-h LC₅₀) is > 0.027 mg/L (limit of solubility). Acute toxicity to *Daphnia Magna* (48-h EC₅₀) is > 0.0022 mg/L (limit of solubility). Acute toxicity to green algae (*Pseudokirchneriella subcapitata*) is E_bC₅₀ (0-72h) and E_rC₅₀ (24-72h) > 0.018 mg/L (limit of solubility). The chronic toxicity in *Daphnia magna* is 21-d EC₅₀ (reproduction) and NOEC (reproduction) > 0.0056 mg/L, 21-d LC₅₀ (parental) > 0.0056 mg/L (limit of solubility). The NOEC values in green alga (*Pseudokirchneriella subcapitata*) are NOEC_b (0-72h) and NOEC_r (24-72h) > 0.018 mg/L (limit of solubility). This mixture is considered to be of low hazard to the aquatic environment as no adverse effects were observed at the limit of solubility in any of the ecotoxicity

tests that have been conducted.

No information was identified concerning toxicity to soil or sediment dwelling organisms.

Exposure

Annual domestic production and imported amounts in Japan was approximately 100,000 tons in 2004. The mixture is used as an internal lubricant to improve the fluidity of plastics during processing, as an internal mold release agent and as an additive for paints and lacquers. The amount of the mixture used in plastics is up to 1% w/w. The main uses of plastics containing the mixture are in electronics equipment and automobile bumpers. The mixture is also approved for use as an additive in food contact materials in the US and EU. No consumer use is known for the mixture.

Occupational exposure to the mixture can occur mainly by inhalation at the production and user sites during operations. The atmospheric concentration was measured at one production site in Japan. A maximum concentration of 20 mg/m³ was recorded during packaging of granulated product however operators wear overalls, gloves, helmets, protective eye goggles and disposable masks during all operations in order to minimize their exposure to the substance. Consumer exposure to the mixture can occur, mainly by the dermal route, through contact with a variety of finished products which contain the mixture. No information is available on the level of exposure.

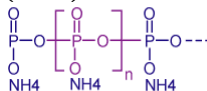
The mixture may enter the environment at the production site and at chemical industries manufacturing the downstream products. In addition the mixture may enter into the environment through disposal via landfill of consumer products, such as electronics equipment, automobile bumpers and waste packaging materials. Release to the environment from disposed products is limited due to its low water solubility.

RECOMMENDATIONS 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 potential.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	7722-76-1, 7783-28-0, 68333-79-9, 8011-76-5, 65996-95-4
Chemical Names	Phosphate category: Monoammonium phosphate (MAP), Diammonium phosphate (DAP), Ammonium polyphosphate (APP), Single superphosphate (SSP), Triple superphosphate (TSP)
Structural Formula	MAP: $\text{NH}_4\text{H}_2\text{PO}_4$ DAP: $(\text{NH}_4)_2\text{HPO}_4$ APP:  SSP: main components: $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O} / \text{CaSO}_4 \cdot \text{H}_2\text{O}$ TSP: $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The category consists of monoammonium phosphate (MAP; CAS No. 7722-76-1), diammonium phosphate (DAP; CAS No. 7783-28-0), ammonium polyphosphate (APP; CAS No. 68333-79-9), single superphosphate (SSP; CAS No. 8011-76-5), and triple superphosphate (TSP; CAS No. 65996-95-4). All members of the category are mainly or exclusively used as fertilizer and have one common functional group (phosphate) that equilibrates between several different ionic species [H_3PO_4 , H_2PO_4^- , HPO_4^{2-} , $\text{H}_2\text{P}_2\text{O}_7^{4-}$, or $\text{P}_3\text{O}_{10}^{5-}$] depending on the pH of the environment. Thus, chemical reactions for all compounds in this category are similar with the exception of the actual dissociation product, which forms calcium or ammonia along with common phosphate moieties. However, the presence of the ammonium ion will influence the observed toxicity and its data are used to conservatively represent the toxicity of the category members.

Under typical environmental conditions, the phosphate would be present as monohydrogen phosphate (HPO_4^{2-}) or dihydrogen phosphate (H_2PO_4^-) with the equilibrium favoring H_2PO_4^- as the acidity of the environment increases. Under these conditions, the proportions of phosphoric acid (H_3PO_4) and the phosphate anion (PO_4^{3-}) would be extremely low.

For the three ammonium phosphates, with increasing pH, a greater portion of the ionized ammonium will be converted to nonionized ammonia. However, an increase of pH may be limited due to the buffering capacity of hydrogenphosphate and dihydrogenphosphate.

In the case of SSP and TSP data from the major compounds calcium superphosphate (CAS No. 7758-23-8) and calcium sulphate have been presented to assist with addressing the physical chemical properties.

Human Health

Phosphates are absorbed from the gastrointestinal tract as orthophosphate. In adults about two thirds of ingested phosphate is absorbed from the gastrointestinal tract and almost entirely excreted into the urine.

The acute oral LD_{50} in rats was >2000 mg/kg bw for MAP, DAP, and APP. No signs of toxicity were observed. Clinical signs in an additional oral study with MAP ($\text{LD}_{50} = 3,250$ mg/kg bw)

included sedation, convulsions, tremors, ataxia, prostration. The acute dermal LD₅₀ in rats was >5000 mg/kg bw (for MAP, DAP, and APP). These dermal studies also showed no clinical signs of toxicity.

The phosphates are slightly irritating to skin and slightly to moderately irritating to eyes in animal studies and a respiratory tract irritant in humans. No animal data are available on skin sensitization.

In a gavage study performed according to OECD TG 422, male and female rats were administered 0, 250, 750 and 1,500 mg/kg bw of DAP for 35 days (7 days/week). In males activated partial thromboplastin time was reduced at 750 and 1,500 mg/kg bw/day. Blood chemistry deviations found in males included alkaline phosphatase levels (increased at 750 and 1,500 mg/kg bw/day), glucose and phosphorous levels (reduced at 1,500 mg/kg bw/day) and total protein (reduced at 750 and 1,500 mg/kg bw/day with a slightly increased albumin/globulin ratio at the high dose). Changes in females were limited to decreased phosphorous levels and non-significantly increased alkaline phosphatase levels at 1,500 mg/kg bw/day. Histological examination of the stomach revealed some submucosal inflammation at all doses, but was not dose-dependent. The NOAEL was set at 250 mg/kg bw/day.

In a similar gavage study (according to OECD TG 422), granular TSP was administered at 0, 250, 750 and 1,500 mg/kg bw for 35 days (7 days/week) to male and female rats. Platelet counts were increased and activated partial thromboplastin time was decreased at 1,500 mg/kg bw in both sexes. White blood cells were increased in females at 750 and 1,500 mg/kg bw. Neutrophil and basophil counts were increased at 1,500 mg/kg bw in females. Total plasma protein level was reduced at 750 and 1,500 mg/kg bw in both sexes. Phosphorus levels were decreased at 750 and 1,500 mg/kg bw in both sexes. Calcium levels were decreased at 750 and 1,500 mg/kg bw in males, and bilirubin levels were decreased at 1,500 mg/kg bw in females. Males at 1,500 mg/kg bw displayed decreased motor activity. Histopathological examination of the stomach revealed degenerative/inflammatory changes at all dose levels in both sexes, probably due to irritant effects of the administered test substance formulation; a dose-response wasn't seen. Minimal cortical tubular basophilia were observed in the kidney among most males in all dose groups and one female per dose group. Horizontal banding of the enamel of the incisors was observed at 750 and 1,500 mg/kg bw in both sexes and one male at 250 mg/kg bw, which may be related to phosphorus or calcium ion imbalances. The NOAEL is considered to be <250 mg/kg bw, because of degenerative changes in the stomach and kidney at all dose levels.

From a spirometer test performed with DAP plant workers, it was concluded that the pulmonary alveoli can be affected after longer exposure resulting in restrictive types of lung disorders.

DAP and TSP were negative in the Ames test with and without metabolic activation and chromosomal aberration test.

In the combined general toxicity and developmental/reproduction studies with DAP and TSP in rats described above, no effects on reproduction were reported up to 1,500 mg/kg bw/d. No developmental effects were observed for DAP up to 1,500 mg/kg bw/d although TSP showed a decrease in body weight of female offspring at 1,500 mg/kg bw/d. The NOAEL for reproductive toxicity was 1500 mg/kg bw/d for DAP and TSP. The NOAEL for developmental toxicity is 750 mg/kg bw/d based TSP.

Environment

The phosphates in this category are soluble in water (18g/L to completely miscible) and their vapour pressures are minimal (although ammonium phosphates may release some ammonia gas). These phosphates decompose at ≥ 150 °C, and their physical state is solid, except APP, which is liquid (at 20°C and 1.013hPa). Any phosphate salt released into the environment will be distributed between water and soil. Land-applied phosphate and ammonium are adsorbed to soil particles. Ammonia may be released from the soil more easily than phosphate by cation exchange. In natural waters with high pH, ammonia containing category members may elicit ammonia toxicity. Soil bacteria may convert ammonium to nitrate, which can be taken up by plants or

denitrified by micro-organisms to nitrogen and nitrous oxide gas.

In water the phosphate salts may result in eutrophication (caused by ammonium and phosphate ions), which may lead to increased algal growth. Decomposition of the algae may in turn result in lower dissolved oxygen concentrations. If dissolved oxygen concentrations are lowered significantly, suffocation of other aquatic organisms may occur.

In acute fish studies, 96-hr LC₅₀ values were >85.9 and >101 mg/L for MAP and APP, respectively in *Oncorhynchus mykiss*. Exposure to DAP of *Cirrhinus mrigala* juveniles resulted in 96-hr LC₅₀ values of 1,700 mg/L for fry and 1,875 mg/L for fingerlings at 21°C.

In an acute study with *Daphnia carinata* using commercial grade superphosphate the 72-hr EC₅₀ value was 1,790 mg/L.

Acute algal tests with *Pseudokirchneriella subcapitata* resulted in NOEC values of 97.1 mg/L for DAP and 87.6 mg/L for TSP.

Exposure

The global market for phosphates is estimated to be ca. 50 million metric tonnes annually. The substances are mainly used as fertilizer and APP is exclusively used as a fertilizer.

Occupational exposure occurs during manufacturing and during use as fertilizer. The dermal and inhalation routes will be the most important routes of exposure.

Environmental exposure is mainly dependent on the amount of fertilizer used on fields, the climatic conditions, and the hydrological conditions of the area of application.

Consumer exposure may occur from food additives (MAP and DAP are generally recognised as safe; 21 CFR 582.1141), fertiliser use, drinking water and use in dental cements and flame retardants.

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

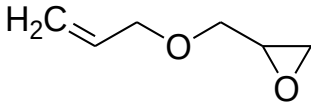
Human Health: The chemicals are of low priority for further work. The chemicals possess properties indicating a hazard for human health (slight skin and eye irritation, and respiratory tract irritation, repeated-dose toxicity, and body weight changes in offspring). These hazards do not warrant further work as they only become evident at extreme exposure levels. They 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.

It is recommended that the use of the chemicals as fertilizers be taken into account when assessing the exposure of nitrite and nitrate to humans through drinking water.

Environment: The chemicals in this category are currently a low priority for further work based on their low hazard profiles. However, the possibility of eutrophication should be considered as well as the potential toxicity of ammonium/un-ionized ammonia at higher pH for the ammonium phosphate compounds.

Note: Additional ammonium salts are being considered at SIAM 24 in the ammonia compounds category.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-92-3
Chemical Names	Allyl 2,3-epoxypropyl ether
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

After i.p. injection in mice allyl glycidyl ether is partly metabolized by epoxidation and/or hydrolysis to diglycidyl ether, 1-allyloxy-2,3-dihydroxypropane and/or 2,3-dihydroxypropyl glycidyl ether.

The acute oral LD₅₀-value is between 260-340 mg/kg bw in mice and 1600 mg/kg bw in rats. Common clinical signs observed comprised distress such as lacrimation, dyspnea and depression. At necropsy, rats that died showed inflammation of the lungs and irritation of the gastroenteric tract. The acute inhalation LC₅₀-value is 1.26 mg/l in mice and 3.12-4.66 mg/l in rats. Considerable lacrimation, nasal and salivary discharge, dyspnea, gasping and corneal opacity were noted. At necropsy, rats that died showed moderate to severe diffuse inflammation and haemorrhage of the lungs. Allyl glycidyl ether is less toxic dermally. Varying degrees of skin irritations were observed. The LD₅₀ is 2550 mg/kg bw in rabbits.

Based on tests with rabbits, allyl glycidyl ether is a skin and severe eye irritant. Based on results from several acute and repeated dose inhalation studies in rat and mice and a respiratory irritation study in mice, allyl glycidylether can be concluded to be a respiratory tract irritant.

No animal tests for sensitisation are available. However, several human case reports indicate that allyl glycidyl ether has potential for skin sensitization.

In several repeated inhalation studies exposure to allyl glycidyl ether revealed effects on body weight gain as well as the respiratory tract (nasal passage), which can be attributed to its irritating properties, at all dose levels. The 14-day NOAEL for inhalation toxicity in rats and mice is lower than 117 mg/m³. The 90-day NOAEL for inhalation toxicity in rat and mice is lower than 19 and 4.7 mg/m³, respectively. The 50-day NOAEL for inhalation toxicity in rats is lower than 1214 mg/m³. The overall NOAEL for inhalation toxicity is set below 4.7 mg/m³ based on the longest exposure period (90 days: 6h/day, 5 days/week) with mice where effects were seen on histopathology in the nasal passage, such as chronic inflammation of the mucosa and squamous metaplasia of the respiratory epithelium.

Allyl glycidyl ether is found to be mutagenic/genotoxic in all *in vitro* tests conducted (Ames, sister chromatid exchange assay and chromosome aberration test) with and without metabolic activation. Allyl glycidyl ether was positive in an *in vivo* mouse micronucleus test as well as *in vivo* drosophila sex-linked recessive lethal test. It is shown *in vitro* as well as *in vivo* that allyl glycidyl ether may form adducts to proteins. In addition, allyl glycidyl ether is capable of producing adducts of DNA *in vitro* and *in vivo* (N-7-guanine, N-1-adenine, N-3-adenine and N-3-cytosine, N-3-uracil) after dermal application and i.p. administration in mice. Based on these results, allyl glycidyl ether is an *in vitro* and *in vivo* genotoxicant.

Carcinogenicity was studied in lifetime inhalation studies in Osborne-Mendel rats and B6C3F1 mice (0, 23.3 and 46.6 mg/m³). The biological significance of three neoplasms observed in the respiratory tract in male rats could not be assessed due to the lack of historical control data in this strain. The number of tumors in mice is limited, but the rarity of the neoplasms seen in this species and the presence of preneoplastic lesions at the site of the tumors suggests carcinogenic potential. Based on these studies and the demonstrated *in vitro* and *in vivo* genotoxicity allyl glycidyl ether is considered to have a carcinogenic potential.

An 8-week pre-mating inhalation study was performed with both rats (0, 140, 467 and 934 mg/m³ and mice (0, 19, 47, 140 mg/m³). In mice, the parental NOAEL was 47 mg/m³ based on decreased body weight gain in males and females. Fertility in mice was not affected up to the highest dose of 140 mg/m³.

In rats however, inhalation of allyl glycidyl ether led to a markedly reduced fertility. The NOAEL for fertility is lower than 140 mg/m³ based on the decreased pregnancy rate when males were exposed. Abnormal sperms are likely to be related to the reduced number of pregnancies. At 934 mg/m³, the percentage of abnormal sperms was increased from 0.64% to 1.11%. Sperm related impairment of fertility is supported by testicular necrosis that was observed in rats after 4 consecutive intramuscular exposures to 400 mg/kg bw allyl glycidyl ether. A parental NOAEL was derived to be 140 mg/m³ based on a decrease in body weight gain. A developmental toxicity study is not available. As it is considered that workplace exposure is well controlled there is no need for further testing.

Environment

Allyl glycidyl ether is a colorless liquid with a freezing point of -100°C, a boiling point of 154°C and a vapor pressure of 5.73 hPa (at 25°C). The substance has a high solubility in water of 128 g/l (at 20.2°C) and a log Kow of 0.34. A half-life for photo-oxidation by reaction with OH-radicals in air (1.5×10⁶ OH/cm³) of 3.25 hours has been calculated (AOPWIN v.1.91).

In a closed bottle test (OECD TG 301D) allyl glycidyl ether was not readily biodegradable. 5-9% of the test substance was degraded after 28d. Based on a GLP test according to OECD TG 111, allyl glycidyl ether is not stable in water and is hydrolyzed within days to weeks, depending on pH conditions. A half-life of 243 hrs at pH 4, 324 hrs at pH 7, and 171 hrs at pH 9 was determined. 3-allyloxy-1,2-dihydroxy propane, which can be formed by opening of the epoxide ring, is expected to be the main hydrolysis product of allyl glycidyl ether. 3-allyloxy-1,2-dihydroxy propane was not readily biodegradable in an OECD 301C guideline test (47% degradation in 28 days). No measured data on bioaccumulation are available for allyl glycidyl ether but the substance is not expected to bioaccumulate due to its low Kow. A BCF of 3.16 (log BCF = 0.5) was calculated with the BCFWIN program (v2.15).

Based on Level I fugacity modeling (EQC Level I, version 3.00) allyl glycidyl ether will partition primarily into water (90%) and air (9.5%). Level III fugacity modeling, assuming continuous discharge of the substance, loss by degradation and advection and non-equilibrium conditions between environmental compartments, indicates that 99.9% of allyl glycidyl ether will stay in water if released only into surface water. When released only into air, 44% will remain in air, 21% will partition to water, 35% to soil and only a negligible amount to the sediment. When released only to soil, 34% of allyl glycidyl ether will partition to water and 66% will remain in soil.

Aquatic testing has resulted in a 96-h LC₅₀ in fish (*Cyprinus carpio*) of 36 mg/l, a 48-h EC₅₀ in aquatic invertebrates (*Daphnia magna*) of 50 mg/l, and a 72-h EC₅₀ in aquatic plants (*Pseudokirchneriella subcapitata*) of higher than 79 mg/l based on growth rate (72-h LC₅₀ = 53 mg/l for biomass; NOEC = 20 mg/l for growth rate and biomass). No data on chronic toxicity to aquatic organisms are available for allyl glycidyl ether.

Exposure

Allyl glycidyl ether is used exclusively as an intermediate for synthesis, mainly of resins and other polymers. Total production volume is not known but the chemical is an HPV substance.

Allyl glycidyl ether is produced and used in closed systems (e.g. pipelines) or in semi-closed systems (e.g. manual filling of reactors). Exposure is thus expected to be minimal for workers. Available short-term occupational monitoring data at several sites indicate airborne concentrations below the detection limits of typically 1 mg/m³. If emission occurs into the workplace atmosphere, appropriate protective equipments are in place (e.g. local exhaust ventilation and use of personal protective equipment such as full face mask, filter mask, gloves and dedicated clothing). Exposure

of the environment is considered to be low as well. Emission is mainly occurring from cleaning operations at the production sites. According to information from the Sponsor Country allyl glycidyl ether is not used in consumer products.

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

Human health:

The chemical is of low priority for further work. The substance possesses properties indicating a hazard for human health (skin and eye irritant, irritant to the respiratory tract, potential skin sensitizer, acute and repeated dose toxicity, genotoxicity, potential carcinogen, toxic to fertility). However, based on data presented by the Sponsor Country, relating to production by three producers in two countries, which accounts for an unknown fraction of global production, exposure to humans is anticipated to be low. 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:

The chemical is of low priority for further work. The substance possesses properties indicating a hazard for the environment (acute toxicity to aquatic organisms between 1 and 100 mg/l). However, based on data presented by the Sponsor Country, relating to production by three producers in two countries, which accounts for an unknown fraction of global production, exposure to the environment is considered to be low. 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-62-6
Chemical Name	Propionic anhydride
Structural Formula	$\text{CH}_3\text{-CH}_2\text{-C(=O)-O-C(=O)-CH}_2\text{-CH}_3$

SUMMARY CONCLUSIONS OF THE SIAR**Analog Justification**

Data for propionic acid and calcium propionate have been used to fulfill the SIDS endpoints for propionic anhydride. Propionic anhydride undergoes exothermic hydrolysis upon contact with water to form 2 moles of propionic acid for each mole of anhydride present. This reaction has been shown to occur with a measured half life of less than 10 minutes at pH 4 to 9. Calcium propionate is a suitable surrogate since it will dissociate in solution to the propionate anion, and propionic anhydride, after hydrolysis in water, will exist predominantly as the propionate anion at neutral pH.

Data for propionic acid (CAS No. 79-09-4) have been used to address or augment all human health endpoints except developmental toxicity. Because propionic anhydride readily hydrolyzes in water to form propionic acid, data for propionic acid are also used to address all environmental endpoints for propionic anhydride. Data for calcium propionate are used to address the developmental toxicity endpoint, and to augment environmental toxicity endpoints (acute toxicity to fish, invertebrates, and algae).

Human Health

No data on metabolism or toxicokinetics are available for propionic anhydride. However, some relevant information is available for propionic acid. Radiolabeled propionic acid administered to rats has appeared in glycogen, glucose, lipids, amino acids, and proteins. The route of metabolism involves interaction with co-enzyme A, carboxylation to form methylmalonyl-coenzyme A, and conversion to succinic acid which then enters the citric acid cycle. No data are available on the toxicokinetics of propionic acid.

No adequate data for propionic anhydride are available for the acute inhalation and dermal endpoints; therefore only data on propionic acid are presented. Limited details were available for an oral study using propionic anhydride, therefore data on propionic acid are also included. There was no mortality among rats exposed for 8 hours to 36 ppm (0.14 mg/L) propionic acid vapor; exposed rats exhibited signs of nasal, ocular and skin irritation. Mortality was 1/20 among rats exposed for 1 hour to 19.7 mg/L propionic acid as a vapor/aerosol atmosphere; exposed rats exhibited signs of nasal, ocular and respiratory irritation. The dermal LD₅₀ for propionic acid in male rabbits was 490 mg/kg bw; necrosis of the skin was observed at the site of application. Animals that died displayed hemorrhage of the lungs and intestines, and congested livers and kidneys. An oral acute toxicity study using propionic anhydride in which only limited details were reported resulted in an LD₅₀ > 1,600 mg/kg (none of the rats died). Clinical signs related to treatment included moderate to severe weakness, gasping, cyanosis, and rough hair coat. The acute oral LD₅₀ value for propionic acid was 426 and 351 mg/kg bw for male and female rats, respectively; hemorrhage of the lungs and gastrointestinal tract, and "burned" surfaces of organs in contact with the gastrointestinal tract were observed in animals that died.

No adequate irritation data for propionic anhydride are available. The supporting chemical, propionic acid causes severe skin and eye irritation and is corrosive. Signs of nasal, ocular, respiratory, and skin irritation were noted in animals exposed to saturated propionic acid in the acute inhalation studies described above. There are no animal sensitization test data for propionic acid. There was no sensitization response in human subjects topically exposed to

the sodium propionate, the sodium salt of propionic acid. Three of 91 human subjects with chronic urticaria (presumed to have had prior exposure to propionic acid as a food preservative) displayed a reproducible positive skin prick response to a 5% solution of propionic acid; none of the 247 control (non-urticarial) subjects displayed a positive response.

No repeated-dose data are available for propionic anhydride. However, repeated-dose data are available for propionic acid from repeated-dose oral toxicity in studies similar to OECD guidelines was evaluated in a 100-day study in dogs and in a 91-day study in rats. In both studies, no systemic toxicity was seen, and only point-of-contact effects were observed, including chronic irritation with associated inflammation and proliferative repair responses. Additional feeding studies in rats range from 28 days to lifetime exposure. However, these studies focused only on point-of-contact effects in the forestomach and the outcome of the studies varied with the consistency of the diet (pelleted vs. powdered).

The dog feeding study is considered the definitive study for the investigation of repeated dose toxicity of propionic acid. Male and female Beagle dogs were exposed to 0, 0.3, 1.0, or 3.0% (0, 196, 660, 1848 mg/kg in males; 0, 210, 696, and 1,832 mg/kg in females) propionic acid in the diet for approximately 100 days. There was no mortality and no clinical signs of toxicity. High-dose animals had point-of-contact effect (diffuse epithelial hyperplasia of the esophageal mucosa). No lesions of the esophagus were observed in the high-dose animals after a 6-week recovery interval, and no lesions were observed in lower-dose animals. The LOAEL for this study was 3% propionic acid in the diet (1,848 mg/kg bw in male dogs and 1,832 mg/kg bw in female dogs). The NOAEL was 1% propionic acid in the diet (660 and 696 mg/kg-bw/day for male and female dogs, respectively).

Male and female Sprague-Dawley rats were exposed to 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 exhibited decrease body weight gain, no other clinical signs of toxicity were observed. Examination of tissues revealed no lesions except point-of-contact changes of the mucosa of the forestomach in the high-dose treatment group, the changes observed in the forestomach were not observed in the post-exposure recovery group. The NOAEL for this study in rats was 2.5% propionic acid (approximately 1600 mg/kg-bw/day) in the diet.

Several repeated-dose dietary studies with different forms of diet (pelleted, powdered, or ground) administered to male rats have suggest that the form of the diet may influence the types of effects observed. In Wistar rats fed 4% test substance (approximately 2,700 mg/kg-bw/day) in a pelleted diet for 24 weeks, no effects on the forestomach or gastric mucosa were observed.

However, when Wistar rats were fed the same amount in powdered feed for 12 weeks, severe changes in the forestomach (including crater-like growths, marginal hyperplasia, and central ulceration) were seen. No changes, however, were observed in the glandular stomach. In a shorter study (9, 15, 21 or 27 days) using 4% in a powdered diet of Fischer 344 rats, histopathological changes were seen in the forestomach at 27 days, including thickened mucosa with acanthosis and hyperkeratosis and some infiltration of white blood cells.

Finally, a study in male rats in which propionic acid was given at 0.4% (approximately 270 mg/kg bw/day) in ground feed for 20 and 24 weeks resulted in a few effects in the forestomach (some hyperplasia and hyperkeratosis). In the same study, ground feed containing 4% (approximately 2,700 mg/kg bw/day) for 20-24 weeks produced papilloma elevations (one with unspecified "carcinomatous" changes), marked squamous hyperplasia of the epidermis, ulceration and hyperplasia of the mucosa of the forestomach. The changes observed upon feeding of high dose of propionic acid in these types of studies are the result of chronic irritation and inflammation and the associated hyperplastic proliferative repair response

No genotoxicity data are available for propionic anhydride. Propionic acid has been tested *in vitro* in bacterial reverse mutation assays using standard plate incorporation and pre-incubation protocols. The compound did not result in gene mutations in either the presence or absence of metabolic activation; it was also negative in an *in vitro* gene mutations assay using *Saccharomyces cerevisiae* (yeast). Propionic acid was negative in a DNA repair assay using *E. coli* in the presence of metabolic activation, but displayed a non-dose-related positive response in the absence of metabolic activation. Propionic acid was also negative in an *in vivo* micronucleus test using male and female Chinese hamsters. There appears to be no potential for induction of gene mutations or chromosomal aberrations by propionic acid.

There are no reproductive or developmental toxicity studies available for propionic anhydride. In a repeated-dose oral toxicity study using *propionic acid*, there were no changes in the reproductive organs of male and female dogs fed up to 3% propionic acid in the diet for approximately 100 days. No changes in reproductive organs were observed in male and female rats fed up to 5% propionic acid in the diet for 91 days. In a developmental toxicity study, calcium propionate was fed to pregnant mice and rats during gestation days 6-15 at dose levels ranging from 3 to 300 mg/kg-bw/day, and to pregnant rabbits during gestation days 6-18 at doses from 4 to 400 mg/kg-bw/day. Pregnant female hamsters were fed calcium propionate during gestation days 6-10 at doses from 4 to 400 mg/kg-bw/day. In all species, there was no effect on maternal or fetal survival, and no effect of fetal or litter size. No increases in fetal or skeletal abnormalities were observed in any species when compared to controls.

Environment

The available physicochemical data are adequate to describe the properties of propionic anhydride. Propionic anhydride has a melting point of -45°C, a boiling point of 167°C, and a vapor pressure of 1.81 hPa at 25°C. It has density of 1.01 g/cm³ at 20 °C. Water solubility and log K_{ow} are not applicable because of its rapid hydrolysis. Propionic anhydride hydrolyzes readily in water to propionic acid, with a hydrolysis half-life of 9, 4, and 2 minutes at pH 4, 7, and 9, respectively.

Because of its rapid hydrolysis to propionic acid, data are also presented for propionic acid. Propionic acid has a vapor pressure of 4.7 hPa at 25 °C and a calculated log K_{ow} value of 0.33 at 25 °C. Propionic acid is miscible with water and the propionate ion will predominate at neutral pH. Therefore, it is not anticipated to volatilize readily from surface waters. The unionized form of the acid will increase as the pH decreases.

In dry environments, vapor phase propionic anhydride is susceptible to photodegradation. The photochemical removal of propionic anhydride in the atmosphere, as mediated by hydroxy radicals, occurs with a calculated half-life between 11.7 and 28.7 days. If hydrolysis of propionic anhydride in contact with water vapor behaves in a manner similar to its hydrolysis in water, it will rapidly hydrolyse to propionic acid. The photochemical removal of vapor-phase propionic acid in the atmosphere as mediated by hydroxyl radicals, occurs with a calculated half-life between 7.7 and 9.2 days.

Hydrolysis of propionic acid is not expected to occur due to the lack of hydrolyzable functional groups. Propionic acid is not likely to bioaccumulate in aquatic organisms based on its log K_{ow}. Based on Level III distribution modeling for propionic acid (assuming equal and continuous releases to air, water and soil), it is estimated that the majority of propionic acid released to the environment will partition into soil (56.6%), water (37.4%), and air (5.5%) with a smaller amount (<0.1%) into sediment. The Fugacity modelling for the acid used the log K_{ow} predicted for the acid in its unionized form. However, because propionic acid will exist primarily as the propionate anion in at neutral pH, the amount of substance partitioning to water may be underestimated in these calculations. Propionic acid is readily biodegradable under aerobic and anaerobic conditions.

Because of the rapid hydrolysis of the anhydride to the acid, aquatic toxicity data (fish, daphnia, and algae) are presented for propionic acid. Propionic acid was tested in 96-hour static test with *Promephales promelas* (fathead minnow), the 96-hour LC₅₀ was 51.8 mg/L. In a static test with *Daphnia magna*, the 48-hour EC₅₀ for propionic acid was 22.7 mg/L. In an OECD guideline test *Scenedesmus subspicatus* (green algae), the 72-hour E_rC₅₀ for propionic acid based on growth rate was calculated to be 48.7 mg/L and the 72-hour E_bC₅₀ for biomass is 43.3 mg/L. In these studies, the test solution was not buffered prior to addition of the test organisms, resulting in low pH in the test solution. Aqueous solutions of calcium propionate do not display significant changes in pH and are less toxic to aquatic organisms. The 96-hr LC₅₀ in fish (*Leuciscus idus*) for calcium propionate is >10,000 mg/L, the 48-hr EC₅₀ in *D. magna* is >500, and the 72-hr EC₅₀ in algae (*S. subspicatus*) (biomass and growth rate) is >500 mg/L. These results suggest that the toxicity observed with propionic acid may be related to changes in pH.

Exposure

In the United States, propionic anhydride is manufactured by one company in a continuous process in enclosed synthesis equipment using engineering controls. Fixed, in-place piping or hoses connected directly to the container are used during production, transfer, and loading operations to minimize exposure, combustibility hazards, and odor complaints. Scrubbers are used to minimize emissions in the stack. Scrubber condensates are redistilled and the recycled organics are used as fuel or sold as solvents. Annual consumption of propionic anhydride is less than 10

thousand metric tons in the United States.

Propionic anhydride is used as a chemical intermediate in the production of alkyd resins, dyestuffs, agricultural chemicals and drugs. Propionic anhydride is not used directly as a component in consumer products.

Because of propionic anhydride's tendency to hydrolyze in an aqueous environment, exposure to propionic acid may result from the hydrolysis of this chemical.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently a low priority for further work. The chemical is corrosive and possesses properties indicating a hazard for human health (skin, eye, and respiratory tract irritation). These hazards do not warrant further work as they are related to acute effects. They should nevertheless be noted by chemical safety professionals and users.

Environment: The chemical is a low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to aquatic species between 1 and 100 mg/l) due to pH effects. However, the chemical is of low priority for further work because of its rapid biodegradation and limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nr.	123-77-3
Chemical Name	Azodicarboxamide
Structural formula	$\text{H}_2\text{NOC-N=N-CONH}_2$

SUMMARY CONCLUSION OF THE SIAR

Human Health Hazards

The LD₅₀ in rats after oral administration is > 2500 mg/kg. 2500 mg/kg led to clinical symptoms, but no mortality. After dermal contact, the LD₅₀ in male rabbits is >500 mg/kg and a dose of 2000 mg/kg bw was not lethal in one female rabbit. The LC₅₀ in rats is > 6100 mg/m³ as dry aerosol.

In rabbits azodicarboxamide is not irritating to the skin and slightly irritating to the eye. Minimal irritation of the respiratory tract was shown in guinea pigs at concentrations up to 97 mg/m³. Azodicarboxamide is a respiratory sensitizer based on human experience. Three cases with positive skin reactions in human with occupational dermatitis give evidence that azodicarboxamide is a skin sensitizer.

The repeated dose toxicity is relatively low. The lowest NOAEL in the most relevant test was 500 mg/kg bw/day in the male rat (90 day study) and 300 mg/kg bw/day in the female rat (1-generation study) for oral treatment and 200 mg/m³ in rats and mice for inhalation exposure.

Azodicarboxamide induces base-pair mutation in bacteria. In contrast, in mammalian cells in vitro and in vivo there is no evidence of genotoxicity. It is therefore unlikely that the mutagenic properties displayed by azodicarboxamide in bacterial systems will be expressed in vivo in mammals.

A recent one-generation study in rats gave no evidence of reproductive or developmental toxicity. The NOAEL for reproductive toxicity was 1000 mg/kg bw (highest tested dose), the NOAEL for parental toxicity was 300 mg/kg bw in females and 1000 mg/kg bw in males.

Final evaluation of carcinogenicity is not possible on the basis of the available data.

Hazards to the Environment

Azodicarboxamide has a water solubility of 35.4 mg/l, a vapor pressure of $2.53 \cdot 10^{-8}$ Pa and a log K_{ow} of -1.7.

With a fugacity model (Mackay I) the hydrosphere was identified as target compartment (100%). Azodicarboxamide can be classified as readily biodegradable failing the 10-day window criterion. The log K_{ow} of -1.7 does not indicate a potential for bio- or geoaccumulation. In the atmosphere the substance is degraded with an estimated half-life of 0.4 d according to Atkinson.

The following results, based on measured concentrations, from ecotoxicity tests with azodicarboxamide are available:

Pimephales promelas: 96h-NOEC > 50 mg/l; *Daphnia magna*: 48 h-EC₅₀ = 11 mg/l; *Scenedesmus subspicatus*: 72 h-E_bC₅₀ = 19.7 mg/l (72 h-E_bC₁₀ = 6.7 mg/l). Based on these data there is a moderate hazard concern to aquatic organisms.

With an assessment factor of 1000 a PNECaqua of 11 µg/l was derived from the 48h-EC₅₀ for *Daphnia magna*.

Exposure

The estimated worldwide production volume of azodicarboxamide is 60,000 to 80,000 t/a. In Germany the substance is produced by one company with an amount of 5,000 – 10,000 t/a. In Germany azodicarboxamide is exclusively used as foaming agent in plastics and rubber industry. During processing the substance will be decomposed into gaseous compounds (nitrogen, carbon monoxide, carbon dioxide, ammonia, water) to a degree of about 99.9 %. In USA the substance is also used as a food-additive (raising agent in baking products).

Releases to the environment are likely to occur during production of azodicarboxamide. During foaming of plastics and rubber significant releases into the environment are not likely to occur. Diffuse releases of undecomposed azodicarboxamide from plastic and rubber goods may occur, however, significant

concentrations in the environment are not expected by this life-cycle step. A significant exposure to the terrestrial compartment could not be identified.

**RECOMMENDATIONS 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 and respiratory sensitizer). 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 the environment (aquatic toxicity values between 1 and 100mg/L). However, the chemical is of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1313-13-9
Chemical Name	Manganese dioxide
Structural Formula	O=Mn=O
SUMMARY CONCLUSIONS OF THE SIAR Human Health A diet containing manganese dioxide (MnO₂) induced significant differences in manganese (Mn) levels in the liver, lung and kidney in mice. Histological examinations revealed some scattered inflammatory foci (macrophages and mononucleated cells) in the lung of rats dosed with MnO₂. The exposure to manganese (as MnO₂) is more readily accumulated in the blood and brain sub-regions via intraperitoneal injection > intratracheal instillation > oral gavage. Following the administration of manganese to rats, some manganese crosses directly from the blood to the bile, but most of the manganese is excreted into the bile. The elimination of manganese from the brain, and in particular, from the cerebrum, is much slower compared to the whole body. Manganese dioxide is of low acute toxicity. The inhalation LC₅₀ is > 1500 mg/m³ for 4-hr exposure in rats [OECD TG 423]. The dermal LD₅₀ is 2000 mg/kg bw in rats [OECD TG 402]. The oral LD₅₀ is > 2197 mg/kg bw in male rats. No reliable animal and human data are available for skin/eye irritation and sensitisation. In humans, high occupational exposure to manganese is known to result in neurotoxicity. In addition, chronic inhalation of manganese dioxide particulates have been reported to lead to lung damage such as cough, bronchitis, pneumonitis, pneumonia, and minor reductions in lung function, and impaired visual reaction time, hand-eye coordination, and hand steadiness at the concentrations of total dust ranging from 0.073 to 17.158 mg/m³ (0.046 - 10.840 mg Mn/m³) and in respirable dust from 0.033 to 2.09 mg/m³ (0.021 - 1.32 mg Mn/m³). Rhesus monkeys were exposed in a repeated inhalation toxicity study to manganese dioxide dust at the concentrations of 0, 0.7 and 3 mg Mn/m³ for 22 hours daily for a duration of 10 months. The LOAEL was 1.1 mg/m³ MnO₂, based on inflammation in the lung. In dietary studies, the short-term or long-term effects of manganese dioxide were investigated with male ddy mice. The LOAELs in male mice were 275 and 276 mg Mn/kg/day based on decreases in the white blood cell count (100-day study), body weight gain and locomotor activity (12-month study). These animal studies had limitations, in particular in relation to the neurotoxicity endpoint and no reliable NOAEL could be derived. A bacterial reverse mutation assay [OECD TG 471] on manganese dioxide with and without metabolic activation suggested that this chemical was not mutagenic in <i>Salmonella typhimurium</i> TA1535, TA100, TA98, TA 1537 and <i>Escherichia coli</i> WP2 <i>uvrA</i>. However, manganese dioxide elicited positive results in <i>in vitro</i> chromosomal aberration test [OECD TG 473] for CHL/IU cell and in <i>in vivo</i> mammalian erythrocyte micronucleus assay [OECD TG 474]. The available information suggests that manganese dioxide is genotoxic. No reliable standard study is available for carcinogenicity. A single dose of manganese dioxide (250 mg/kg) in rabbits caused severe degenerative changes in the seminiferous tubules and these effects led to sterility. In an inhalation study in mice, effects on pup body weight and locomotor activity were observed at the dose of 61mg/m³/day, the only dose used. A NOAEL for developmental toxicity could therefore not be derived. In humans, firm conclusions on the reproductive toxicity of manganese dioxide cannot be determined from the equivocal fertility data reported for male workers and the lack of data for females. Environment Manganese dioxide is a brownish-black powder with a density of 5.08g/cm³. It occurs in nature as the mineral pyrolusite. No reliable measured data are available for water solubility, however based on thermodynamic considerations, manganese dioxide is considered to be almost insoluble in surface water.	

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Due to its inorganic properties, no applicable data are available for vapour pressure, partition coefficient in n-octanol/water, photodegradation and biodegradation. Regarding hydrolysis, this chemical is stable in water and soil. The oxidation state of manganese of MnO_2 is +4 which exists mostly as a precipitated form.

Manganese dioxide is of low toxicity to aquatic organisms (fish, aquatic invertebrate and algae) and earthworm (*Eisenia foetida*). The following toxicity tests for manganese dioxide with aquatic organisms are available:

Acute toxicity:

Oryzias latipes: 96-hour LC_{50} : no effects at saturation, (100 mg/L, nominal concentration)

Daphnia magna: 48-hour EC_{50} : no effects at saturation, (100 mg/L, nominal concentration)

Pseudokirchneriella subcapitata : 72-h ErC_{50} , 72-h EbC_{50} : no effects at saturation (100 mg/L, nominal concentration)

Eisenia foetida: $\text{LC}_{50} > 1000 \text{ mg/kg}$

Exposure

Manganese dioxide is used in the manufacturing of dry cell batteries and in the chemical industry as an oxidizing agent for the production of potassium permanganates and other manganese chemicals. In addition, it is commonly used in the production of matches, fireworks, porcelain and glass-bonding materials, and amethyst glass. In the Republic of Korea, releases into the environment are controlled during production and processing by employing bag filters, scrubbers, waste treatment plants, etc.

In the Republic of Korea, estimated usage volume of manganese dioxide was 2914 tonnes in 2002. In addition, the import volumes of manganese dioxide were decreased by 1.7%, 4591 tonnes in 2001 to 4515 tonnes, in 2002. However, in 2003, importing rates of manganese dioxide were increased by 7.4% (4819 tonnes) and 19.2% (5782 tonnes) in 2004.

In the user facilities of the Republic of Korea, filtered air is emitted and dust collected in the filter is deposited in the landfills. Wastewater is treated in the facilities and transported via the sewage system to wastewater treatment plants, and then the sludge is deposited in landfills. Waste and defective batteries are also disposed to landfill sites. The monitoring data showed that ranges of manganese concentrations in ambient air and in sewages are of $7.87\text{--}27.6 \text{ mg/m}^3$ and of $0.150\text{--}0.699 \text{ mg/L}$, respectively. The Mn concentrations are below the emission limit values of 100 mg/m^3 and 10 mg/L , respectively. Therefore, the exposure to the environment is expected to be low.

In the Republic of Korea, the occupational exposures are controlled during processing by wearing personal protective equipment (PPE) such as dust masks, goggle, and protective clothing. The material including MnO_2 is transferred into closed pipes or containers automatically excluding loading and packaging process and therefore occupational exposure would be considered low. According to the monitoring data, the 8hr-TWA (Time Weighted Average) concentrations of manganese were $0.0177\text{--}0.0631 \text{ mg/m}^3$ in the workplaces, which are below the occupational exposure limit of 5 mg/m^3 . Although there is some potential for consumer exposure to MnO_2 via batteries, this is considered to be unlikely under normal handling conditions and therefore consumer exposure is considered to be very low.

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

Human Health: Manganese dioxide is of low priority for further work. This chemical possesses properties indicating a hazard for human health such as repeated dose toxicity, genetic toxicity, and reproductive toxicity including developmental toxicity. Based on data presented by the Sponsor country related to an unknown fraction of global production and relating to the use pattern in one country, 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: This chemical is of low priority for further work because of its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1338-23-4
Chemical Name	2-Butanone, peroxide (MEKP)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

2-Butanone, peroxide (Methyl Ethyl Ketone Peroxide; MEKP) is a shock and heat sensitive substance. It is only available in the presence of diluents which are used in the manufacturing process to reduce the potential explosion hazard of MEKP. Most studies used a commercial product made of about 40% MEKP and 60% dimethyl phthalate. The typical purity for MEKP as a marketed substance is 17 – 35%. Purity greater than 35% has not been reported, and can be considered a maximum. MEKP is a mixed product consisting of dimers (50%), trimers (25%), and monomeric peroxy compounds. Currently the primary diluent used for commercial MEKP is 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (CAS No. 6846-50-0; 23 -70%).

Human Health

There are no available toxicokinetic, metabolism or distribution data for MEKP. A number of standard acute toxicity studies are available in rats and mice via the inhalation and oral routes of exposure. The acute inhalation of MEKP is most commonly associated with observations of ocular and respiratory irritation, salivation, erythema, decreased motor activity, and respiratory congestion. The 4 hour inhalation LC_{50} of a blend of 7 manufactured MEKP samples in rats was determined to be > 200 mg/L (ca. $>28,080$ ppm). The 4 hour inhalation observable LC_{50} for non-blended MEKP products range from 15.4 mg/L (2162.2 ppm; male rats) to 53.6 mg/L (female rats; 7525.4 ppm). The acute oral LD_{50} of MEKP ranges from 681 mg/kg bw (for a 42% sample in dimethyl phthalate) to 1017 mg/kg bw (40% MEKP sample in corn oil). Observed clinical signs range from none to mydriasis, bradypnea, dyspnea, hypoactivity, flaccidity, ataxia, sedation, hypothermia, prostration and death. MEKP is a moderate to severe dermal irritant, extremely irritating and corrosive to the eye, and is a respiratory irritant. MEKP is not a skin sensitizer.

In a combined reproductive/developmental toxicity screening study (OECD TG 421, described below), MEKP (32% with a mixture of diluents) was administered orally by gavage to 12 male rats per dose group for up to 29 days and to 12 female rats per dose group for up to 45 days if mated or for 52 days if not mated. The NOAEL for systemic toxicity was 50 mg/kg bw/day. Systemic toxicity was observed at 100/75 mg/kg bw/day as mortality/moribundity, reductions in body weight and food consumption, and macroscopic and microscopic findings in the stomach.

Following dermal application of MEKP to the skin of 10 male and 10 female rats per dose group for 13 weeks, a NOAEL was not reached, with hyperkeratosis occurring in rats at 1.07 mg/animal (ca. 3.2-8.4 mg/kg bw/day in males; ca. 5.2-9.9 mg/kg bw/day in females; estimated based on day 1 and last day of study group mean body weights). A LOAEL of 50.6 mg/kg bw/day was identified in rats (thick, crusty skin at the application site in several animals at the lowest dose tested) following application of MEKP (45% in diluent) to the skin of five males and five females per dose group for 2 weeks. Dermal application of MEKP (45% in dimethyl phthalate) to the skin of 10 male and 10

female mice per treatment group for 13 weeks resulted in a LOAEL of 0.357 mg/animal (ca. 10.6-14.8 mg/kg bw/day in males; ca. 12.7-18.1 mg/kg bw/day in females; estimated based on day 1 and last day of study group mean body weights) (minimal to mild acanthosis at the lowest dose tested). A LOAEL of 112.5 mg/kg bw/day (thickened, crusty, hardened skin, and, in some animals, sloughed, including at the lowest dose tested) was identified in mice following application of MEKP (45% in dimethyl phthalate) to the skin of five males and five females per dose group for 2 weeks. The results of these studies suggest that significant amounts of MEKP in DMP do not become systemically available and that, as expected, the primary toxicity associated with contact with these chemicals is limited to the application site.

In three bacterial reverse mutation assays, MEKP produced a weak mutagenic response in a single bacterial tester strain (TA1535) in the presence of metabolic activation. MEKP induced chromosome aberrations, exchange of sister chromatids and DNA mutations (mutation assay) in in vitro mammalian test systems. MEKP is genotoxic.

There are no reliable data to indicate whether MEKP is carcinogenic in animals.

In the combined reproductive/developmental toxicity screening study (OECD TG 421), rats were exposed to 0, 25, 50 and 100/75 mg/kg bw/day MEKP (32% in diluent) by oral gavage for at least 14 days prior to mating. Males continued to receive the test article throughout mating and through the day prior to euthanasia for a total of 28 to 29 doses. Females continued to receive MEKP throughout mating, gestation, and lactation day 2 for a total of 39 to 45 doses. The highest dose was lowered to 75 mg/kg/day after 2 days due to the lethal effects in 1 male and 2 female animal. No specific signs of reproductive or developmental toxicity were seen. The NOAEL for reproductive toxicity was 75 mg/kg bw/day (no effect at highest dose tested). The NOAEL for general toxicity was 50 mg/kg bw/day (statistically significant decrease in male and female body weights) and the NOAEL for developmental toxicity was 50 mg/kg bw/day (statistically significant decrease in neonatal body weights). No specific signs of reproductive toxicity were seen in dermal toxicity studies with rats and mice; the NOAEL for reproductive effects are 107 mg/animal (rat) and 35.7 mg/animal (mouse), respectively

Environment

MEKP is only available in the presence of diluents added to reduce the potential explosion hazard; it is not possible to isolate the substance for testing. The use of diluent to stabilize MEKP interferes with the determination of physico-chemical properties and so values are estimated. MEKP is a mixed product consisting of dimers (50%), trimers (25%), and monomeric peroxy compounds that exist in equilibrium; modeling was performed on each component and a range provided. The estimated melting point range of MEKP is 39.63– 126.1°C and the estimated boiling point range is 242.9-351.2°C. MEKP is only available in the presence of diluents to reduce potential explosion hazard, such that determination of the melting point and boiling point is not applicable. The self accelerating decomposition temperature for MEKP ranges from 63-85°C. The estimated vapor pressure range is 0.84 -1.61x10⁻⁵ hPa at 25°C. The estimated water solubility range of MEKP is 1.4x10⁺⁵ - 2.7 mg/L; the estimated log Kow range is -0.429– 4.3; and the estimated log Koc range is 13.2– 3.3x10⁺⁵. MEKP is a strong oxidizing agent. MEKP is hydrolytically stable over a range of environmentally relevant pH and temperature conditions (half-lives of 204, 1155, and 224 hours at 25°C and pH 4.0, 7.0 and 9.0, respectively) following OECD TG 111. The overall reaction half-life in air is estimated to range from 13.93 -10.3 hrs; however, based on results of fugacity modeling MEKP is not expected to distribute significantly to air and the results of this modeling may not be relevant. MEKP is not expected to directly photolyze due to the lack of absorption in the environmental UV spectrum. Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 1000 kg/h for each medium, shows the following percent distribution range: Air = 0.06– 3.2e-5%; Soil = 54.6-8.1%; Water = 45.3- 87%; Sediment = 0.08– 4.9%. MEKP is likely readily biodegradable (87% biodegradable over 28 days). Bioaccumulation is not anticipated as the estimated BCF for MEKP is 3.16.

The 96-hour LC₅₀ of MEKP (diluent: dimethyl phthalate) for *Poecilia reticulata* is 44.2 mg/L. The 48-hour EC₅₀ of MEKP (diluent: dimethyl phthalate) is 39 mg/L for *Daphnia magna*. MEKP (diluent: dimethyl phthalate) toxicity to *Pseudokirchneriella subcapitata* provided a 72-hour EC₅₀ of 3.2 and 5.6 mg/L for biomass and growth rate, respectively. In each case, the toxicity of MEKP in dimethyl phthalate was similar or more toxic than dimethyl phthalate alone, suggesting the diluent is not affecting the interpretation of these results.

Exposure

MEKP is a reactive substance that is consumed during use. MEKP is only available in the presence of diluents and in 2005, the worldwide production volume was equivalent to 7168 tonnes of neat material. Applications include polymerization initiators for acrylics, polymerization of unsaturated polyester, vinyl ester, styrenic and other resins with vinyl unsaturation. MEKP is also used for the manufacture of paints, plastics and rubber. MEKP is sold to and used primarily by industrial customers. A few organic peroxide manufacturers sell MEKP to other manufacturers who make products for markets such as auto body patching compounds.

Releases to the environment can occur during handling in industrial settings. However, environmental exposure is limited due to engineering controls (closed system) during its manufacture. In addition, most residual MEKP is removed by environmental controls such as waste water treatment systems. During processing there is some reuse and recycling of containers, minimizing release of residual MEKP.

Potential industrial worker exposure is limited to use in a supervised industrial setting for spray applications and transfer from small packages (mostly one gallon), in which they are shipped to a charge tank, reactor or mixing vessel. The industries in which these peroxides are used are subject to federal and/or state Occupational Safety and Health Administration regulations that define the measures and equipment required to minimize worker exposure to chemicals. OSHA has set a permissible exposure limit (PEL) ceiling limit of 0.7 ppm (5 mg/m³). The National Institute for Occupational Safety and Health (NIOSH) ceiling limit is 0.2 ppm (1.5 mg/m³) which the American Conference of Governmental Industrial Hygienists (ACGIH) also uses as the ceiling limit for its Threshold Limit Values (TLV) and Biological Exposure Indices (BEI). The most likely potential routes of exposure would be skin contact from liquid peroxide splash and the contact from the mixed spray from spray operations, which is minimized by the use of personal protective equipment (e.g. goggles, gloves). An additional route of exposure includes the potential for inhalation during supervised industrial for spray applications. Inhalation exposures will be minimized by the use of personal protective equipment. Once decomposed to free radicals, i.e., to initiate polymerization or curing, the MEKP as made and "listed" no longer exists. The end use product (articles produced with MEKP as a catalyst in the polymerization process) may contain low ppm of MEKP; it is bound within the final product and will not be released. In the United States, MEKP is subject to the Emergency Planning and Community Right-to-Know Act (EPCRA) and Section 112(r) of the Clean Air Act. No data are available for 2004 on releases to the environment in the U.S. Environmental Protection Agency (EPA) Toxic Releases Inventory (TRI). MEKP is classified as a hazardous waste regulated under the Resource Conservation and Recovery Act (RCRA) (40 CFR 261) by the U.S. EPA.

Consumer exposure to MEKP is expected to be minimal during normal use. A few organic peroxide manufacturers sell MEKP to other manufacturers who make products for markets such as auto body patching compounds. A formulated MEKP product is for use in a two-part system. The retail customer mixes a small amount of the MEKP with the resin to cure the resin. Once the MEKP has been combined with the resin, residual MEKP is not released from the final product, and is therefore not available for consumer exposure.

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

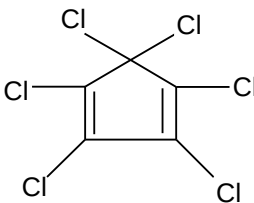
Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (irritation at the point of contact, genotoxicity *in vitro* and repeated-dose toxicity). Based on data presented by the Sponsor country, relating to production in one country (which accounts for >59% 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: 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 of low priority for further work for the environment because of its likely

ready biodegradation (87% biodegradable over 28 days, 40% MEKP in dimethyl phthalate) and its limited potential for bioaccumulation.

The dominant hazard of this substance is its shock and heat sensitivity.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	77-47-4
Chemical Name	Hexachlorocyclopentadiene (HCCP)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

The exact oral absorption figure of HCCP cannot be derived, although the minimal amount of oral absorption ranges from approximately 18% to 39% after a single gavage administration (7 - 61 mg/kg bw dose), and from 5.5% to 12.2% when applied via the diet for 30 days. No studies on the kinetics of HCCP following dermal application were available. However, HCCP is absorbed via the dermal route as is indicated by toxic responses reported in acute dermal toxicity studies. From the inhalation studies, it is concluded that complete respiratory absorption cannot be excluded.

After oral administration, kidneys and liver, and in some studies fat, gonads and lungs were the major sites of residue deposition. In urine, at least four metabolites of HCCP were present. Both rats and mice were capable of extensively degrading HCCP, with no intact HCCP found in excreta or tissues. The faeces were found to be the primary route of elimination.

The 4-hr inhalation LC_{50} ranged from 0.018-0.041 mg/l for rats; the 3.5-hr LC_{50} for rabbits was <0.0158 mg/l. Effects of HCCP in the acute inhalation studies included ocular and nasal discharge, irregular breathing and damage to the respiratory tract. The dermal LD_{50} for rabbits ranged from <200-780 mg/kg bw; for rats this value was >2000 mg/kg bw. In both species HCCP caused marked effects on the skin. Furthermore, in all skin irritation studies, mortality was observed in rabbits. The oral LD_{50} ranged from 505-1500 and 679 mg/kg bw for rats and mice, respectively. Upon acute oral exposure, clinical signs included diarrhoea, lethargy and decreased respiration.

Mortality was also observed in all tested animals (4 male and female rabbits) in the eye irritation study in which 0.1 ml of HCCP was placed into the conjunctival sac of the right eye.

HCCP is irritating and corrosive to the skin and eyes and irritating to the respiratory tract in animal studies and workers. HCCP may also cause sensitisation by skin contact.

The overall NOAEC for local and systemic effects after semichronic inhalatory exposure is 0.45 mg/m³ (observed in mice after 13 weeks of exposure). After inhalatory exposure to dose levels of 1.67 mg/m³ and higher, decreased absolute body weight and squamous metaplasia of the larynx or trachea in mice were observed. An overall NOAEC for chronic inhalatory exposure could not be established since the lowest dose tested still induced treatment related local effects (LOAEC: 0.11 mg/m³). This LOAEC is derived from a two 2-year chronic inhalation toxicity study with rats and mice. Concentrations of ≥ 0.11 mg/m³ HCCP caused toxicity to the respiratory tract, i.e. an increase in the incidence of pigmentation of the respiratory epithelium of the nose, trachea, and the bronchi and bronchioles of the lung in both rats and mice. In addition, in rats a significantly higher incidence of squamous metaplasia of the laryngeal

epithelium of females exposed to concentrations of $\geq 0.11 \text{ mg/m}^3$ HCCP was observed. No increased incidence in neoplasms was found. The NOAEC for systemic effects after chronic exposure is 0.11 mg/m^3 . This NOAEC is based on the higher incidences of suppurative ovarian inflammation in mice exposed to 0.56 and 2.28 mg/m^3 .

Two 13-week oral (gavage) toxicity studies with rats (doses 0, 10, 19, 38, 75 and 150 mg/kg bw/day) and mice (doses 0, 19, 38, 75, 150 and 300 mg/kg bw/day) were performed. The local and systemic NOAEL for rats was 10 mg/kg bw/day based on effects in the forestomach and increased relative kidney weight, respectively. The systemic LOAEL of 19 mg/kg bw in mice was also based on relative kidney weight. The local NOAEL in mice based on effects in the forestomach was 10 mg/kg bw/day .

HCCP does not appear to be a bacterial mutagen and does not induce gene mutations in mammalian cells in vitro. HCCP did induce chromosome aberrations in mammalian cells in vitro, though under conditions of clear toxicity. No induction of sex-linked recessive lethal mutations was noted in germ cells of treated male *Drosophila Melanogaster*. In mice no micronucleated erythrocytes were found after 13 weeks of inhalation exposure to various doses of HCCP including a maximally tolerated dose. HCCP is considered not to have mutagenic activity under in vivo conditions.

Based on a 2-year chronic inhalation study with rats and mice, HCCP is not considered to be a carcinogenic compound for this route. Data on carcinogenic effects of HCCP after dermal or oral exposure are lacking. Due to the absence of mutagenic activity of HCCP in vivo and the absence of carcinogenic potential in rats and mice after chronic inhalation exposure, it is concluded that HCCP is not likely to be a carcinogenic substance.

No specific inhalation and dermal studies on toxicity of HCCP for reproduction are available. In several inhalation repeated dose studies (rats and mice exposed for 13 weeks up to at least 4.46 mg/m^3 ; rats and monkeys exposed for 14 weeks up to 2.28 mg/m^3 ; rats exposed for 30 weeks up to 6.34 mg/m^3 ; rats and mice exposed for 2 years up to 2.28 mg/m^3) male and female reproduction organs were histopathologically examined, but no biologically relevant histopathological treatment related effects with regard to fertility were observed. Therefore, the inhalation NOAEC for fertility effects was established at 6.34 mg/m^3 .

No standard oral studies on toxicity of HCCP for reproduction are available. In an oral repeated dose study (13 weeks; rats exposed up to 150 mg/kg bw and mice exposed up to 300 mg/kg bw), male and female reproduction organs were also histopathologically examined. No biologically relevant histopathological treatment related effects were observed. Therefore, the oral NOAEL for fertility effects was established at 150 mg/kg bw for rats and 300 mg/kg bw for mice.

In oral teratogenicity studies with mice and rats, no teratogenic effects were found. The overall NOAEL for maternal and developmental toxicity is concluded to be 25 mg/kg bw/day based on the study with rabbits. In rabbits, one minor skeletal variation (13 rib(s)) was seen more frequently among the foetuses of rabbits given 75 mg/kg/day , in the presence of significant maternal toxicity (severe diarrhoea and death).

Environment

HCCP is a pale, yellow-green liquid with a melting point of -9°C and a boiling point of 239°C . The vapour pressure is 10 Pa at 25°C . The Henry's Law Constant is determined to be $2.7\text{E-}02 \text{ atm m}^3/\text{mol}$ at 25°C . The substance has a measured water solubility of $1.03\text{-}1.25 \text{ mg/l}$ at $22^\circ\text{C} \pm 1^\circ\text{C}$. In a shake-flask experiment the log Kow was measured to be 5.04. The bioconcentration factor of HCCP in the fathead minnow was 29 and <11 . In ^{14}C studies higher BCF-values were reported (323 and 1297 in Goldfish and 1230 in the Mosquitofish). The lower BCF values reported represent the steady-state bioconcentration factor that was measured in 30-day flow through exposures to constant levels of HCCP, and the higher values that are derived from ^{14}C studies are based on total radioactivity and so may include persistent metabolites.

HCCP will be removed via reaction with photochemically-generated hydroxyl radicals in the atmosphere (estimated rate constant is $5.6 \times 10^{-13} \text{ cm}^3/\text{molecule} \times \text{sec}$ and corresponding to a half-life of 29 days.). Based on the highly chlorinated structure of HCCP, it is expected that reaction of this compound with ozone molecules in the atmosphere would be too slow to be environmentally significant. Degradative processes for removal of HCCP from water include

photolysis, hydrolysis and biodegradation. Hydrolysis of HCCP in water occurs much more slowly than photolysis and the half-life in water seems to be dependent on pH. In shallow or flowing waters, photolysis is the predominant fate process; in deeper waters hydrolysis and biodegradation may be more important environmental fate processes. A hydrolysis half-life of HCCP of 3.3 days was found at pH 7 and 30°C. The calculated half-life for photolysis in water is 10.7 minutes. HCCP strongly adsorbs to organic carbon and is considered to be immobile in soil (measured K_{oc} for HCCP is 4265). These available dataset for biodegradation did not give definitive results because their designs could not easily differentiate removal or degradation via abiotic processes (adsorption, volatilisation, hydrolysis, photolysis) from that via biodegradation. However, results suggest that HCCP will biodegrade at a slow to moderate rate in aqueous environments and is therefore considered to be inherently biodegradable on the basis of a weight of evidence approach. Under anaerobic conditions dehalogenation will occur and one or more chlorinated metabolites will be formed. The persistence of HCCP in soil is low, with degradation of >90% of applied HCCP to non-polar products within approximately 7 days. Based on Level III distribution modeling using EPISUITE (assuming equal and continuous releases to air, water and soil), it is estimated that the majority of HCCP released to the environment will partition into soil (74.1%) and sediment (19.5%) with smaller amounts to water (3.68%) and air 2.66%. The SimpleBox model (v2.0), a Mackay level III model, can be used to estimate the percentage of distribution to soil, air or water when 100% of the substance will initially be emitted to one of these compartments.

	Air	Water	Soil
Receiving compartment			
Air	91.7	2.5	5.8
Water (incl. sediment)	1.7	98.3	0
Soil	0.5	0	99.5

The 96 h-LC₅₀ values for freshwater fish range from 7-240 µg/l, of which the lowest 96 h-LC₅₀ of 7µg/l (measured) was found for the freshwater fish *Pimephales promelas*. The marine 96-h LC₅₀ values varied from 37-48µg/l. The 48 h-LC₅₀ values for freshwater invertebrates range from 39-52.2µg/l. In marine species 96-h LC₅₀ values range from 7 - 371 µg/l. In freshwater and marine algae species, growth was reported to be inhibited by 50% at exposure levels ranging from 3.5 to 240µg/l.

In a 30-day early-life stage flow-through toxicity test with fathead minnows using 1 day old larvae the 96-h LC₅₀ value was 7µg/l (reached within 4 days). Based on the toxicity and growth data it can be concluded that 3.7µg/l is the highest concentration of HCCP that produces no adverse effects (NOEC) on fathead minnow larvae. For *Daphnia magna* a 21-day NOEC of 9µg/l was found. For marine invertebrate species (*Mysidopsis bahia*) a NOEC of 0.3µg/l (reproduction) was found.

A 0.5 h EC₅₀ > 100 mg/l HCCP was found for activated sludge micro-organisms.

The toxicity of HCCP to lettuce (*Lactuca sativa*) was determined in soil and nutrient solution. The EC₅₀ of HCCP on growth was 10 mg/kg d.w., based on nominal concentrations.

Exposure

World-wide production volume was estimated to be approximately 15,000 tonnes in 1988, shared almost equally between the United States and The Netherlands. Production of HCCP is currently thought to be limited to only one company in the United States.

HCCP is used as an intermediate in the production of many chlorinated cyclodiene pesticides like dieldrin, aldrin, endrin, endosulfan, chlordane, Mirex and Pentac. It is also used as an intermediate in the production of chlorendic acid (HET-acid) or its anhydride (chlorendic anhydride) which are used as a copolymer to produce flame retardant and corrosion proof polyesters and alkydresins. HCCP is also used to produce Dechlorane Plus, which is an additive in the production of flame retardant plastics. Minor HCCP applications are its use as an intermediate in the production of dyes and pharmaceuticals. In Europe only two major applications of HCCP are relevant. HCCP is used as an intermediate in the production of endosulfan and it is used in the synthesis of HET-acid. In the year 2000 a maximum of 6000 tonnes HCCP was imported into Europe.

Environmental release of HCCP may occur during industrial use as an intermediate in the production of cyclodiene pesticides and HET-acid. Hexachlorocyclopentadiene may also be released during pesticide application and from the

production and industrial use of flame-retardant polymers and paints. The total estimated environmental release of HCCP resulting from residual amounts of HCCP in processed HET-acid (resins and paints) are found to be very low. In the case of endosulfan the residual content of HCCP is about 0.1%.

Occupational exposure is possible in chemical industries where HCCP is used as an intermediate during the manufacturing of pesticides and flame retardants. These products are produced in closed systems and occupational exposure may occur during connecting and disconnecting of transfer lines. Occupational exposure may also occur when products containing HCCP are added to chemical processes (e.g. containing flame retardants in unsaturated polyesters, paints and thermoplastics). Unintentional exposure to HCCP as a reaction product is possible in the semiconductor industry through drumming of waste products and maintenance activities. It might be possible that in some workplaces adequate worker protection measures are already being applied. Occupational Exposure Limits (OEL values) are available, but not harmonized.

The expected consumer exposure to HCCP in the use as an intermediate (in the production of pesticides and in the production of flame retardant chemicals) can be considered negligible.

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, corrosive to skin and eyes, respiratory tract irritation, sensitization, repeated dose toxicity). Therefore, member countries are invited to perform an exposure assessment for workers and if indicated a risk assessment.

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

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to freshwater and marine aquatic organisms below 1 mg/l). However, based on data presented by the Sponsor country (which relates to the use in several OECD countries) emissions to the environment are low. Countries may wish to investigate any exposure scenarios for the environment that were not presented by the Sponsor Country.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-09-4
Chemical Name	Propionic Acid
Structural Formula	CH ₃ -CH ₂ -COOH

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

Data for calcium propionate (CAS No. 4075-81-4) are used to satisfy the developmental toxicity endpoint for propionic acid and to augment some environmental endpoints (acute toxicity to fish, invertebrates and algae). Calcium propionate dissociates in water to yield propionate ions.

Human Health

Radiolabeled propionic acid administered to rats has appeared in glycogen, glucose, lipids, amino acids, and proteins. The route of metabolism involves interaction with co-enzyme A, carboxylation to form methylmalonyl-coenzyme A, and conversion to succinic acid which then enters the citric acid cycle. No data are available on the toxicokinetics of propionic acid.

There was no mortality among rats exposed for 8 hours to approximately 0.14 mg/L (a nominal value of 36 ppm) propionic acid vapor; exposed rats exhibited signs of nasal, ocular and skin irritation. There was one death among 20 rats exposed for 1 hour to 19.7 mg/L propionic acid as a vapor/aerosol atmosphere; exposed rats exhibited signs of nasal, ocular and respiratory irritation. The dermal LD₅₀ in male rabbits was 490 mg/kg-bw. Animals that died displayed hemorrhage of the lungs and intestines, and congested livers and kidneys. The range of acute oral LD₅₀ values reported for propionic acid in rats was between 351 and 3470 mg/kg bw. The reason for the variation in these values may be due to the age, body weights, or prandial state of the test animals. Clinical signs included squatting posture, agitation or apathy, dyspnea, cyanosis, and ruffled fur. Ascites, hemorrhage of the lungs and gastrointestinal tract, and "burned" surfaces of organs in contact with the gastrointestinal tract were observed in animals that died.

Propionic acid causes severe skin and eye irritation and is irritating to the respiratory tract. Signs of nasal, ocular, respiratory, and skin irritation were seen in animals exposed to propionic acid in the acute inhalation studies described above. There are no animal sensitization data for propionic acid. In humans topically exposed to sodium propionate, there was no sensitization response. Three of 91 human subjects with chronic urticaria (presumed to have had prior exposure to propionic acid as a food preservative) displayed a reproducible positive skin prick response to a 5% solution of propionic acid; none of the 247 control (non-urticarial) subjects displayed a positive response.

Repeated-dose oral toxicity in studies similar to OECD guidelines was evaluated in a 100-day study in dogs and in a 91-day study in rats. In both studies, no systemic toxicity was seen, and only point-of-contact effects were observed, including chronic irritation with associated inflammation and proliferative repair responses. Additional feeding studies in rats range from 28 days to lifetime exposure. However, these studies focused only on point-of-contact effects in the forestomach and the outcome of the studies varied with the consistency of the diet (pelleted vs.

powdered).

The dog feeding study is considered to be the definitive study for the investigation of the repeated dose toxicity of propionic acid. Male and female Beagle dogs were exposed to 0, 0.3, 1.0, or 3.0% propionic acid (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 approximately 100 days. There was no mortality and no clinical signs of toxicity. Three high-dose animals had point-of-contact effects that included diffuse epithelial hyperplasia of the esophageal mucosa. The incidence of lesions of the esophagus in the high-dose animals after a 6-week recovery interval was similar to controls. The LOAEL for this study was 3% propionic acid in the diet (1,848 mg/kg-bw/day in male dogs, and 1,832 mg/kg-bw/day in female dogs). The NOAEL was 1% propionic acid in the diet (660 and 696 mg/kg bw-day for male and female dogs, respectively).

Male and female Sprague-Dawley rats were exposed to 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%) exhibited decrease body weight gain. No other clinical signs of toxicity were observed. Point-of-contact effects were observed in the epithelium of the rat forestomach mucosa in rats in the high dose group; these changes were not observed after a 6-week recovery interval. The NOAEL for male and female rats in this study was 2.5% propionic acid in the diet (approx. 1600 mg/kg-bw/day).

Repeated-dose dietary studies with different forms of diet (pelleted, powdered, or ground) administered to male rats suggest that the form of the diet may influence the types of effects observed. In Wistar rats fed 4% test substance (approximately 2,700 mg/kg-bw/day) in a pelleted diet for 24 weeks, no effects on the forestomach or gastric mucosa were observed.

However, when Wistar rats were fed the same amount in powdered feed for 12 weeks, severe changes in the forestomach (including crater-like growths, marginal hyperplasia, and central ulceration) were seen. No changes, however, were observed in the glandular stomach. In a 4-week study using 4% in a powdered diet of Fischer 344 rats, histopathological changes were seen in the forestomach at 27 days, including thickened mucosa with acanthosis and hyperkeratosis and some infiltration of white blood cells.

Finally, a study in male rats in which propionic acid was given at 0.4% (approximately 270 mg/kg bw/day) in ground feed for 20 and 24 weeks resulted in a few effects in the forestomach (some hyperplasia and hyperkeratosis). In the same study, ground feed containing 4% (approximately 2,700 mg/kg bw/day) for 20-24 weeks produced papilloma elevations (one with unspecified "carcinomatous" changes), marked squamous hyperplasia of the epidermis, ulceration and hyperplasia of the mucosa of the forestomach. The changes observed upon feeding of high dose of propionic acid in these types of studies are the result of chronic irritation and inflammation and the associated hyperplastic proliferative repair response.

Propionic acid has been tested *in vitro* in bacterial reverse mutation assays using *Salmonella typhimurium* strains TA98, 100, 102, 104, 1535, 1537, 1538 with standard plate incorporation and pre-incubation protocols. The test substance did not result in gene mutations in either the presence or absence of metabolic activation; it was also negative in an *in vitro* gene mutations assay using *Schistosaccharomyces pombe* (yeast). Propionic acid was negative in a DNA repair assay using *E. coli* in the presence of metabolic activation, but displayed a non-dose-related positive response in the absence of metabolic activation. Propionic acid was also negative in an *in vivo* micronucleus test using male and female Chinese hamsters. Based on these results, propionic acid has shown no potential to induce gene mutations or chromosomal aberrations.

There are no reproductive, fertility, or developmental toxicity studies available for propionic acid. In a repeated-dose oral toxicity study, there were no changes in the reproductive organs of male and female dogs fed up to 3% propionic acid (up to 1,848 and 1,832 mg/kg-bw/day in males and females, respectively) in the diet for approximately 100 days. There were no changes in the reproductive organs (testes and ovaries) of male and female rats fed up to 5% propionic acid in the diet for 91 days.

In a developmental toxicity study, calcium propionate was fed to pregnant mice and rats during gestation days 6-15 at

dose levels from 3 to 300 mg/kg-bw/day. Pregnant rabbits and hamsters were fed calcium propionate at doses ranging from 4 to 400 mg/kg-bw/day during gestation days 6-18 (rabbits) or gestation days 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 in any species when compared with controls.

Environment

Propionic acid has a melting point of -21.5°C and a boiling point of 141°C. It has a vapor pressure of 4.7 hPa at 25°C, a log K_{ow} value of 0.33 at 25°C, and is miscible with water. With a pKa of 4.9, the propionate ion will predominate at neutral pH; the unionized form may be found in significant concentrations in acidic environments.

Hydrolysis is not expected to occur due to the lack of hydrolyzable functional groups. The photochemical removal of vapor-phase propionic acid in the atmosphere, as mediated by hydroxyl radicals, occurs with a calculated half-life between 7.7 and 9.2 days. Based on Level III distribution modelling for propionic acid (assuming equal and continuous releases to air, water and soil), it is estimated that the majority of propionic acid released to the environment will partition into air (5.5%), water (37.4%) and soil (56.5%) with a smaller amount (<0.1%) into sediment. The Fugacity modelling for the acid used the log K_{ow} predicted for the acid in its unionized form. However, because propionic acid will exist primarily as the propionate anion at neutral pH, the amount of substance partitioning to water may be underestimated in these calculations. Propionic acid is not anticipated to volatilize readily from surface waters (calculated volatilization half-lives for propionic acid are 61 days from a model river and 1.83 years from a model lake). Propionic acid is readily biodegradable under aerobic and anaerobic conditions. Propionic acid is not likely to bioaccumulate in aquatic organisms based on its log K_{ow} value.

Acute aquatic toxicity data (fish, daphnia, and algae) are available for propionic acid. A 96-hour static test with the fathead minnow (*Pimephales promelas*) resulted in a 96-h LC_{50} of 51.8 mg/L. In a static test with *Daphnia magna*, the 48-h EC_{50} was 22.7 mg/L. In a test with green algae (*Scenedesmus subspicatus*), the 72-hr E_rC_{50} (growth rate) was calculated as 48.7 mg/L and the 72-hr E_bC_{50} (biomass) was calculated to be 43.3 mg/L. In these studies, the test solution was not buffered prior to addition of the test organisms, resulting in low pH in the test solution. Aqueous solutions of calcium propionate do not display significant changes in pH and are less toxic to aquatic organisms. The 96-hr LC_{50} in fish (*Leuciscus idus*) is >10,000 mg/L, the 48-hr EC_{50} in *D. magna* is >500, and the 72-hr EC_{50} (both growth rate and biomass) in algae (*S. subspicatus*) is >500 mg/L. These results suggest that the toxicity observed with propionic acid may be related to changes in pH.

Exposure

Approximately 115 thousand metric tons were produced in the United States and 124 thousand metric tons were produced in Western Europe; annual production in Japan is reported to be 3 thousand metric tons. In the United States, propionic acid is manufactured by three companies in a closed continuous synthesis and distillation process. At the manufacturing facility, fixed, in-place piping or hoses connected directly to the container are used during production, transfer, and loading operations to minimize exposure, flammability hazards, and odor complaints. Scrubbers are used to limit emissions from the stack. Scrubber condensates are redistilled and the recycled organics are used as fuel or sold as solvents. Annual consumption of propionic acid in the United States was about 91 thousand metric tons in 2003.

Propionic acid is used as a chemical intermediate for the production of propionate salts that are used as feed and corn preservatives and herbicides. When used as an intermediate, propionic acid is typically received and transported to reactors via hard-piped lines which decreases the potential for exposure. Propionic acid is also used directly as a grain preservative and as an additive to control bacteria and fungi in drinking water for livestock and poultry. Occupational exposure may occur during application of propionic acid as a feed preservative, especially when applied to growing crops or crops after harvest.

Propionic acid is also used as a chemical intermediate for the production of cellulose propionate plastics and other polymers, and in pharmaceuticals. Additional smaller uses include the manufacture of propionic anhydride, methyl

propionate, and chlorinated derivatives.

Propionic acid is also used in the manufacture of synthetic flavoring agents. It is also used as a preservative in food for human consumption.

The 8-hour occupational exposure limit for propionic acid in the Sponsor country is 10 ppm (30 mg/m³).

Propionic acid is found naturally in humans as a normal intermediary metabolite that represents up to 4% of the normal total plasma fatty acids. It is formed as a result of catabolism of amino acids, as a terminal 3-carbon fragment in the oxidation of longer-chained fatty acids, and from the oxidation of the side chain of cholesterol. Propionic acid occurs naturally in foods, and together with other short-chain fatty acids, is ubiquitous in the gastrointestinal tract of humans and other mammals as end-products of microbial digestion.

The general population may be exposed to propionic acid as a fugitive emission, or from ingestion of foods that contain propionic acid naturally or as a preservative, or as an endogenous chemical. Propionic acid may also be released from food, landfills, and sewage. Propionic acid is considered "generally regarded as safe" or GRAS material by the U.S. Food and Drug Administration for direct addition to human food when used as a preservative, and the allowable daily intake (ADI) is considered to be "unlimited" by the FAO/WHO Expert Committee on Food Additives.

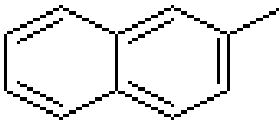
Propionic acid has been detected in the air possibly as a result of photooxidation of anthropogenic compounds during long-range transport. In the 1970s and 1980s it was detected in ground water near a coal gasification site and as a contaminant with leachates from municipal and industrial landfills and hazardous waste sites.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently a low priority for further work. The chemical is corrosive and possesses properties indicating a hazard for human health (skin, eye and respiratory tract irritation). These hazards do not warrant further work as they are related to acute toxicity. They should nevertheless be noted by chemical safety professionals and users.

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) due to pH effects. However the chemical is readily biodegradable and has limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	91-57-6
Chemical Name	2-methylnaphthalene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Following absorption, 2-Methylnaphthalene enters the systemic circulation and is widely distributed to liver and other organs. The distribution to the tissues was similar regardless of exposure routes. 2-Methylnaphthalene is metabolised to 2-naphthuric acid and 2-naphthoric acid after oral administration. 2-Methylnaphthalene is cleared from the body within 1-3 days via urinary excretion

2-Methylnaphthalene has a low acute toxicity. Dermal LD₅₀ values are greater than 2,000 mg/kg bw in rats [OECD TG 402], an oral LD₅₀ value is 1,630 mg/kg in rats, a inhalation RD₅₀ (concentration depressing the respiratory rate to 50%) value is considered 67 mg/m³ in mice.

No information is available on the irritation and sensitization potential of 2-methylnaphthalene.

In the chronic oral dietary study in mice, mortality was observed in males and females at all dose groups. Body weight gains were decreased in males of 113.8 mg/kg/day group. 2-methylnaphthalene revealed systemic effects at all dose levels on kidney and brain weights in males. The most sensitive effects were neutral fat level and pulmonary alveolar proteinosis at all treated groups. A LOAEL of 54.3 and 50.3 mg/kg/day 2-methylnaphthalene (0.075% in diet) was noted in males and females respectively.

In sub-chronic dermal examinations in B6C3F₁ mice (50-week), methylnaphthalene (1-methyl and 2-methylnaphthalene mixture) revealed some pulmonary toxicity at all dose levels (118.8 or 237.6 mg/kg/day) with proteinosis and increased cholesterol and dipalmitoylglycerophosphocholine contents in the lung. The LOAEL of methylnaphthalene was estimated to be 29.7 mg/kg bw/day in female mice based on the increase in lipid pneumonia.

2-Methylnaphthalene did not induce reverse mutations in *Salmonella typhimurium* TA 97, 98, 100 and 1535 regardless of metabolic activation. In mammalian *in vitro* systems, 2-methylnaphthalene did not induce chromosomal aberrations in Chinese hamster lung cells. No information is available on *in vivo* genotoxicity.

2-Methylnaphthalene in diet showed no oncogenic potential in mice after daily oral exposure for 81 weeks.

There is no standard study for reproductive toxicity. The only available information comes from histopathological investigations of reproductive tissues in repeated dose toxicity. No adverse histopathological changes in gonads were observed in repeated dose dietary study (81 weeks) at the highest dose tested (113.8 mg/kg/day and 107.6 mg/kg/day in male and female mice, respectively) in mice.

There is no information available for 2-methyl naphthalene developmental toxicity. The only information available comes from standard developmental toxicity studies conducted with structurally related substance, naphthalene. 2-methyl naphthalene is anticipated to have similar toxicokinetic and toxicodynamic properties to naphthalene. Therefore, developmental toxicity studies with naphthalene are used as supporting information. Prenatal developmental

toxicity of naphthalene following oral application was investigated in rats and rabbits. The exposure to naphthalene via oral route led to maternal toxicity at the high concentrations (150 or 450 mg/kg/day) and suggested the signs of central nervous toxicity and body weight changes. The NOAEL for maternal toxicity was 50 mg/kg/day and the NOAEL for fetal developmental toxicity was 450 mg/kg/day, the highest dose. Based on the studies conducted with naphthalene, 2-methyl naphthalene is not predicted to be a developmental toxicant. Additional studies on the developmental toxicity are not considered to be necessary due to low exposure.

Environment

2-Methylnaphthalene is a white solid. It has a melting point of 34.6°C, a boiling point of 241.1°C, a density of 1.0058 g/cm³ at 20°C, a water solubility of 24.6 mg/L at 25°C, a log K_{OW} value of 3.86 at 25°C. A vapour pressure of 0.055 mmHg at 25°C, and a Henry's law constant of 5.18×10⁻⁴ atm m³/mole at 25°C designate this substance is semi-volatile.

2-Methylnaphthalene distributes in environmental compartments according to a fugacity level III model as follows: 2-methylnaphthalene is mainly distributed to soil (98.3%). If the substance is emitted to air, it will partition into air (51.1%) and soil (43.8%), and if it is released to water, it will remain in water (72.8%). If it is released to soil, it will mainly remain in soil (99.8%). If released to soil, 2-methylnaphthalene is expected to have slight to no mobility based upon K_{OC} values ranging from 4400 to 8500. A Henry's Law constant of 5.18×10⁻⁴ atm m³/mole at 25°C suggests that volatilization of 2-methylnaphthalene from environmental waters may be significant.

2-Methylnaphthalene was readily biodegradable in activated sludge (61.9% biodegradation in 28-d according to OECD TG 301C). Vapour-phase 2-methylnaphthalene is degraded in the atmosphere via the reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 7.4 hours. The direct aqueous photolysis half-life for midday, midsummer sunlight at 40 deg N latitude was predicted to be 54 hours.

2-Methylnaphthalene is moderately bioaccumulative (BCF 100-895 measured in fish muscle tissues in three studies).

The following studies for aquatic organisms are available:

Fish (<i>Oncorhynchus mykiss</i>):	LC ₅₀ (96 h) = 1.46 mg/L (measured concentration)
Invertebrates (<i>Daphnia magna</i>):	EC ₅₀ (48 h) = 1.42-2.99 mg/L (measured concentration)
Green algae (<i>Pseudokirchneriella subcapitata</i>):	E _r C ₅₀ (72 h) = 2.3 mg/L (measured concentration), E _b C ₅₀ (72 h) = 0.72 mg/L

Exposure

The estimated amount of production for 2-methylnaphthalene was 4183 tons in the Republic of Korea in 2002.

2-Methylnaphthalene is produced as a by-product (0.14%) during the production of naphthalene in the chemical manufacturing industry in the Republic of Korea. This substance's production and use as a synthetic intermediate may result in its release to the environment through waste streams. This chemical is a product of combustion and can be released to the environment via natural fires associated with lightening, volcanic activity, and spontaneous combustion. Monitoring data indicate that consumers would be exposed to 2-methylnaphthalene via the food as a volatile component of cassava and cooked meat (mutton, beef, chicken and pork) etc., drinking water, and dermal contact with this chemical and products containing 2-methylnaphthalene. The 2-methylnaphthalene contents are 2.8-49.2 ppb in assorted vegetables and 344.3-4,800.5 ppb in crab meat.

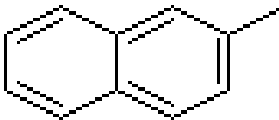
However, occupational and consumer exposures are expected to be negligible in the sponsor country, because 2-methylnaphthalene is produced in a closed system as a by-products and therefore, a direct exposure is not likely to occur from final products in the sponsored country.

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 has possible toxicity to human health (acute toxicity via inhalation and repeated dose toxicity). Based on the data presented by the sponsor country, exposure is 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 chemical has properties indicating a hazard for the environment (acute aquatic toxicity to fish, invertebrates and algae). Member countries are invited to perform an exposure assessment, and if necessary, a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	91-57-6
Chemical Name	2-methylnaphthalene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Following absorption, 2-Methylnaphthalene enters the systemic circulation and is widely distributed to liver and other organs. The distribution to the tissues was similar regardless of exposure routes. 2-Methylnaphthalene is metabolised to 2-naphthuric acid and 2-naphthoric acid after oral administration. 2-Methylnaphthalene is cleared from the body within 1-3 days via urinary excretion

2-Methylnaphthalene has a low acute toxicity. Dermal LD₅₀ values are greater than 2,000 mg/kg bw in rats [OECD TG 402], an oral LD₅₀ value is 4050 mg/kg in rats, a inhalation RD₅₀ (concentration depressing the respiratory rate to 50%) value is considered 67 mg/m³ in mice.

No information is available on the irritation and sensitization potential of 2-methylnaphthalene.

In the chronic oral dietary study in mice, mortality was observed in males and females at all dose groups. Body weight gains were decreased in males of 113.8 mg/kg/day group. 2-methylnaphthalene revealed systemic effects at all dose levels on kidney and brain weights in males. The most sensitive effects were neutral fat level and pulmonary alveolar proteinosis at all treated groups. A LOAEL of 54.3 and 50.3 mg/kg/day 2-methylnaphthalene (0.075% in diet) was noted in males and females respectively.

In sub-chronic dermal examinations in B6C3F₁ mice (50-week), methylnaphthalene (1-methyl and 2-methylnaphthalene mixture) revealed some pulmonary toxicity at all dose levels (118.8 or 237.6 mg/kg/day) with proteinosis and increased cholesterol and dipalmitoylglycerophosphocholine contents in the lung. The LOAEL of methylnaphthalene was estimated to be 29.7 mg/kg bw/day in female mice based on the increase in lipid pneumonia.

2-Methylnaphthalene did not induce reverse mutations in *Salmonella typhimurium* TA 97, 98, 100 and 1535 regardless of metabolic activation. In mammalian *in vitro* systems, 2-methylnaphthalene did not induce chromosomal aberrations in Chinese hamster lung cells. No information is available on *in vivo* genotoxicity.

2-Methylnaphthalene in diet showed no oncogenic potential in mice after daily oral exposure for 81 weeks.

There is no standard study for reproductive toxicity. The only available information comes from histopathological investigations of reproductive tissues in repeated dose toxicity. No adverse histopathological changes in gonads were observed in repeated dose dietary study (81 weeks) at the highest dose tested (113.8 mg/kg/day and 107.6 mg/kg/day in male and female mice, respectively) in mice.

There is no information available for 2-methyl naphthalene developmental toxicity. The only information available comes from standard developmental toxicity studies conducted with structurally related substance, naphthalene. 2-methyl naphthalene is anticipated to have similar toxicokinetic and toxicodynamic properties to naphthalene. Therefore, developmental toxicity studies with naphthalene are used as supporting information. Prenatal developmental

toxicity of naphthalene following oral application was investigated in rats and rabbits. The exposure to naphthalene via oral route led to maternal toxicity at the high concentrations (150 or 450 mg/kg/day) and suggested the signs of central nervous toxicity and body weight changes. The NOAEL for maternal toxicity was 50 mg/kg/day and the NOAEL for fetal developmental toxicity was 450 mg/kg/day, the highest dose. Based on the studies conducted with naphthalene, 2-methyl naphthalene is not predicted to be a developmental toxicant. Additional studies on the developmental toxicity are not considered to be necessary due to low exposure.

Environment

2-Methylnaphthalene is a white solid. It has a melting point of 34.6°C, a boiling point of 241.1°C, a density of 1.0058 g/cm³ at 20°C, a water solubility of 24.6 mg/L at 25°C, a log K_{OW} value of 3.86 at 25°C. A vapour pressure of 0.055 mmHg at 25°C, and a Henry's law constant of 5.18×10⁻⁴ atm m³/mole at 25°C designate this substance is semi-volatile.

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2-Methylnaphthalene was readily biodegradable in activated sludge (61.9% biodegradation in 28-d according to OECD TG 301C). Vapour-phase 2-methylnaphthalene is degraded in the atmosphere via the reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 7.4 hours. The direct aqueous photolysis half-life for midday, midsummer sunlight at 40 deg N latitude was predicted to be 54 hours.

2-Methylnaphthalene is moderately bioaccumulative (BCF 100-895 measured in fish muscle tissues in three studies).

The following studies for aquatic organisms are available:

Fish (<i>Oncorhynchus mykiss</i>):	LC ₅₀ (96 h) = 1.46 mg/L (measured concentration)
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Exposure

The estimated amount of production for 2-methylnaphthalene was 4183 tons in the Republic of Korea in 2002.

2-Methylnaphthalene is produced as a by-product (0.14%) during the production of naphthalene in the chemical manufacturing industry in the Republic of Korea. This substance's production and use as a synthetic intermediate may result in its release to the environment through waste streams. This chemical is a product of combustion and can be released to the environment via natural fires associated with lightening, volcanic activity, and spontaneous combustion. Monitoring data indicate that consumers would be exposed to 2-methylnaphthalene via the food as a volatile component of cassava and cooked meat (mutton, beef, chicken and pork) etc., drinking water, and dermal contact with this chemical and products containing 2-methylnaphthalene. The 2-methylnaphthalene contents are 2.8-49.2 ppb in assorted vegetables and 344.3-4,800.5 ppb in crab meat.

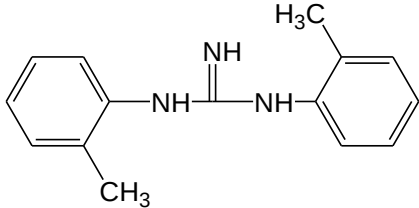
However, occupational and consumer exposures are expected to be negligible in the sponsor country, because 2-methylnaphthalene is produced in a closed system as a by-products and therefore, a direct exposure is not likely to occur from final products in the sponsored country.

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 has possible toxicity to human health (acute toxicity via inhalation and repeated dose toxicity). Based on the data presented by the sponsor country, exposure is 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 chemical has properties indicating a hazard for the environment (acute aquatic toxicity to fish, invertebrates and algae). Member countries are invited to perform an exposure assessment, and if necessary, a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	97-39-2
Chemical Name	1,3-di- <i>o</i> -tolylguanidine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

No information on toxicokinetics or metabolism is available.

1,3-Di-*o*-tolylguanidine is known to be a selective ligand for the sigma site in the mammalian central nervous system. Behavioral changes, such as hypothermia, reduced pain behaviour, circling behaviour, and decreased locomotor activity in mice and/or rats were observed after intraperitoneal, subcutaneous, intravenous and/or intranigral injection.

The oral LD₅₀ (rat) was 85.3 mg/kg bw and 56.0 mg/kg bw for males and females, respectively. No information is available regarding acute toxicity via the dermal or inhalation routes.

Based on studies available in the secondary literature, the substance was not a skin irritant, but was irritating to eyes in animals.

No information is available concerning sensitisation in animals. No effect was reported in human sensitization studies that are less valid.

In a 28-day repeated dose toxicity study [Japanese TG equivalent to OECD TG 407], rats were administered 1,3-di-*o*-tolylguanidine by gavage at 0 (vehicle), 7.5, 15, 30 or 60 mg/kg bw/day. At 60 mg/kg bw/day, one male and one female in the test group and six females in the recovery group died during the administration period. Clinical observation revealed mydriasis, salivation, tremors, decrease in locomotor activity, bradypnea, hypothermia, soiling of the lower abdomen, adoption of a prone or lateral position and gasping in males and females at 60 mg/kg. Mydriasis and salivation were also observed in males and females at 30 mg/kg. Body weights and food consumption were decreased in males and females at 60 mg/kg, but there was no significant difference by the end of the recovery period. Urinalysis showed a tendency for increase in urine volume in males at 30 and 60 mg/kg and increased urine volume in females at 15 mg/kg and higher, with resulting low values for osmotic pressure and specific gravity. Hematological examination revealed a shortened APTT in males at 30 and 60 mg/kg. Blood chemical examination revealed a low value for total protein, and high values for GPT and potassium in males and females at 60 mg/kg. A low value for albumin, high values for ALP and blood urea nitrogen were observed in males at 60 mg/kg. Low values for GOT and sodium, high values for total cholesterol, triglycerides and phospholipids were observed in females at 60 mg/kg. High values for total cholesterol and phospholipids were also observed in females at 30 mg/kg. Relative liver weights were higher in females at 30 and 60 mg/kg. Necropsy revealed light red spots on the mucosa of the glandular stomach, which were histopathologically confirmed to be erosion in one dead female at 60 mg/kg. Histopathological examination revealed hypertrophy of the centrilobular

hepatocytes in one surviving female at 60 mg/kg. The above-mentioned changes recovered after cessation of treatment. As for hypertrophy of the centrilobular hepatocytes, restoration was not confirmed because examination of recovery was not performed for females at 60 mg/kg. Based on mydriasis and salivation and changes in total cholesterol and phospholipids levels in plasma at 30 mg/kg bw/day, the NOAEL from this study is 15 mg/kg bw/day for males and females.

In a reproduction/developmental toxicity screening test [OECD TG 421], rats were administered 1,3-di-*o*-tolylguanidine by gavage at 0 (vehicle), 8, 20, or 50 mg/kg bw/day. Males were dosed for a total of 49 days, from 14 days before mating, and females were dosed from 14 days before mating throughout the mating and pregnancy period to day 3 of lactation (40-49 days). Two males and three females at 50 mg/kg died. Salivation, mydriasis, hypoactivity, bradypnea, adoption of a prone position and/or tremors were observed in males and females at 20 and 50 mg/kg. Decreased body weight gain and food consumption in males and females at 50 mg/kg group and decreased food consumption in females at 20 mg/kg were observed. No effects related to administration of the test substance were noted at necropsy, or on organ weight or histopathological examination in any treatment group. Based on the behavioral changes, the NOAEL for repeated dose toxicity is considered to be 8 mg/kg bw/day in males and females.

In a prenatal developmental toxicity study [OECD 414], rats (24 females/group) were administered 1,3-di-*o*-tolylguanidine by gavage at 0 (vehicle), 10, 20 or 40 mg/kg bw/day on days 6-19 of pregnancy. The rats were terminated and examined on day 20 of pregnancy. A total of four females died at 40 mg/kg. The incidences of females showing mydriasis at 20 and 40 mg/kg and showing decreased locomotor activity at 40 mg/kg were increased. Alopecia, bradypnea, prone position and tremor were also observed at 40 mg/kg. The maternal body weight gain at 20 and 40 mg/kg and food consumption at 40 mg/kg were reduced. The NOAEL for maternally repeated dose toxicity is considered to be 10 mg/kg bw/day.

Based on the behavioural changes at 20 mg/kg and higher, the overall NOAEL for repeated dose toxicity is considered to be 8-10 mg/kg bw/day in male and female rats.

1,3-Di-*o*-tolylguanidine was not mutagenic in bacteria [OECD TG 471] and did not induce chromosomal aberrations in mammalian cells in vitro [OECD TG 473] without S9 mix. However, structural chromosomal aberrations were induced in the presence of S9 mix in CHL cells at 600µg/ml. The substance was non-clastogenic in an in vivo mouse micronucleus assay [OECD TG 474] These data indicate that this substance is not genotoxic in vivo.

No information on carcinogenicity is available.

In a reproduction/developmental toxicity screening test [OECD TG 421], no effects related to administration of 1,3-di-*o*-tolylguanidine were observed on the estrous cycle, number of corpora lutea or implantations, implantation index, copulation index, male or female fertility indices, number of days required for copulation, length of gestation or gestation index. With respect to developmental toxicity, decrease in the litter size and live newborns, birth index, body weights of the male and female live newborns and viability index on day 4, and increase in the incidence of pups with external malformations were observed at 50 mg/kg. There were no effects related to administration of the test substance on the stillbirth index or sex ratio of the live newborn. These data indicate that this substance adversely affects development, but not reproduction, at parentally toxic doses. Based on the lack of reproductive effects and decreased viability and weight of pups, the NOAELs for reproductive performance of the parents and for development of the offspring are considered to be 50 and 20 mg/kg bw/day, respectively.

In a prenatal developmental toxicity study [OECD 414], rats (24 females/group) were administered 1,3-di-*o*-tolylguanidine by gavage at 0 (vehicle), 10, 20 or 40 mg/kg bw/day on days 6-19 of pregnancy. The rats were terminated and examined on day 20 of pregnancy. A decreased weight of the gravid uterus, increased incidence of postimplantation loss, decreased number of live fetuses, and lowered weights of fetuses and placentae were found at 40 mg/kg. The incidences of fetuses with external malformations at 40 mg/kg and with skeletal malformations at 20 and 40 mg/kg were increased. Higher incidences of fetuses with brachydactyly and short tail and defects of caudal vertebrae, phalanges and metacarpals were observed at 40 mg/kg. Delayed ossification was also noted at 40 mg/kg. These data indicate that

this substance is developmentally toxic at maternally toxic doses. The NOAEL for developmental toxicity is considered to be 10 mg/kg bw/day in rats.

Environment

1,3-Di-*o*-tolylguanidine is a white crystal with melting point of 174.4 – 176.0 °C. Boiling point is not observed as this chemical is decomposed at 194 °C. Vapour pressure is 6.89×10^{-5} Pa at 25 °C. Partition coefficient (Log K_{ow}) is measured as 2.90 with neutral form, and water solubility is 70.0 mg/L at 20 °C.

Hydrolysis test according to OECD Test-guideline 111 shows no hydrolysis at pH4, pH7 and pH9 at 50 °C for 5 days. As the dissociation constant (pKa) is 10.67, 1,3-di-*o*-tolylguanidine mainly exists with its protonated form at environmentally relevant pH values. In the atmosphere, indirect photo-oxidation by reaction with hydroxy radicals is predicted to occur with a half-life of 1.2 hours. 1,3-Di-*o*-tolylguanidine is not readily biodegradable under aerobic conditions (Biodegradability by BOD = 1 % after 28 days). Bioaccumulation potential seems to be low based on the Log K_{ow} of 2.90, which is supported by a calculated BCF value with BCFWIN of 34.

Fugacity Model Mackay level III calculation indicates that 1,3-di-*o*-tolylguanidine will be distributed mainly to soil (95.8 %) and water (4.2 %) compartments if released to air. If released to water, this chemical will distribute mainly to water compartment (98.2 %). If released to soil, this chemical will be almost distributed to soil compartment (98.3 %). If released simultaneously to air, soil and water, 1,3-di-*o*-tolylguanidine will be distributed mainly to soil (86.5 %) and water (13.3 %) compartments with minor distribution to sediment (0.243 %) and negligible amount in air (0.0 %). These results should be treated with caution as the calculation are based on log K_{ow} of 2.90 with its neutral form although 1,3-di-*o*-tolylguanidine exists with its protonated form in the aqueous compartment. Henry's Law constant is 8.67×10^{-12} atm.m³/mole.

Eco-toxicity data of this chemical were available in aquatic species from three trophic levels. The 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*) were conducted.

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

Oryzias latipes; 96 h LC₅₀ = 19 mg/L
Daphnia magna; 48 h LC₅₀ = 7.2 mg/L
Pseudokirchneriella subcapitata; 72 h ErC₅₀ = 8.9 mg/L (growth rate method)
Pseudokirchneriella subcapitata; 72 h EbC₅₀ = 5.6 mg/L (area under growth curve method)

The chronic toxicities on daphnids (OECD TG 211, *Daphnia magna*) and on algae (OECD TG 201, *Pseudokirchneriella subcapitata*) were available according to the GLP tests. The following chronic toxicity values have been determined for aquatic invertebrates and algae:

Daphnia magna; 21 d NOEC = 2.8 mg/L
Pseudokirchneriella subcapitata; 72 h NOErC = 2.3 mg/L (growth rate method)
Pseudokirchneriella subcapitata; 72 h NOEbC = 3.8 mg/L (area under growth curve method)

Exposure

1,3-Di-*o*-tolylguanidine is commercially produced with an annual production volume of 100 – 500 tonnes in Japan. Worldwide production volume outside Japan is not available. 1,3-Di-*o*-tolylguanidine is produced with raw materials of *o*-toluidine and cyanogen chloride. 1,3-Di-*o*-tolylguanidine is used for vulcanization accelerator mainly for tyres.

In the sponsor country, 1,3-di-*o*-tolylguanidine is produced and processed in a closed system. At production and processing sites, small amounts of 1,3-di-*o*-tolylguanidine might be released into waste-water stream. However, the waste water stream is treated in the waste-water treatment plant with bio-chemical treatment, adsorption and filtration. Therefore, emission of 1,3-di-*o*-tolylguanidine from the production and processing sites into the environment is anticipated to be low in the sponsor country. However, there is no emission monitoring data

available. 1,3-Di-*o*-tolylguanidine is degraded in the vulcanization process, and it does not remain in the final rubber products. Therefore, consumer exposure is considered to be negligible.

Occupational exposure through inhalation of airborne dust and dermal contact is possible. Workers are using personal protective equipments to minimize intake.

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

Human Health: The chemical is of low priority for further work. The substance possesses properties indicating a hazard for human health (acute oral toxicity, repeated dose toxicity, and developmental toxicity). Based on data presented by the Sponsor Country, relating to production by one producer in one country which accounts for an unknown fraction of global production and relating to the use pattern in 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 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 aquatic toxicity to fish, daphnids and algae are between 1 and 100 mg/L). Based on data presented by the Sponsor country, exposure to the environment 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.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category Name	Alkyl Sulfates, Alkane Sulfonates and α -Olefin Sulfonates
CAS No. / Chemical Name	<u>Alkyl Sulfates:</u>
139-96-8	Sulfuric acid, mono-dodecyl ester, compound with triethanolamine (1:1) (C₁₂ ASO₄ TEA)
142-31-4	Sulfuric acid, mono-octyl ester, sodium salt (C₈ ASO₄ Na)
142-87-0	Sulfuric acid, mono-decyl ester, sodium salt (C₁₀ ASO₄ Na)
151-21-3	Sulfuric acid, mono-dodecyl ester, sodium salt (C₁₂ ASO₄ Na)
1072-15-7	n-Nonylsulfate, sodium salt (C ₉ ASO ₄ Na)
1120-01-0	Sulfuric acid, mono-hexadecyl ester, sodium salt (C ₁₆ ASO ₄ Na)
1120-04-3	Sulfuric acid, mono-octadecyl ester, sodium salt (C ₁₈ ASO ₄ Na)
1191-50-0	Sulfuric acid, mono-tetradecyl ester, sodium salt (C ₁₄ ASO ₄ Na)
2235-54-3	Sulfuric acid, mono-dodecyl ester, ammonium salt (C₁₂ ASO₄ NH₄)
3026-63-9	1-Tridecanol, hydrogen sulfate, sodium salt (C ₁₃ ASO ₄ Na)
4706-78-9	Potassium dodecyl sulphate (C ₁₂ ASO ₄ K)
7065-13-6	Potassium hexadecyl sulphate (C ₁₆ ASO ₄ K)
7739-63-1	Potassium decyl sulphate (C ₁₀ ASO ₄ K)
13393-71-0	Sulfuric acid, mono-pentadecyl ester, sodium salt (C ₁₅ ASO ₄ Na)
39943-70-9	Sulfuric acid, monodecyl ester, compd. with 2,2',2''-nitrilotris[ethanol] (1:1) (C ₁₀ ASO ₄ TEA)
68081-96-9	Sulfuric acids, mono-C₁₀₋₁₆-alkyl esters, ammonium salts (C₁₀₋₁₆ ASO₄ NH₄)
68081-97-0	Sulfuric acids, mono-C ₁₀₋₁₆ -alkyl esters, magnesium salts (C ₁₀₋₁₆ ASO ₄ Mg)
68081-98-1	Sulfuric acids, mono-C₁₄₋₁₈-alkyl esters, sodium salts (C₁₄₋₁₈ ASO₄ Na)
68585-47-7	Sulfuric acid, mono-C₁₀₋₁₆-alkyl esters, sodium salts (C₁₀₋₁₆ ASO₄ Na)
68611-55-2	Sulfuric acid, mono-C ₁₀₋₁₆ -alkyl esters (C ₁₀₋₁₆ ASO ₄)
68890-70-0	Sulfuric acids, mono-C₁₂₋₁₅-alkyl esters, sodium salts (C₁₂₋₁₅ ASO₄ Na)
68955-19-1	Sulfuric acids, mono-C₁₂₋₁₈-alkyl esters, sodium salts (C₁₂₋₁₈ ASO₄ Na)
68955-20-4	Sulfuric acids, mono-C₁₆₋₁₈-alkyl esters, sodium salts (C₁₆₋₁₈ ASO₄ Na)
73296-89-6	Sulfuric acids, mono-C₁₂₋₁₆-alkyl esters, sodium salts (C₁₂₋₁₆ ASO₄ Na)
85665-45-8	Sulfuric acids, mono-C ₈₋₁₄ -alkyl esters, compounds with triethanolamine (C ₈₋₁₄ ASO ₄ TEA)
85586-07-8	Sulfuric acids, mono-C₁₂₋₁₄-alkyl esters, sodium salts

This document may only be reproduced integrally. The conclusions and recommendations (and their rationale) in this document are intended to be mutually supportive, and should be understood and interpreted together.

	(C₁₂₋₁₄ ASO₄ Na)
85681-68-1	Sulfuric acid, mono-(C ₁₄₋₁₈ and C ₁₆₋₁₈ –unsatd.alkyl) esters, sodium salts (C ₁₄₋₁₈ and C ₁₆₋₁₈ = ASO ₄ Na)
86014-79-1	Sulfuric acid, mono-C ₁₃₋₁₅ -alkyl esters, sodium salts (C ₁₃₋₁₅ ASO ₄ Na)
90583-10-1	Sulfuric acid, mono-C ₈₋₁₄ -alkyl esters, ammonium salts (C ₈₋₁₄ ASO ₄ NH ₄)
90583-12-3	Sulfuric acids, mono-C₁₂₋₁₆-alkyl esters, ammonium salts (C₁₂₋₁₆ ASO₄ NH₄)
90583-13-4	Sulfuric acid, mono-C ₁₂₋₁₈ -alkyl esters, ammonium salts (C ₁₂₋₁₈ ASO ₄ NH ₄)
90583-16-7	Sulfuric acid, mono-C ₁₂₋₁₄ -alkyl esters, compounds with ethanolamine (C ₁₂₋₁₄ ASO ₄ MEA)
90583-18-9	Sulfuric acids, mono-C₁₂₋₁₄-alkyl esters, compounds with triethanolamine (C₁₂₋₁₄ ASO₄ TEA)
90583-19-0	Sulfuric acid, mono-C ₈₋₁₄ -alkyl esters, lithium salts (C ₈₋₁₄ ASO ₄ Li)
90583-23-6	Sulfuric acids, mono-C ₁₂₋₁₄ -alkyl esters, magnesium salts (C ₁₂₋₁₄ ASO ₄ Mg)
90583-24-7	Sulfuric acids, mono-C₁₂₋₁₈ alkyl esters, potassium salts (C₁₂₋₁₈ ASO₄ K)
90583-27-0	Sulfuric acids, mono-C ₈₋₁₆ -alkyl esters, sodium salts (C ₈₋₁₆ ASO ₄ Na)
90583-31-6	Sulfuric acids, mono-(C ₁₄₋₁₈ and C _{18-unsaturated})-alkyl esters, sodium salts (C ₁₄₋₁₈ and C ₁₈ = ASO ₄ Na)
91648-54-3	Sulfuric acids, mono-C ₁₄₋₁₅ -alkyl esters, sodium salts (C ₁₄₋₁₅ ASO ₄ Na)
91783-22-1	Sulfuric acids, mono-C ₁₂₋₁₃ -alkyl esters, potassium salts (C ₁₂₋₁₃ ASO ₄ K)
91783-23-2	Sulfuric acids, mono-C ₁₂₋₁₃ -alkyl esters, sodium salts (C ₁₂₋₁₃ ASO ₄ Na)
96690-75-4	Sulfuric acid, mono-C ₁₂₋₁₄ -alkyl esters, ammonium salts, compds. with triethanolamine (C ₁₂₋₁₄ ASO ₄ TEA)
117875-77-1	Sulfuric acids, mono-C₁₀₋₁₆-alkyl esters, compounds with triethanolamine (C₁₀₋₁₆ ASO₄ TEA)
	Sulfuric acids, mono-C ₁₅₋₁₆ -alkyl esters (C ₁₅₋₁₆ ASO ₄)*
	Sulfuric acids, mono-C ₁₂₋₁₈ -alkyl esters, magnesium salts (C ₁₂₋₁₈ ASO ₄ Mg)*
	Potassium undecyl sulphate (C ₁₁ ASO ₄ K)*
<u>Alkane Sulfonates:</u>	
2386-53-0	Sodium dodecane-1-sulfonate (C ₁₂ ASO ₃ Na)
5324-84-5	1-Octanesulfonic acid, sodium salt (C₈ ASO₃ Na)
13419-61-9	Sodium decane-1-sulfonate (C ₁₀ ASO ₃ Na)
13893-34-0	Sodium octadecane-1-sulfonate (C ₁₈ ASO ₃ Na)
27175-91-3	Sodium tetradecane-1-sulfonate (C ₁₄ ASO ₃ Na)
68815-15-6	Sulfonic acids, C ₁₅₋₁₈ -alkane, sodium salts (C ₁₅₋₁₈ ASO ₃ Na)
<u>α-Olefin Sulfonates:</u>	
11067-19-9	Sodium hexadecene-1-sulfonate (C ₁₆ =/OHASO ₃ Na)

	30965-85-6 Dodecene-1-sulfonic acid, sodium salt (C₁₂ =/OHASO₃ Na) 68439-57-6 Sulfonic acids, C₁₄₋₁₆-alkane hydroxy and C₁₄₋₁₆-alkene, sodium salts (C₁₄₋₁₆ =/OHASO₃ Na) 93686-14-7 Sulfonic acids, C₁₄-alkane hydroxy and C₁₄-alkene, sodium salts (C₁₄ =/OHASO₃ Na) 85536-12-5 Sulfonic acids, C₁₂₋₁₄-alkane hydroxy and C₁₂₋₁₄-alkene, sodium salts (C₁₂₋₁₄ =/OHASO₃ Na) 863609-89-6 Sulfonic acids, C₁₄₋₁₈-alkane hydroxy and C₁₄₋₁₈-alkene, sodium salts (C₁₄₋₁₈ =/OHASO₃ Na) 91082-14-3 Sulfonic acids, C₁₅₋₁₈-alkane hydroxy and C₁₅₋₁₈-alkene, sodium salts (C₁₅₋₁₈ =/OHASO₃ Na) 91722-28-0 Sulfonic acids, C₁₆₋₁₈-alkane hydroxy and C₁₆₋₁₈-alkene, sodium salts (C₁₆₋₁₈ =/OHASO₃ Na) Sulfonic acids, C_{14/16/18}-alkane hydroxy and C_{14/16/18}-alkene, sodium salts (1:1:1) (C_{14/16/18} =/OHASO₃ Mg)* Bold: HPV chemicals *CAS number not available
Structural Formula	<u>Alkyl Sulfates (AS):</u> R-OSO₃⁻ cation⁺ where R = predominantly linear alkyl group of chain length C8 – C18 <u>Primary Alkane Sulfonates (PAS):</u> R-SO₃⁻ cation⁺ where R = predominantly linear alkyl group of chain length C8 – C18 <u>α-Olefin Sulfonates (AOS):</u> R'-CH(OH)-(CH₂)_m-SO₃⁻ Na⁺ where m = 2 or 3 and R'-CH=CH-(CH₂)_n-SO₃⁻ Na⁺ where R' = alkyl group and n = 1 - 3 total alkyl chain length: C12 – C18
<u>SUMMARY CONCLUSION OF THE SIAR</u> Category Justification This category consists of three structurally related classes of anionic surfactants: alkyl sulfates with a predominantly linear alkyl chain length of C₈-C₁₈, C₈-C₁₈ alkane sulfonates, and alpha-olefin sulfonates with linear aliphatic chains of typically C₁₄-C₁₈. Most chemicals of this category are not defined substances, but mixtures of homologues with different alkyl chain lengths. Alpha-olefin sulfonates are mixtures of alkene sulfonate and hydroxyl alkane sulfonates with the sulfonate group in the terminal position and the double bond, or hydroxyl group, located at a position in the vicinity of the sulfonate group. The surfactants of this category are produced and transported as either pure solids or as aqueous solutions with typically between 30 and 95 % of active substance. Twenty-one (21) of the chemicals included in this category have HPV status in one or more OECD regions. In addition, data from 40 non HPV-chemicals were used for read-across	

between the three sub-groups and the category as a whole.

The most important common structural feature of the category members is the presence of a predominantly linear aliphatic hydrocarbon chain with a polar sulfate or sulfonate group, neutralized with a counter ion (i.e., Na^+ , K^+ , NH_4^+ , or an alkanolamine cation).

The hydrophobic hydrocarbon chain (with a length between C_8 and C_{18}) and the polar sulfate or sulfonate groups confer surfactant properties and enable the commercial use of these substances as anionic surfactants. The close structural similarities result in physico-chemical properties and environmental fate characteristic which follow a regular pattern. Common physical and/or biological pathways result in structurally similar breakdown products, and are, together with the surfactant properties, responsible for similar environmental behavior and essentially identical hazard profiles with regard to human health. The structural similarities result in the same mode of ecotoxic action. Within each subcategory the most important parameter influencing ecotoxicity is the varying length of the alkyl chain. Although the counter ion may also influence the physico-chemical behaviour of these chemicals, the chemical reactivity and classification for the purpose of this assessment is not expected to be affected by the difference in counter ion.

Human Health

Alkyl Sulfates, alkane sulfonates and α -olefin sulfonates are well absorbed after ingestion; penetration through the skin is however poor. After absorption, these chemicals are distributed mainly to the liver. Alkyl sulfates, alkane sulfonates and most probably also α -olefin sulfonates are metabolized by cytochrome P450-dependent ω -oxidation and subsequent β -oxidation of the aliphatic fatty acids. End products of the oxidation are a C_4 sulfate or sulfonate (even numbered chain lengths) and a C_3 or C_5 sulfate or sulfonate (odd numbered chain lengths). For the alkyl sulfates in addition sulfate is formed as a metabolite. The metabolites are rapidly excreted in the urine.

Acute dermal LD_{50} values in rabbits were 200 mg a.i. (active ingredients)/kg bw for the C_{12} - and greater than 500 mg a.i./kg bw for the C_{12-13} - and C_{10-16} - alkyl sulfates, respectively; apart from moderate to severe skin irritation, clinical signs included tremor, tonic-clonic convulsions, respiratory failure, and body weight loss in the study with the C_{12} -alkyl sulfate and decreased body weights after administration of the C_{10-16} - alkyl sulfates. No data are available for alkane sulfonates but due to a comparable metabolism and effect concentrations in long-term studies effect concentrations are expected to be in the same range as found for alkyl sulfates. No specific systemic toxicity occurred in acute dermal toxicity studies with the α -olefin sulfonate $\text{C}_{14-16}=\text{OHASO}_3\text{Na}$ on rats or rabbits at the highest tested dose level (740 mg a.i./kg bw in rats, 2325 mg a.i./kg bw in rabbits).

Acute oral LD_{50} values in rats and/or mice of alkyl sulfates were between 290 and 580 mg a.i./kg bw for C_{10} , between 1000 and 2000 mg a.i./kg bw for C_{10-16} , and C_{12} , greater than 2000 mg a.i./kg bw for C_{12-14} , C_{12-15} , C_{12-16} , C_{12-18} and C_{16-18} , and greater than 5000 mg a.i./kg bw for C_{14-18} and $\text{C}_{16-18}=\text{alkyl sulfates}$. The counter ion does not appear to influence the toxicity in a substantial way. The clinical signs observed were non-specific (piloerection, lethargy, decreased motor activity and respiratory rate, diarrhea). At necropsy the major findings were irritation of the gastrointestinal tract and anemia of inner organs. The LD_{50} in rats of the C_8 alkane sulfonate (sodium salt) was >5000 mg a.i./kg bw with no clinical signs of intoxication and no adverse findings at necropsy reported. LD_{50} values in rats for the $\text{C}_{14-16}-\alpha$ -olefin sulfonates (sodium salts) were between 578 and 2200 mg a.i./kg bw. Based on limited data, the acute oral LD_{50} values of alkane sulfonates and α -olefin sulfonates of comparable chain lengths are assumed to be in the same range.

There are no data available for acute inhalation toxicity of alkyl sulfates, alkane sulfonates or α -olefin sulfonates.

In skin irritation tests performed on rabbits in accordance with OECD TG 404, the ca. 30% aqueous solutions of C_{8-14} - and C_{8-16} , the 90% solution of C_{12-14} , and the 60% solution of $\text{C}_{14-18/18}=\text{alkyl sulfates}$ were all corrosive. At 25%, and under occlusive conditions, C_{12} - and C_{12-14} - and at $\geq 5\text{-}7\%$ C_{12} -, C_{12-15} -, C_{13-15} - and C_{15-16} -alkyl sulfates were moderate to strong irritants. $\text{C}_{16-18}\text{ASO}_4\text{Na}$ showed only slight irritation up to concentrations of 31.5%. The α -olefin sulfonate $\text{C}_{14-16}=\text{OHASO}_3\text{Na}$ was irritating when tested at a concentration of 40% according to OECD TG 404. 5 % of an α -olefin sulfonate ($\text{C}_{14-18}=\text{OHASO}_3\text{Na}$) were only very slightly irritating. Comparative studies investigating skin effects like transepidermal water loss, epidermal electrical conductance, skin swelling, extraction of amino acids and proteins or development of erythema in human volunteers consistently showed a maximum of effects with $\text{C}_{12}\text{ASO}_4\text{Na}$. 20% $\text{C}_{12}\text{ASO}_4\text{Na}$ is routinely used as a positive internal control giving borderline irritant reactions in skin irritation studies performed on humans. With $\text{C}_{12}\text{ASO}_4\text{Na}$ being the most irritant alkyl sulfate it can be concluded that in humans 20% is the threshold concentration for irritative effects of alkyl sulfates in general. When formulated in consumer products, alkyl sulfates are usually used in conjunction with other surfactants. These mixed surfactant

systems form micelles that typically lead to a reduction in irritation potential of the mixture, compared to the irritation potential of the individual ingredients. No data were available with regard to the skin irritation potential of alkane sulfonates. Based on the similar chemical structure they are assumed to exhibit similar skin irritation properties as alkyl sulfates or α -olefin sulfonates of comparable chain lengths.

C₁₂-containing alkyl sulfates (at concentrations $\geq 10\%$) were severely irritating to the eyes of rabbits and caused irreversible corneal effects. With increasing alkyl chain length, the irritating potential decreases, and C₁₆₋₁₈ASO₄Na, at a concentration of 25%, was only a mild irritant. Concentrated C₁₄₋₁₆- α -olefin sulfonates were severely irritating, but caused irreversible effects only if applied as undiluted powder. At concentrations below 10 % mild to moderate, reversible effects were found. No data were available for alkane sulfonates.

Alkyl sulfates and C₁₄₋₁₈ α -olefin sulfonates were not skin sensitizers in animal studies performed according to OECD TG 406. In humans, the sensitizing potential of C₁₂ASO₄ Na is very low and C₁₄₋₁₆ α -olefin sulfonate was not found to have any sensitising potential. No reliable data were available for alkane sulfonates. Based on the similar chemical structure, no sensitization is expected.

For repeated dermal application a "No Observed Adverse Effect Level" (NOAEL) of 400 mg a.i./kg bw/day for systemic effects was found in mice treated twice weekly for 3 or 13 weeks with 0.2 ml of C₁₂₋₁₅ ASO₄ Na at concentrations of 0, 5, 10, 12.5 or 15% in water (corresponding to ca. 0, 200, 400, 500, or 600 mg a.i./kg bw/day). At 10% concentration, epidermal hyperplasia, and at concentrations of $\geq 12.5\%$ in addition epidermal cytotoxicity (ulceration) was found. Increased water intake and elevated liver, kidney and heart weights were associated with concentrations $>10\%$.

After repeated oral application of alkyl sulfates with chain lengths between C₁₂ and C₁₈, the liver was the only target organ for systemic toxicity. Adverse effects on this organ included an increase in liver weight, enlargement of liver cells, and elevated levels of liver enzymes. The "Lowest observed adverse effect level" (LOAEL) for liver toxicity (parenchymal hypertrophy and increase in relative liver weight) was found for C₁₆₋₁₈ ASO₄ Na in a 13-week dietary study on rats at 230 mg a.i./kg bw/day. The lowest NOAEL in rats was at 55 mg a.i./kg bw/day in a 13-week study with C₁₂ ASO₄ Na.

NOAELs of about 100 mg a.i./kg bw/day were found for rats in comprehensive oral 6 month- and 2-year studies with C₁₄₋ and C₁₄₋₁₆- α -olefin sulfonates. At 200-250 mg a.i./kg bw/day, a reduction in body weight gain was the only adverse effect in these studies.

No data were available with regard to the repeated dose toxicity of alkane sulfonates. Based on the similarity of metabolic pathways between alkane sulfonates, alkyl sulfates and α -olefin sulfonates, the repeated dose toxicity of alkane sulfonates is expected to be similar with NOAEL and LOAEL values in the same range as for alkyl sulfates and α -olefin sulfonates, i.e. 100 and 200-250 mg a.i./kg bw/day, respectively, with the liver as potential target organ.

Alkyl sulfates of different chain lengths and with different counter ions were not mutagenic in standard bacterial and mammalian cell systems (only Na salts were tested in the latter) both in the absence and in the presence of metabolic activation. There was also no indication for a genotoxic potential of alkyl sulfates in various *in vivo* studies on mice (micronucleus assay, chromosome aberration test, and dominant lethal assay).

α -Olefin sulfonates were not mutagenic in the Ames test, and did not induce chromosome aberrations *in vitro*. No genotoxicity data were available for alkane sulfonates. Based on the overall negative results in the genotoxicity assays with alkyl sulfates and α -olefin sulfonates, the absence of structural elements indicating mutagenicity, and the overall database on different types of sulfonates, which were all tested negative in mutagenicity assays, a genotoxic potential of alkane sulfonates is not expected

Alkyl sulfates were not carcinogenic in good quality feeding studies with male and female Wistar rats fed diets with C₁₂₋₁₅ ASO₄ Na for two years (corresponding to doses of up to 1125 mg /kg bw/day). No carcinogenicity studies were available for the alkane sulfonates.

α -Olefin sulfonates were not carcinogenic in mice and rats after dermal application, and in rats after oral exposure. Dermal applications in mice were carried out 3 times weekly for 92 weeks with a volume of 0.02 ml of either C₁₄₋₁₆ – or C₁₄₋₁₈ α -olefin sulfonates at concentrations of 20 or 25%. Rats were treated twice weekly for 104 weeks with a 10% solution of C₁₄₋₁₆ =/OHASO₃ Na. In the oral study, Sprague-Dawley rats were dosed with up to 259 mg C₁₄₋₁₆ =/OHASO₃ Na/kg bw/day

No fertility studies were performed with alkyl sulfates and alkane sulfonates. Oral dosing of male mice with C₁₂ ASO₄

Na (1 % over 2 or 0.1 % over 6 weeks) caused no adverse effects on epididymal spermatozoa, and a NOAEL for male fertility was derived at 1000 mg a.i./kg bw/day in an earlier SIDS document for sodium dodecyl sulfate. No indication for adverse effects on reproductive organs was found in various oral studies with different alkyl sulfates. For the α -olefin sulfonates a modern two generation reproductive toxicity study in male and female CD rats was performed with a mixture of C₁₄:C₁₆:C₁₈ blend (1:1:1 ratio) of α -olefin sulfonate, Mg salt. Two batches with an active ingredient content of ca. 95 % were used and the animals were continuously dosed with 0, 1250, 2500 or 5000 ppm (corresponding to about 1040 mg a.i./kg bw/day) in the diet with a protocol comparable to OECD TG 416. The animals showed no adverse effects up to and including the highest test concentration of 5000 ppm.

The developmental toxicity of various alkyl sulfates (C₁₂ ASO₄ Na, C₁₂₋₁₄ ASO₄ Na, C₁₂₋₁₅ ASO₄, C₁₃₋₁₅ ASO₄ Na, C₁₅₋₁₆ AS Na, C₁₆₋₁₈ ASO₄ Na) was tested on rats, rabbits and mice. Effects on litter parameters were restricted to doses that caused significant maternal toxicity (anorexia, weight loss, and death at doses between 300 and 500 mg a.i./kg bw for rats and at 300 mg a.i./kg bw/day for mice and rabbits), the principal effects being higher fetal loss and increased incidences of total litter losses. The incidences of malformations and visceral and skeletal anomalies were unaffected apart from a higher incidence of delayed ossification or skeletal variation in mice at ≥ 500 mg a.i./kg bw/day indicative of a delayed development. The lowest reliable NOAEL for maternal toxicity was about 200 mg a.i./kg bw/day in rats, while the lowest NOAELs in offspring were 250 mg a.i./kg bw/day in rats and 300 mg a.i./kg bw/day for mice and rabbits.

For the α -olefin sulfonates no adverse effects were reported in rats (dams and offspring) dosed with up to 600 mg a.i./kg bw/day of C₁₄₋₁₆ =/OHASO₃ Na during days 6-15 of pregnancy, i.e. the NOAEL was 600 mg a.i./kg bw/day both for maternal and developmental toxicity. From a parallel study with mice and rabbits no clear NOAEL can be derived due to an unusual spreading of the applied doses (0, 0.2, 2, 300 and 600 mg a.i./kg bw/day). At 2 mg a.i./kg bw/day no adverse effects were found, while at 300 mg a.i./kg bw/day adverse effects both in dams and offspring were observed.

No data were available for the reproductive and developmental toxicity of alkane sulfonates. Based on the available data, the similar toxicokinetic properties and a comparable metabolism of the alkyl sulfates and alkane sulfonates, alkane sulfonates are not considered to be developmental toxicants.

Although the database for category members with C_{<12} is limited, the available data are indicating no risk as the substances have comparable toxicokinetic properties and metabolic pathways. In addition, longer-term studies gave no indication for adverse effects on reproductive organs with different alkyl sulfates.

Environment

For sodium salts of alkyl sulfates, measured melting points are in the range of 181 °C (C₈) to 193 °C (C₁₆). Calculated melting points are in the range of 232 °C (C₈) to 286 °C (C₁₆).

Measured melting points for alkane sulfonates, alkene sulfonates, and hydroxy alkane sulfonates are not available. Calculated melting points are in the ranges of 227 - 281 °C (C₈₋₁₈ alkane sulfonates), 250 - 283 °C (C₁₂₋₁₈ alkene sulfonates) and 274 - 296 °C (C₁₄₋₁₈ hydroxy alkane sulfonates).

As ionic substances, all members of this category have extremely low vapor pressures. Calculated values are in the ranges 10⁻¹¹ to 10⁻¹⁵ hPa (C₈₋₁₈ alkyl sulfates), 4.3·10⁻¹¹ to 9·10⁻¹⁵ hPa (C₈₋₁₈ alkane sulfonates), 2.1·10⁻¹³ to 6.9·10⁻¹⁵ hPa (C₁₄₋₁₈ alkene sulfonates) and 3.3·10⁻¹⁷ to 5.8·10⁻¹⁹ hPa (C₁₄₋₁₈ hydroxy alkane sulfonates). Therefore, they decompose before reaching their theoretical boiling points.

Measured water solubilities are available only for alkyl sulfates; they are in the range 196 000 mg/l (C₁₂) to 300 mg/l (C₁₆) and by factors of 50 to 300 higher than calculated values (C₁₂: 617 mg/l, C₁₆: 5 mg/l).

As surfactants have a tendency to concentrate at hydrophilic/hydrophobic boundaries rather than to equilibrate between phases K_{OW} is not a good descriptor of surfactant hydrophobicity and only of limited predictive value for the partitioning of these compounds in the environment.

All calculated physico-chemical properties of surfactants should be treated with caution, because the estimation models do not take into account surfactant properties. In addition, the results are doubtful for ionic substances.

Deduced from physico-chemical and surfactancy properties the target compartment for the substances of this category is the hydrosphere. Based on the ionic structure partitioning into the atmosphere can be excluded. In water, the

compounds are stable to hydrolysis under environmental conditions.

Taking into account the low BCF factors (≤ 73) up to C_{16} that were determined for alkyl sulfates, any significant bioaccumulation is not expected.

Soil sorption increases with chain length. Strong sorption on soils would be expected for chain length 14 upwards. Sediment concentrations were between 0.0035 and 0.021 mg/kg dw indicating that accumulation in sediments is low. Under certain conditions of reduced moisture in soil, i.e. in arid or semi-arid regions, accumulation in soil cannot be excluded.

The substances of this category are readily biodegradable. Significant biodegradation of alkyl sulfates in the raw sewage, i.e. in the sewer system before reaching the WWTPs is very likely. The substances of this category are quantitatively removed in WWTP's, mainly by biodegradation. Because of the anaerobic degradation of alkyl sulfates in sewage sludge, exposure of agricultural soils due to application of sludge as fertilizer is not expected. However, for alkane sulfonates and α -olefin sulfonates this exposure pathway cannot be excluded due to their recalcitrant or limited anaerobic degradability.

The aquatic toxicity is influenced by a number of parameters, the length of the alkyl chain being most important. The pH and temperature of water bodies can affect the EC/LC₅₀ values for compounds that contain ammonium ions.

The most sensitive trophic level in tests on the toxicity of **alkyl sulfates** were invertebrates, followed by fish. Algae proved to be less sensitive. The key study for the aquatic hazard assessment is a chronic test on *Ceriodaphnia dubia*, which covers a range of the alkyl chain length from C_{12} to C_{18} . A parabolic response was observed with the C_{14} chain length being the most toxic (NOEC = 0.045 mg/l).

There are a number of valid acute toxicity data for many species from all trophic levels available. Taking the data from the whole subcategory into account chronic and subchronic data for all 3 trophic levels are available.

For **alkane sulfonates**, the acute toxicity on *Daphnia magna* has been determined for chain length $C_8 - C_{14}$. Results were comparable to AS in the range between C_8 and C_{10} , while C_{12} and C_{14} are significantly less toxic. Chronic data obtained for C_{12} ASO₃ Na and C_{12} ASO₄ Na with the rotifer *Brachionus calicyflorus* similarly show that alkane sulfonates might be less toxic than AS. C_{16} and C_{18} alkane sulfonates are assumed to exhibit the same toxicity than AS of comparable chain lengths. No data are available concerning the toxicity of alkyl sulfonates on fish and algae. However, a similar toxicity might be assumed because of structural and physico-chemical similarities between the three subcategories.

For **α -olefin sulfonates**, reliable short-term tests on fish, invertebrates and algae are available. The results indicate that toxicity is increasing as the alkyl chain length increases. The lowest available effect value is the 96 h-LC₅₀ = 0.5 mg/l, determined in tests on *Oryzias latipes*, *Rasbora heteromorpha* and *Salmo trutta*. For several substances of this subcategory the base set was incomplete (only 2 trophic levels covered). The data base for chronic toxicity is also rather small. For the whole subcategory, only one chronic *Daphnia* test, one algae NOEC and 2 subchronic fish tests are available, which were however not conducted with the most toxic substance from the acute tests. In a long-term test with sodium C_{11-14} olefin sulfonate as test substance, NOECs of 1.70 mg/l were determined for early ontogenetic stages of both the loach *Misgurnus fossilis* and the trout *Oncorhynchus mykiss*. In a test on the chronic toxicity to *Daphnia magna*, a NOEC of 4.4 mg/l for C_{14} =/OHASO₃ Na was obtained.

The effect of C_{12} ASO₄ Na on natural periphyton communities was assessed in a flow-through laboratory microcosm system. The 28 d-NOEC for algal periphyton communities was 0.055 mg/l. The ecotoxicological response of benthic and lotic microbial and invertebrate stream communities to C_{12} ASO₄ Na was assessed in a P&G experimental stream facility under outdoor conditions. The protozoan species richness increased with test substance concentrations, the 55 d-EC₂₀ was determined to be 0.063 mg/l.

Tests on the toxicity to **microorganisms** were only conducted with alkyl sulfates as test substances. A test on the inhibition of respiration of activated sludge resulted in an 3 -h-EC₅₀ of 135 mg/l (nominally). The lowest effect value for protozoa was obtained from a test on *Uronema parudczii* using C_{12} ASO₄ Na as test substance, the 20 h-EC₅ was 0.75 mg/l

Experimental test results on benthic organisms in a water-sediment system are not available. However, due to sediment-water partitioning coefficients $K_d < 350$, no significant risk for organisms in this compartment is to be expected.

For **terrestrial organisms** no valid experimentally derived test results are available. The available toxicity data were

excerpted from insufficiently documented studies. However, the data indicate that toxic effects on soil organisms might only be expected at high concentrations for alkyl sulfates. Toxicity of alkane sulfonates and α -olefin sulfonates can not be assessed because test results for terrestrial organisms are not available.

Exposure

In 2003, alkyl sulfate quantities of totally 118 000 t/a were consumed in the USA and Canada, 105 000 t/a in Western Europe, and 11 500 t/a in Japan.

The consumption of alkane sulfonates in Western Europe (the only significant user of alkane sulfonates) is estimated at 60 000 t/a in 2003.

The consumption of α -olefin sulfonates in Western Europe was about 6000 t/a and in Japan 3000 t/a, while the consumption in the USA and Canada is not reported (2003).

The chemicals of this category are anionic surfactants that are used at typical concentrations between 3 and 5% and up to 20% in consumer cleaning and personal care products, usually in conjunction with other surfactants. They function as laundry and liquid dishwashing detergents, dispersing agents, hard surface cleaners, shampoos, hair conditioners, liquid soaps, cleansing and other personal care products. There are no commercial or industrial process intermediate uses of the chemicals of this category. The predominant disposal route following use of the products that contain chemicals of this category is via wastewater.

Analytical measurements of alkyl sulfates reveal that the concentrations in effluents of waste water treatment plants are mostly below 10 $\mu\text{g/l}$. In the receiving surface waters, in the 1980s and 1990s, most of the available values were below 5 $\mu\text{g/l}$, with a maximum of 10.2 $\mu\text{g/l}$. No monitoring data are available for alkane sulfonates. Concentrations of α -olefin sulfonates (sum of C_{14} to C_{18}) measured in 2004 show a maximum of 0.16 $\mu\text{g/l}$.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

This category of chemicals is currently of **low priority** for further work.

These chemicals possess properties indicating a hazard for human health (corrosion/irritation, serious effects on the eye, acute toxicity). These hazards do not warrant further work as they are related to effects which may only become evident at exposure levels that are higher than formulated in consumer products. It should nevertheless be noted by chemical safety professionals and users of the raw materials. In the Sponsor country, occupational exposure is controlled and adequate risk reduction measures are in place by way of Material Safety Data Sheets. Member countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment:

The following chemicals are currently of low priority for further work due to their low hazard profiles:

AS: $\text{C}_8 - \text{C}_9$ (acute aquatic EC/LC_{50} values $>100 \text{ mg/l}$)

PAS: $\text{C}_8 - \text{C}_{12}$ (acute aquatic EC/LC_{50} values $>100 \text{ mg/l}$; chronic aquatic $\text{NOEC} >1 \text{ mg/l}$)

The following chemicals have properties indicating a hazard for the environment:

AS: $\text{C}_{10} - \text{C}_{14}$ & C_{18} (acute aquatic EC/LC_{50} values $>1 - \leq 100 \text{ mg/l}$; $\text{NOEC} \leq 1 \text{ mg/l}$)

PAS: C_{14} & C_{18} (acute aquatic EC/LC_{50} values $>1 - \leq 100 \text{ mg/l}$)

AOS: $\text{C}_{12} - \text{C}_{16}$ (acute aquatic EC/LC_{50} values $>1 - \leq 100 \text{ mg/l}$)

However they are of low priority for further work for the environment because of their rapid biodegradation under aerobic conditions and their limited potential for bioaccumulation.

The following chemicals have properties indicating a hazard for the environment (acute and chronic aquatic effects at concentrations below 1 mg/l):

AS: C₁₅ – C₁₆ (acute aquatic EC/LC₅₀ values $\leq$ 1 mg/l, NOEC $\leq$ 1mg/l)

PAS: C₁₅ – C₁₆ (acute aquatic EC/LC₅₀ values $\leq$ 1 mg/l, NOEC $\leq$ 1mg/l)

AOS: C₁₄₋₁₈ – C₁₆₋₁₈ (acute aquatic EC/LC₅₀ values $\leq$ 1 mg/l)

Therefore, they are candidates for further work. Furthermore, member countries are invited to perform an exposure assessment and if necessary a risk assessment.

Note:

The chemicals are supplied commercially under various CAS numbers which describe varying compositions. As a result of this variability it is not possible to state explicitly CAS numbers in the environmental recommendation, rather chain length ranges are used. The toxicity of these mixtures should take into account the toxicities of the individual homologues and their relative amount in the mixture.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	7631-99-4 7757-79-1 no CASRN 6484-52-2 15245-12-2 no CASRN 15978-77-5
Chemical Names	<u>Nitrate category:</u> sodium nitrate potassium nitrate potassium sodium nitrate ammonium nitrate calcium nitrate fertilizer calcium ammonium nitrate (CAN) nitrogen solutions (UAN)
Structural Formula	NaNO ₃ KNO ₃ NaNO ₃ /(KNO ₃) _x NH ₄ NO ₃ Ca(NH ₄) _x (NO ₃) _y (NH ₄ NO ₃) _z /CaCO ₃ and/or CaMg(CO ₃) ₂ CH ₄ N ₂ O and H ₄ N ₂ O ₃ blend

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

The nitrate category for fertilizer materials includes sodium nitrate (CAS No: 7631-99-4), potassium nitrate (CAS No: 7757-79-1), potassium sodium nitrate (CAS No: not available), ammonium nitrate (CAS No: 6484-52-2), 'nitric acid, ammonium calcium salt' (calcium nitrate fertilizer: CAS No: 15245-12-2), calcium ammonium nitrate (CAN: CAS No: not available) and nitrogen solutions (UAN; urea ammonium nitrate: CAS No: 15978-77-5).

The nitrate category members are all inorganic salts which are solid under ambient conditions (except UAN, which is a solution). Volatility of inorganic salts should be considered insignificant; any measurable vapor pressure is due to decomposition and release of ammonia gas from some ammonium containing category members (ammonium nitrate, calcium nitrate fertilizer, calcium ammonium nitrate and UAN). The nitrate salts are soluble in water and dissociate into the nitrate ion and the corresponding cations in biological fluids and aquatic environments. Based on similar environmental fate, ecotoxicological and toxicological properties, these nitrate compounds can be considered part of the same category.

Read-across is used for SIDS data gaps using data from other nitrate category members. The salts in the nitrate category will dissociate directly into nitrate ion and the corresponding cations, i.e. sodium, potassium and calcium. The cations are not expected to play a significant toxicological role at low doses. Data for urea and ammonium nitrate are also used as read-across for any data gaps.

Urea (CAS No. 57-13-6) has been presented in the OECD HPV Chemicals Programme and the dossier is published on the UNEP website (<http://www.chem.unep.ch/irptc/sids/oecd/sids/sidspub.html>). Urea data are provided in the context of the UAN category member. Data on the toxicity of the ammonium ion/*un-ionized* ammonia equilibrium in aqueous environments are available from the Ammonia category which was also previously presented in the OECD HPV Chemicals Programme, Ammonia Category (<http://cs3->

hq.oecd.org/scripts/hpv/).

Human Health

After uptake into biological systems, the salts in the nitrate category will dissociate directly into nitrate ion and the corresponding cations, i.e. sodium, potassium and calcium. The cations will enter the body electrolyte pool, and are not expected to play a significant toxicological role at low doses. Animal studies indicated that after intestinal absorption, ammonium ions are converted to urea in the liver, and subsequently excreted in urine (within 6 hours). After ingestion of nitrate, it will be partly reduced to nitrite in the saliva in the mouth (and the gastro-intestinal tract) in humans and nitrite is less efficiently absorbed in the rat than in humans. In humans most of ingested nitrate is excreted via the urine (65-75%). ADME data were not available for sodium nitrate or ammonium nitrate.

The acute oral LD₅₀ values range from 2,680 mg/kg bw for sodium nitrate (rabbit), 1,900 mg/kg bw for potassium nitrate (rabbit), and >2,000 mg/kg bw for potassium sodium nitrate, as well as for UAN (rat). No adverse clinical effects were observed. Reliable data were not available for the acute oral toxicity of ammonium nitrate. No acute oral study is available for calcium nitrate fertilizer. Dermal LD₅₀ values for potassium nitrate and ammonium nitrate were >5,000 mg/kg bw in rats. No signs of toxicity were observed. Potassium nitrate is fatal to humans at an oral dose of 214-500 mg/kg bw.

No reliable data were available on irritation and the sensitisation potential of the nitrates in animals or humans.

In a six-week dietary study with sodium nitrate, there was a slight or moderate reduced weight gain in rats at 5,000 or 10,000 mg/kg bw/day and at autopsy the abnormal colour of the blood and spleen due to methaemoglobin was marked in these same animals. In an OECD TG 422 study, rats were exposed to 0, 250, 750 and 1,500 mg/kg bw/day potassium nitrate via the oral route for 28 days. The NOAEL was 1,500 mg/kg bw/d based on the absence of adverse effects. Administration of sodium nitrate (0 and 4,000 mg/L) to rats in a drinking water study resulted in a LOAEL of 4,000 mg/L based on a decrease of vitamin E levels as well as an increased incidence of pulmonary lesions. A NOAEL was not established in this study.

Potassium nitrate and ammonium nitrate were not genotoxic *in vitro* in either bacterial or mammalian cell systems. Sodium nitrate was negative in an Ames test with and without metabolic activation and negative in *in vitro* micronucleus and chromosome aberration tests with mammalian human lymphocyte cells. The nitrate category members are not considered genotoxic *in vitro*.

Nitrates taken up in food may be implicated in the formation of N-nitroso compounds that are known mutagens and/or carcinogens. Sodium nitrate was found to promote urinary bladder cancer in rats after induction with N-butyl-N-(4-hydroxybutyl)-nitrosamine. However, no data indicating carcinogenicity of nitrate category members were available. No positive relationship has been found between cancer incidence and nitrate intake in several epidemiological studies.

In an OECD TG 422 reproductive/developmental toxicity screening study, rats were exposed to 1, 250, 750 and 1,500 mg/kg bw/day potassium nitrate. The NOAEL for reproduction and developmental toxicity was 1,500 mg/kg bw/d based on the absence of adverse effects. Potassium nitrate was given by gavage during gestation at doses up to 400 mg/kg (mice), up to 280 mg/kg (hamsters), up to 1980 mg/kg (rats) and up to 206 mg/kg (rabbits). No adverse effects of potassium nitrate were reported on nidation, maternal or fetal survival, or incidence of soft or skeletal tissue abnormalities. In a reproductive study in guinea pigs given potassium nitrate at concentrations of 300, 2,500, 10,000, and 30,000 ppm up to 204 days, the NOAEL for maternal reproductive toxicity was 10,000 ppm. In a two-generation rabbit study, sodium nitrate at dose levels of 0, 8, 250 or 500 mg/L in drinking water had no effect on the number of pregnancies, litter size or pup weights. Sodium nitrate was given by gavage during gestation at doses up to 400 mg/kg for groups of mice and hamsters and up to 250 mg/kg for groups of rats and rabbits. No effects of sodium nitrate were reported on nidation, maternal or fetal survival, or incidence of soft or skeletal tissue abnormalities. Sodium nitrate did not induce abnormalities of sperm heads in mice treated for three days but following 14 days of treatment with sodium nitrate, sex chromosomal univalency and abnormal sperm-head frequency were significantly higher in mice. However, statistically significant

reductions in fertility and litter size were not observed. Based on the available data, members of the nitrate category are not considered reproductive or developmental toxicants.

Members of the ammonia category, as previously discussed in the OECD HPV Chemicals Programme, are not considered reproductive or developmental toxicants.

Environment

All nitrate compounds in this category, except UAN (liquid), are solid under ambient conditions, very soluble in water and dissociate upon release into water. The melting points of the category members range from 169.6 to 334 °C. The category members decompose upon heating at temperatures greater than 210 °C. The vapor pressure of the nitrate category members is negligible for the inorganic salts and for UAN. In addition, in an aqueous environment the chemical behavior of ammonium nitrate is pH-dependent. Nitrate is denitrified by micro-organisms to nitrogen and nitrous oxide. Nitrates are not expected to bioaccumulate based on the fact that they are salts that dissociate in aqueous environments. Nitrate can be taken up by plants or denitrified again to yield nitrogen and nitrous oxide gas. As nitrates are biodegradable and very soluble in water, they are not expected to bioaccumulate in aquatic organisms. However, nitrates can have indirect and long-term effects on ecosystems, e.g. eutrophication. Nitrite may accumulate in plant tissue. Ammonium nitrate is capable of undergoing detonation if heated under confinement.

The ammonia/ammonium ion will exist in equilibrium depending on the pH. Under many environmental conditions (pH 5 to 8), the predominant form will be NH_4^+ . At pH 9 the ratio of ammonia to ammonium ion ($\text{NH}_3/\text{NH}_4^+$), should approach unity; at higher pHs, the proportion of NH_3 should increase. As pH decreases, the concentration of ammonium ion increases with respect to decreases of unionized ammonia concentrations. However, the toxicity of the unionized ammonia is considered several orders of magnitude greater than the more abundant ammonium ion.

The 96-hour LC_{50} values for fish (*Lepomis macrochirus* and *Oncorhynchus mykiss*) were greater than 100 mg/L (nominal) for all category members. For urea, the 96-hour LC_{50} was > 9100 mg/L in *Barilius barna*. For sodium nitrate and potassium nitrate the 48-hour EC_{50} values for *Daphnia magna* were 490 and 3,581 (analytical not specified) mg/L, respectively. For ammonium nitrate, the 7-day EC_3 for algae was 83 mg/L. Studies in several algal species (*Gyrosigma spencerii*, *Navicula spp.*, and *Nitzschia spp.*) with potassium nitrate indicate that the 7 or 10 d EC_{50} was > 1700 mg/L. In a cell multiplication inhibition test, the toxicity threshold for urea for *Scenedesmus quadricauda* for 192 hours was > 10,000 mg/L; the toxicity threshold for Green algae (*Scenedesmus quadricauda*) for 192 hours was > 10,000 mg urea/L. Based on the available data, members of the nitrate category are not considered toxic to aquatic organisms.

Exposure

Ammonium nitrate is predominantly produced in Europe and the USA (ca. 14,000 ktonnes). Calcium ammonium nitrate is produced mainly in Europe (ca. 10,000 ktonnes) whereas nitrogen solution is mainly produced in the USA (ca. 10,000 ktonnes). Calcium nitrate fertilizer, sodium nitrate, potassium nitrate and potassium sodium nitrate are produced in substantially lower volumes (< 7,500 ktonnes). The substances are mainly used as fertilizers.

Occupational exposure may occur in general during production, transport and processing of the substances. Field exposure to workers is possible during use as a fertilizer. The dermal and inhalation routes will be the most important routes of exposure. In the United States, the Occupational Safety and Health Administration (OSHA) has set permissible exposure limits (PEL) of 15 mg/m³ (as total dust); PEL (as respirable fraction) = 5 mg/m³ (8 hour Time Weighted Average). The OSHA PEL for particulates not otherwise regulated applies to all fertilizer dusts.

Consumer exposure may occur when using fertilizers. In the USA, sodium nitrate is also used as a direct

and indirect food additive and is regulated by the Food and Drug Administration. Consumer exposure to potassium nitrate may also occur from its use in toothpaste and to ammonium nitrate from its use in inks and adhesives. Ammonium nitrate is also used in explosive materials such as fireworks. In the USA, the water quality criterion for nitrate in water is 10 mg/L. Sodium nitrate, potassium nitrate, ammonium nitrate and nitric acid, ammonium calcium salt are also used as inert materials in pesticide formulations.

Environmental exposure is mainly limited to soil and water after fertilizer use.

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

Human Health: The chemicals in this category are of low priority for further work for human health due to their low hazard profile.

Note: It is recommended that the use of the chemicals as fertilizers be taken into account when assessing the exposure of nitrate and nitrite through drinking water.

Environment: The chemicals in this category are of low priority for further work for the environment due to their low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	Organoclays Category
CAS numbers and Chemical Names	71011-26-2: Quaternary ammonium compounds, benzyl(hydrogenated tallow alkyl)dimethyl, chlorides, compounds with hectorite, (Benzyl monoalkyl chain quaternary ammonium compound <i>[B(Alk)2M] hectorite</i>). Same as CAS numbers 94891-33-5 and 12691-60-0. 68953-58-2: Quaternary ammonium compounds, bis(hydrogenated tallow alkyl)dimethyl, salts with bentonite, (Dialkyl chain quaternary ammonium compound <i>[2M(2Alk)] bentonite</i>). Same as CAS numbers 1340-69-8 and 73138-28-0. 71011-27-3: Quaternary ammonium compounds, bis(hydrogenated tallow alkyl)dimethyl, chlorides, compounds with hectorite, (Dialkyl chain quaternary ammonium compound <i>[2M(2Alk)] hectorite</i>). Same as CAS numbers 94891-31-3, 97280-96-1 and 12001-31-9. 68153-30-0: Quaternary ammonium compounds, benzylbis(hydrogenated tallow alkyl)methyl, chlorides, compounds with bentonite, (Benzyl dialkyl chain quaternary ammonium compound <i>[B(2Alk)M] bentonite</i>). Same as CAS numbers 121888-66-2 and 89749-77-9. 97952-68-6: Quaternary ammonium compounds, benzylbis(hydrogenated tallow alkyl)methyl, salts with montmorillonite, (Benzyl dialkyl chain quaternary ammonium compound <i>[B(2Alk)M] montmorillonite</i>). 71011-24-0, 71011-25-1, 121888-68-4 and 89749-78-0: Quaternary ammonium compounds, benzyl(hydrogenated tallow alkyl)dimethyl, chlorides, compounds with bentonite; (Benzyl monoalkyl chain quaternary ammonium compound <i>[B(Alk)2M] bentonite</i>). 91080-57-8 and 91080-56-7: Quaternary ammonium compounds, benzyl (hydrogenated tallow alkyl) dimethyl, chlorides, compounds with smectite (Benzyl monoalkyl chain quaternary ammonium compound <i>[B(Alk)2M] smectite</i>). Note that 91080-56-7 is [di-C10-C22 alkyl, dimethyl]. 68911-87-5: Bis(hydrogenated tallow alkyl)dimethylammonium with montmorillonite (Dialkyl chain quaternary ammonium compound <i>[2M(2Alk)] montmorillonite</i>). 91081-06-0: Bis(hydrogenated tallow alkyl)dimethylammonium with smectite (Dialkyl chain quaternary ammonium compound <i>[2M(2Alk)] smectite</i>). Note this substance is [di-C10-C22 alkyl, dimethyl]. 121888-67-3: Quaternary ammonium compounds, benzylbis(hydrogenated tallow alkyl)methyl, salts with hectorite (Benzyl dialkyl chain quaternary ammonium compound <i>[B(2Alk)M] hectorite</i>).
Structural Formula	Variable molecular structures The quaternary ammonium compounds (cations) have the following general formula: $N^+ R_1 R_2 R_3 R_4$ where R₁, R₂, R₃, and R₄ are substitutions on the N (nitrogen atom) of the quaternary compound (salt) as follows: - methyl – 1 or 2 substitutions - benzyl – 0 or 1 substitutions - alkyl (C₁₄₋₂₂) – 1, 2 or 3 substitutions The clays (anions) are made of silicon, hydrogen and oxygen (hectorite, montmorillonite,

	bentonite and smectite); and sodium, lithium, and magnesium, (hectorite); sodium, calcium, aluminum, magnesium (montmorillonite, bentonite); or aluminum (smectite).

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

A key factor supporting the grouping of compounds within the Organoclays Category is structural similarity. Four clays (bentonite, smectite, montmorillonite, and hectorite) are represented by the CAS numbers in this category. These clays are closely related and, in some cases, have been used interchangeably to describe structurally similar clay minerals. Bentonite is a naturally occurring material consisting predominantly of the clay mineral montmorillonite, which is in turn in the family of sheet silicates called smectites. Hectorite is also included in the smectite group (along with stevensite and saponite). Deposits in which one of these clay minerals predominate are more commonly referred to by that clay mineral's name. Thus, considering the similarity in the clay minerals of this category, the defining differentiation between the groups is the organic cation which is reacted with the clay.

All smectite clay minerals (which include hectorite and montmorillonite in this category) possess similar structural properties. They are two-dimensional inorganic polymers with a layered structure. Each individual crystal is one unit cell (or about one nanometer) thick, up to 1000 nanometers across, and carries a net negative charge typically between 0.8-1.5 meq/g. This charge attracts cations to the large exterior surfaces of the individual clay crystals. The sodium and calcium cations common in naturally-occurring smectites give the layer surfaces a strongly hydrophilic nature, and the calcium cation binds to the clay more tightly than the sodium cation. The cations can be readily exchanged with quaternary ammonium cations to produce the organoclay compounds. In contrast to the calcium and sodium cations, the quaternary ammonium ions are tightly held to the clay, resulting in organoclay compounds ("salts") that are very hydrophobic in nature.

CAS numbers have been assigned in a way that suggests a category of many distinct compounds. The apparent complexity of this category results from (1) the same quaternary compound (salt) complexed with the three different clay types, and (2) the same alkyl (C14-22) moiety originating from different sources (tallow or vegetable oil).

Human Health

Based on the toxicokinetic data with B(Alk)2M bentonite, organoclay compounds are not expected to be absorbed following oral (gavage) exposure and will be excreted directly and rapidly in feces with negligible elimination via urine and bile. There is no evidence of any tissue retention or systemic uptake of these substances. Based on reported particle size distribution data for consumer and industrial products, these materials are not expected to be respirable. These materials are also not expected to be absorbed through the skin based on the physical chemical properties as well as these reported particle sizes.

Numerous acute toxicity studies have been conducted with all organoclay category members except B(2Alk)M monomontmorillonite. The studies show a low order of toxicity with inhalation 4-hr LC₅₀s and oral (gavage) LD₅₀s greater than 5.0 mg/L and 5,000 mg/kg bw, respectively. The inhalation 1 hr LC₅₀ > 200 mg/L for B(Alk)2M hectorite. Common clinical signs associated with acute inhalation in several studies included transient weight loss and respiratory irregularity. Clinical signs observed in the oral studies included diarrhea, rapid breathing, piloerection, swollen abdomen, ataxia and lethargy. Acute dermal toxicity studies were not located for the organoclays. The organoclays are not irritating to the skin. Eye irritation is generally minimal in humans (irritation due to the physical nature of the compounds were noted), although observations of moderate irritation have been reported in animals. Skin sensitization tests conducted with 2M(2Alk) bentonite, and B(Alk)2M bentonite and B(2Alk)M hectorite indicate the organoclay materials are not sensitizers.

Repeated-dose toxicity studies by the oral route of exposure (gavage or dietary) and using methods similar to OECD TG 407 have been conducted with 2M(2Alk) bentonite, and B(Alk)2M bentonite and B(2Alk)M hectorite. The NOAEL for 2M(2Alk) bentonite in a 12-week rat dietary study was 25% (approx. 12,500-25,000 mg/kg-bw/day), the

highest dose tested. The NOAEL for B(Alk)2M bentonite in a 28-day rat oral (gavage) study was 1,000 mg/kg bw/d, the only dose tested. The LOAEL for B(2Alk)M hectorite in a 28-day rat oral (gavage) study was 1,000 mg/kg bw/d, the only dose tested based on decreased thrombotest time, decreased chloride and calcium levels, and increased adrenal weights. The repeated-dose toxicity of the remaining members of the Organoclays Category (B(Alk)2M hectorite, 2M(2Alk) hectorite, B(2Alk)M bentonite and B(2Alk)M montmorillonite) is expected to be similar.

The category members B(Alk)2M hectorite, 2M(2Alk) bentonite, and 2M(2Alk) hectorite were tested in bacterial reverse mutation assays (with and without metabolic activation) and B[Alk]2M hectorite was tested *in vitro* using mouse lymphoma cells; these substances were negative for gene mutations in these assays. B(Alk)2M bentonite, was also negative in a reverse mutation assay. In *in vivo* chromosomal aberrations and *in vivo* micronucleus assays, B[Alk]2M bentonite and B[2Alk]M hectorite were both negative for chromosomal aberrations. Further testing is not appropriate due to the physical chemical properties of these materials.

There are no data available regarding the carcinogenicity of these materials. The impurity, respirable crystalline silica, (which may be present at levels of 0.2% in B(Alk)2M hectorite; 0.1-5% in 2M(2Alk) bentonite; and 0.1-10% in B(2Alk)M bentonite) is considered a known human carcinogen (Group 1 according to IARC).

A one-generation reproduction study using B(2Alk)M hectorite at dose levels of 0, 50, 225, and 1,000 mg/kg bw/d has been conducted for the potential to cause developmental toxicity in rats. The compound was not found to be teratogenic, nor was there any reproductive toxicity at any dose level. Based on the lack of reproductive toxicity or developmental effects with B(2Alk)M hectorite, the sponsored organoclay materials are not expected to cause developmental toxicity or to demonstrate reproductive toxicity at doses up to 1,000 mg/kg bw/day.

Environment

Although there may be some degradation when subjected to extreme heat beginning at about 180°C up to approximately 600°C, the organoclays do not melt or boil. Organoclays are free flowing solid powders that are essentially insoluble in water, in organic solvents and in lipids, and have no volatility under ambient conditions. Vapor pressure is not relevant because all members of the category are powders and are not volatile. Since organoclays are essentially insoluble in both water and lipids, the partition coefficient cannot be accurately determined. Densities of the substances range from 1.4 to 1.8. Organoclays are not inherently explosive, nor are they oxidizers.

Organoclays are anticipated to be found primarily in soil or sediment, although it is possible that smaller particles will be suspended in water. Estimates of atmospheric photodegradation are also not relevant due to the nature of these compounds. Organoclays will not hydrolyze because they resist base or acid attack over a pH range of 3-11. Because of their physico-chemical nature the organoclays cannot be evaluated using EPIWIN for distribution among environmental compartments.

In three separate OECD TG 306 biodegradation tests using B(2Alk)M bentonite, biodegradation ranged from 4.7 to 33.4% in 28 days, depending on the test. Based on these data as well as the structural and chemical properties of these compounds, it is assumed that other organoclay category members will also show limited biodegradation. It should be noted that biodegradation relates only to the organic component of the organoclays (i.e. the alkyl quaternary ammonium salts).

Fish acute toxicity studies have been performed with B(Alk)2M bentonite. The 96-hr LC₅₀ was > ca. 500 mg/L (nominal) in freshwater rainbow trout. In a semi-static test with rainbow trout (*Oncorhynchus mykiss*), the 21-day LC₅₀ was >1.0 mg/L (nominal) for this substance.

Acute aquatic invertebrate tests have been conducted. The nominal EC₅₀ values for the water flea (*Daphnia magna*) were >100 mg/L (48 hrs) for the category member 2M(2Alk) bentonite, 300 mg/L (96 hrs) and < 500 mg/L (48 hrs) for B(Alk)2M bentonite, and >100 mg/L (96 hrs) for B(2Alk)M hectorite. The value of < 500 mg/L for B(Alk)2M bentonite is presented because an EC₅₀ could not be determined from this study that used only one concentration. EC₅₀ values in other species (*Mysidopsis*, *Acartia tonsa*) for category members were similar or showed lower toxicity.

Data on acute toxicity to the aquatic plant *Skeletonema costatum* are available. The 72-hr ErC_{50} (growth rate) was >1,000 mg/L (nominal) for 2M(2Alk) bentonite. In three tests using B(2Alk)M bentonite, the 72-hr ErC_{50} values were 23.8, 82.3 and >1,000 mg/L. It is likely that physical toxicity occurred in some studies, including the study reporting an EC_{50} of 23.8 mg/L; however, the study did not provide additional information regarding evidence of dispersed material. For B(2Alk)M hectorite, the 72-hr EbC_{50} , ErC_{50} (0-24 hr), and NOEC were >100, >100, and 100 mg/L (nominal), respectively.

Chronic aquatic toxicity studies are also available for B(2Alk)M hectorite. A 21-day EC_{50} (reproduction) in *Daphnia magna* was 7.6 mg/L (nominal) and the NOEC was 3.2 mg/L. Mortalities (immobilization) that occurred at 32 mg/L were considered to be due in part to physical effects of the test material.

The LC_{50} s for 2M(2Alk) bentonite, 2M(2Alk) hectorite, and B(2Alk)M bentonite were >10,000, >1,269, and >10,000 mg/kg, respectively, when assessed for toxicity to a sediment re-worker mud shrimp (*Corophium volutator*).

Several terrestrial tests have also been conducted. In an earthworm acute toxicity test, the 14-d NOEC was 1,000 mg/kg for B(Alk)2M bentonite and B(2Alk)M hectorite. In a study of emergence and early growth stages of cress seedlings (*Lepidium sativum*) using B(2Alk)M hectorite, the LOEC was 1 mg/kg (no NOEC determined) and the LC_{50} was 9 mg/kg. The EC_{50} s were >100 mg/kg for the emergence and early growth stages of wheat and radish seedlings (*Triticum aestivum* and *Raphanus sativus*, respectively) exposed to B(2Alk)M hectorite. The NOECs were both 100 mg/kg, the highest doses tested.

Exposure

The 2005 production volumes for the USA (Sponsor country) were:

B(Alk)2M) hectorite = 1.46 million pounds (ca. 662 tonnes);
 2M(2Alk) bentonite = 73.04 million pounds (ca. 33,130 tonnes);
 2M(2Alk) hectorite = 9.31 million pounds (ca. 3223 tonnes);
 B(2Alk)M) bentonite = 15.67 million pounds (ca. 7108 tonnes);
 B(2Alk)M) montmorillonite = 0 million pounds (0 tonnes).

The common functional feature of the Organoclays Category is their use as rheological agents and/or additives for non-aqueous fluids. Rheological additives are materials that affect in a controlled and predictable way the flow properties of liquids or powders. Selection of the clay type, specific quaternary ammonium compound, and reaction conditions enables design of organoclays for specific applications.

The downstream uses of organoclay rheological additives, including approximate percentage, are:

coatings including paints (43%);
 oil field applications including drilling muds (37%);
 printing inks (13%);
 cosmetics (3%); and,
 other, including remediation and nanocomposites (4%).

Closed systems are used in some facilities. In these facilities, the material is delivered in bags, dumped into a hopper with a capture exhaust. At other facilities, a portion of the processing may occur in of open systems (e.g., loading of the material, discharging of final product, or the bagging station may be open), while other portions may be closed (e.g., drying and other processes). Some types of engineering controls are used in all manufacturing facilities. For example, depending on the facility, material loading will have a suction system; local area ventilation is used in areas not fully enclosed; dust collectors and simple ventilation are used and capture exhaust is employed. The product is stored in warehouses in sealed multi-wall craft paper bags, palletized, and heat-shrink-wrapped. The product leaves the manufacturing facility in sealed bags on trucks and is transferred to barges where the products are placed in shipping containers of various types. Generally, about 10-20 metric tons are sent by ship. On rare occasions (e.g. emergencies), less than one metric ton is shipped by airplane.

Worker exposure is most likely to occur during loading, discharging, bagging and sampling. There may also be minimal equipment leaks of fugitive dust. All routes of exposure (inhalation, dermal, and ingestion) are possible at the manufacturing level. However, the most likely exposure route is inhalation of dust, followed by dermal contact. At the bagging station, local area ventilation is used at all plants to ensure workers do not exceed 8 hour time-weighted exposure limits established by for example, ACGIH TLVs for Cristobalite silica, and Quartz silica; ACGIH TLV's and OSHA PEL's for Respirable Dust and Total Dust. Respirators are available for additional protection as needed. Dermal contact is minimized through the use of protective clothing. Industrial hygiene monitoring assessments for airborne contaminants have been conducted during manufacturing operations at two confidential locations. These assessments showed worker exposures that were less than the respective occupational exposure limits.

At the industrial customer level, use is predominantly in open systems, although some industrial customers' systems are closed. For example, the 50-lb bags are opened at the customer site and dumped into a hopper. The hopper generally has suction, which draws the material into the process. Most customers use local area ventilation in areas that are not enclosed (for example, to minimize dust generation during bag emptying into mixing tanks). Exposures are most likely to occur at the bag dumping stations. As at the manufacturer, the industrial customer also typically employs a combination of local area ventilation and respirators at the majority of facilities to ensure workers do not exceed 8-hour time-weighted exposure limits for cristobalite and quartz silica as well as total and respirable dust established by ACGIH or OSHA.

Organoclay materials are used in industrial and personal consumer products such as solvent-borne paints and stains, in specialty coatings and adhesives, specialty sealants, cosmetics and personal care products (antiperspirants) and drilling fluids. When used in paints or adhesives, the organoclay material is encapsulated in the final product. Use of organoclays in cosmetics or personal care products may result in dermal and inhalation exposure. In paint, the average amount of organoclay in the final product is 0.5 to 0.7 %. Most other consumer products contain 1-3% or less of the total formulation. However, some products (e.g., for fireplace/stove home maintenance) may contain higher percentages (e.g., < 45% 2M(2Alk) bentonite in fireplace/stove repair paste and 1-10% 2M(2Alk) bentonite in plumbing putty). For oil drilling, most products contain 1-3% w/w of the total formulation. Less than 1% of organoclay powders as supplied will have particle sizes below 10 µm. For high quality consumer applications such as paints and coatings, inks, lubricating grease, cosmetic applications, etc., these materials are typically ground to an average particle size of ca. 75 µm. For organoclay agglomerates, principally used in oil based drilling fluids, particle sizes may range up to ca. 6 mm in diameter.

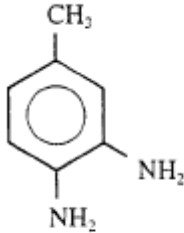
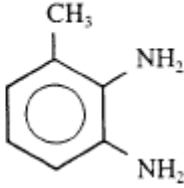
The quaternary ammonium compounds in the organoclays are tightly held to the clay by strong ionic forces and through chemisorption to the clay. In situations where the quaternary compounds are included in excess of the exchange capacity of the clay, that "excess" is likely to be chemisorbed to the clay and not fugitive. Under normal conditions of use it is very unlikely there would be exposure to the quaternary ammonium compounds themselves.

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

Human Health: The chemicals are currently of low priority for further work. The chemicals possess properties indicating a hazard for human health (minimal to moderate eye irritation, respiratory irritation observed in acute studies using high exposure levels, potential carcinogenicity from crystalline silica, which is an impurity in amounts up to 10 percent for some of the substances). Based on data presented in the sponsor country (relating to production in the Sponsor country which accounts for an unknown fraction of global production and relating to the use pattern in the Sponsor country), risk management measures are being applied in occupational settings (occupational limits for cristobalite silica and quartz silica and for respirable and total dust). Countries may desire to check their own risk management measures to determine whether there is a need for additional measures.

Environment: The chemicals are currently of low priority for further work due to their low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	2687-25-4, 496-72-0, 25376-45-8 and 26966-75-6
Chemical Names	o-TDA <u>category</u> : 2,3-toluenediamine (2,3-TDA), 3,4-toluenediamine (3,4-TDA) and commercial TDA mixture (2,3/3,4-TDA (40/60))
Structural Formula	 Toluene-3,4-diamine  Toluene-2,3-diamine

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

The o-TDA category consists of two individual compounds, 3,4-TDA (CAS No. 496-72-0) and 2,3-TDA (CAS No. 2687-25-4), and a commercially supplied mixture in which these isomers are the major constituents in a 60/40 ratio, respectively (CAS No. 25376-45-8 and 26966-75-6 referred to as commercial TDA mixture (2,3/3,4-TDA (40/60))). Only the isometric mixture (2,3/3,4-TDA (40/60)) is available commercially. The following structural analogue of the sponsored substances is used to address the endpoints for biodegradation, repeat dose toxicity and reproductive toxicity: 2,4-toluenediamine (2,4-TDA; CAS number 95-80-7, presented and agreed upon at SIAM 22). 2,4-TDA is a structural isomer of the sponsored substances, differing in the substitution pattern of the amine groups on the tolyl ring; having similar physical chemical properties; similar environmental fate; and similar health effects (acute toxicity and genotoxicity). As a result, data from 2,4-TDA can be used for read across to 2,3-TDA, 3,4-TDA and commercial TDA mixture (2,3/3,4-TDA (40/60)).

It should be noted that CAS number 25376-45-8 is used to represent all of the individual mixed TDA isomers (m, o, and p). In the context of this assessment, the sponsored mixed isomer data consist of only o-TDA which is a commercial TDA mixture of 2,3/3,4-TDA (40/60) using CAS numbers 25376-45-8 and 26966-75-6. A dossier for m-TDA CAS number 25376-45-8 was previously created and presented at SIAM 22 and only consisted of those data representing m-TDA commercial mixture (2,4/2,6-TDA (80/20) isometric mixture. In order to distinguish between the two isomeric mixtures that are represented by the same CAS number (25376-45-8), two separate dossiers were created.

Human Health

Metabolism data are not available on commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3- and 3,4-TDA. Data on the close structural analogue 2,4-TDA are available. Toluene-2,4-diamine (2,4-TDA) is almost completely absorbed via the gastrointestinal tract in animals and well absorbed via the skin (54% in monkeys and 24% in humans over an exposure time of 24 h). No data are available on absorption by

inhalation. In rats, the highest tissue concentrations were measured in liver and kidney after oral or i.p. administration. Concentrations in heart, lungs, spleen, and testes were significantly lower. There are no species-related differences in tissue distribution between mice and rats.

In rats, rabbits, and guinea pigs, unchanged 2,4-TDA was excreted via urine in concentrations from 0.1 to 3%. 2,4-TDA is mainly hydroxylated at the ring under formation of aminophenols (major pathway) and additionally N-acetylation occurs. The excretion of metabolites predominantly occurs via urine in rats and mice. Similar findings are anticipated for commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3- and 3,4-TDA.

The oral LD₅₀ of mixed commercial TDA mixture (2,3/3,4-TDA (40/60)) in rats was = 660 mg/kg bw; for 2,3-TDA the value was = 812 mg/kg bw. Clinical signs during exposure to commercial TDA mixture (2,3/3,4-TDA (40/60)) included decreased locomotor activity, ptosis, piloerection and death. 2,3-TDA exposure produced clinical signs including ruffed fur and very sluggish behaviour. Gross necropsy revealed congestion throughout the lungs and abdominal viscera, mottled livers, and effects on the stomach and intestines. The dermal LD₅₀ of commercial TDA mixture (2,3/3,4-TDA (40/60)) and 2,3-TDA (rabbits) was = >5750 mg/kg bw (highest dose tested) and = 1120 mg/kg bw, respectively.

Mild/slight skin irritation is expected following exposure to commercial TDA mixture (2,3/3,4-TDA (40/60)). Mild/slight eye irritation was observed following exposure to commercial TDA mixture (2,3/3,4-TDA (40/60)). Similar effects are anticipated for 2,3- and 3,4-TDA.

Repeated dose studies are not available for the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA or 3,4-TDA. Based on structural similarities, data from 2,4-TDA presented at SIAM 22 are used to fulfil this endpoint. Animal studies have shown that the main toxic effect associated with dietary exposure of 2,4-TDA is hepatotoxicity. In short-term studies effects were characterized by a decrease in body weight and an increase in the liver: body weight ratios. In long-term studies toxic effects on the liver accelerated the development of chronic renal disease in rats, an effect that contributed to a marked decrease in survival. In a 2-year feeding study in rats (doses 5.9 and 13 mg/kg bw/d, OECD TG 452), the lower dose of 5.9 mg/kg bw/d showed toxic effects in the liver and kidneys and increased tumor incidences in the liver (male rats, female rats, female mice), and in the mammary gland (female rats) (LOAEL). An overall NOAEL was not demonstrated.

In vitro, 3,4-TDA is considered positive in bacterial gene mutation assays and mammalian mutagenicity studies

In vivo, there was a clear indication of a clastogenic effect of the commercial TDA mixture (2,3/3,4-TDA (40/60)) administered i.p. in a somatic cell test system (mouse micronucleus assay). 3,4-TDA induced chromosomal damage in the bone marrow of mice at doses of 244 mg/kg bw and above following i.p. injection. Inhibition of DNA synthesis was observed in mice injected i.p. once with 500 mg/kg bw. The available data suggest that commercial TDA mixture (2,3/3,4-TDA (40/60)) and 3,4-TDA are likely to be genotoxic.

No data for carcinogenicity are available for mixed commercial TDA mixture (2,3/3,4-TDA (40/60)), 3,4-TDA and 2,3-TDA. Supplemental data from 2,4-TDA is provided for informational purposes. 2,4-TDA is carcinogenic in long-term animal studies similar to OECD TG 453. In F344 rats, liver tumors are produced in both genders and mammary tumors in females after oral administration with doses of 5.9 and 13 mg/kg bw/d. 2,4-TDA was also carcinogenic for female B6C3F1 mice, inducing hepatocellular carcinomas at doses of 15 and 30 mg/kg bw/d. Local sarcomas were demonstrated after subcutaneous application of 25 mg/kg bw/d to SD rats over a 2-year period (doses 8.3 and 25 mg/kg bw/d). The available data suggest that commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA may have a carcinogenic potential.

Effects on fertility studies are not available for the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA. Data from the close structural analogue, 2,4-TDA are used to address this endpoint. Severe testicular atrophy in rats was shown at 28 mg/kg bw/d 2,4-TDA in a 15-month study. Inhibited spermatogenesis (66%) associated with a significant reduction in the weights of seminal vesicles and epididymides, morphological damage of Sertoli cells as well as with a diminished level of serum

testosterone and an elevation of serum LH was observed at 15 mg/kg bw/d in a 10-week male rat feeding study with dose levels of ca. 5 and 15 mg/kg bw/d. 5 mg/kg bw day is considered as marginal LOAEL for effects in reproductive organs as it causes a decrease in epididymal sperm reserves. No NOAEL was established.

Rats exposed to the commercial TDA mixture (2,3/3,4-TDA (40/60)) showed significantly reduced body weights and body weight gains at 300 mg/kg bw/day. Fetal body weights at 300 mg/kg bw/day were also significantly reduced, along with a significant increase in the number of incomplete vertebrae at 100 and 300 mg/kg bw/day. Fetuses at 300 mg/kg bw/day also showed increased incidence of missing sternebrae and incomplete skull closure. The occurrence of hemorrhagic abdomen was increased at 10, 100 and 300 mg/kg/day. The NOAEL (maternal) = 100 mg/kg bw/day and the NOAEL (developmental) = 30 mg/kg bw/day. In rabbits, swollen, red or pink eyelids were documented and in maternal animals body weight and body weight gains were significantly reduced at 100 mg/kg/day bw. The percentage of dams that resorbed their entire litter was significantly increased and fetal weights were significantly reduced at 100 mg/kg bw/day. Fetal survival was significantly reduced at 100 mg/kg/day. Examination of the skeletal and soft tissue revealed no significant differences between any of the test groups and the controls. The NOAEL (maternal) = 30 mg/kg bw/day and the NOAEL (developmental) = 30 mg/kg bw/day. As a result of these data the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA are considered to be reproductive and developmental toxicants.

Environment

The commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA are in solid form for shipping but are heated into a molten liquid for transfer. The melting points of the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA range from 40 - 50°C, 63-64 °C and 88.5-93 °C, respectively. The boiling points for the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA are >250°C, 255 °C and 265 °C at 1013 hPa. The vapor pressures are 2.96 hPa at 100 °C (commercial TDA mixture (2,3/3,4-TDA (40/60))) and, 0.00074 hPa (2,3-TDA) and 0.00084 hPa (3,4-TDA) at 25 °C. In the case of 2,3-TDA measured vapor pressure values are also available indicating 6.66, 26.6 and 133 hPa at 119, 149 and 198°C, respectively. Model estimates of water solubility and partition coefficient estimates are not appropriate for mixtures such as the commercial TDA mixture (2,3/3,4-TDA (40/60)) isomer. However, estimates are available for 2,3-TDA and 3,4-TDA. The estimated water solubility for both 2,3-TDA and 3,4-TDA is 13.85 g/L at 25 °C. The estimated partition coefficient for 2,3-TDA is 0.71 at 25°C while the experimental value for 3,4-TDA is 0.66 at 25°C. The Henry's Law Constant is estimated to be 7.43E^{-10} for both 2,3 and 3,4 TDA via the bond method.

Photodegradation half-lives based on default input parameters in EPIWIN v3.12 for both 2,3- and 3,4-TDA indicate a half-life of 0.6 hours with the overall OH rate constant being 200.1360E^{-12} ($\text{cm}^3/(\text{molecule} \cdot \text{sec})$). Model estimates for the mixed isomer are not appropriate.

A hydrolysis study was attempted on the commercial TDA mixture (2,3/3,4-TDA (40/60)) mixture following OECD TG 111. Results of this study conclude that the commercial TDA mixture (2,3/3,4-TDA (40/60)) shows degradation reactions in aqueous buffer solutions which are easily influenced by different factors (pH with faster degradation occurring at lower pHs and oxidation).

Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 300 kg/h for each media, using default input parameters shows the following percent distribution for the individual constituents, 2,3-TDA: Air = 0.0142%, Water = 48%, Soil = 51.9%, and Sediment = 0.0928%; and 3,4-TDA: Air = 0.0143%, Water = 48.3, Soil = 51.6% Sediment = 0.0929%. Fugacity estimations are not applicable to mixtures such as the commercial TDA mixture (2,3/3,4-TDA (40/60)).

Available data on 3,4-TDA indicate the substance to not be readily biodegradable (0% degradation after 28 days) this is further supported by data from 2,4-TDA. Similar findings are anticipated for the commercial TDA mixture (2,3/3,4-TDA (40/60)) and 2,3-TDA. These substances are not anticipated to bioaccumulate. The estimated BCF for 2,3-TDA and 3,4-TDA is 3.16. Model estimates are not appropriate for the commercial TDA mixture (2,3/3,4-TDA (40/60)), but BCF values are expected to be similar.

In fish (*Brachydanio rerio*), the 96-hour LC_{50} was = 20 mg/L for 3,4-TDA. Results from ECOSAR v0.99h

indicate that the predicted 96 hr LC_{50} = 14.769 mg/L for both 3,4 and 2,3-TDA.

In an acute aquatic invertebrate study in *Daphnia magna* conducted with the commercial TDA mixture (2,3/3,4-TDA (40/60)), the 48h EC_{50} is 1.73 mg/L (nominal). Analyses were only conducted on the three highest test concentrations (1, 3, and 10 mg/L). Recoveries were within 20% of nominal in the two highest concentrations. In the lowest concentration (1 mg/L) recovery was within 60% of nominal concentration. Results from ECOSAR v0.99h indicate that the predicted 48 hr LC_{50} = 0.421 mg/L for both 3,4 and 2,3-TDA. In an inhibition of growth to aquatic plants study (OECD TG 201), the following 72 hour EC_{50} values were reported based on nominal concentrations: (E_rC_{50}) = 0.94 mg/L and (E_yC_{50}) = 0.040 mg/L. However, in the test concentrations decreased markedly by test end and analysis was only conducted on the three highest concentrations (1, 3 and 10 mg/L.) From the analytical recoveries recorded for these three concentrations a general correction was made for all test concentrations. On this basis the 72 hour EC_{50} measured values are: (E_rC_{50}) = 0.38 mg/L and (E_yC_{50}) = 0.021 mg/L. As effects were seen at all test concentrations a NOEC can not be determined. Results from structure activity relationship tools, ECOSAR v0.99h indicate that the predicted 96 hr EC_{50} = 0.134 mg/L for both 3,4 and 2,3-TDA.

Exposure

Global production volumes of the commercial TDA mixture (2,3/3,4-TDA (40/60)), including 2,3-TDA and 3,4-TDA, are not available. United States production volumes are estimated to be in the range of 1 to 10 million pounds. The commercial TDA mixture (2,3/3,4-TDA (40/60)) is manufactured in closed systems and primarily used on-site.

The only potential for exposure as a result of manufacture is during loading of the product(s). Occupational monitoring records indicate that occupational levels are kept below the American Industrial Hygiene Association recommended value. The commercial TDA mixture (2,3/3,4-TDA (40/60)) is available in 55 gallon non-returnable drums, 5,000 gallon tank trucks, 5,000 gallon isocontainers and 20,000 gallon tank rail cars.

There is no known use in consumer products.

Under normal use, the only potential exposures to the environment from the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA would be due to accidental spills or releases.

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

Human Health: The chemicals in this category are candidates for further work. These chemicals possess properties indicating a hazard for human health (repeated dose toxicity (body weight, lung, liver and kidney), genotoxic, carcinogenic, reproductive and developmental effects). Member countries are invited to perform an exposure assessment and if then indicated a risk assessment.

Environment: The chemicals in this category are candidates for further work. These chemicals possess properties indicating a hazard for the environment (acute toxicity to aquatic invertebrate and algae (< 1 mg/L)). Member countries are invited to perform an exposure assessment and if then indicated a risk assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	17855-14-0 7778-80-5 7778-18-9
Chemical Names	<u>Sulfate category:</u> potassium magnesium sulfate calcium sulfate potassium sulfate
Structural Formula	$K_2Mg(SO_4)_2$ K_2SO_4 $CaSO_4$

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

The sulfate category consists of the inorganic salts; potassium magnesium sulfate, potassium sulfate and calcium sulfate. In biological fluids and aquatic environments, the soluble portion of each category member completely dissociates into the sulfate ion (SO_4^{2-}) and the corresponding cations; potassium (K^+), magnesium (Mg^{2+}) and calcium (Ca^{2+}) at neutral pH. Based on similar physicochemical, ecotoxicological and toxicological properties, these sulfate compounds can be considered part of the same category. Available data for calcium sulfate, dihydrate (CAS No. 10101-41-4), the hydrated form of the category member, and previously presented in the OECD HPV program, is used as read-across to fill data gaps for the category members.

Human Health

Upon uptake into biological systems the inorganic salts in the sulfate category will dissociate into the sulfate ion and the corresponding cations. Potassium, magnesium and calcium will enter the body electrolyte pool, and are not expected to play a significant toxicological role except at extremely high doses. Sulfate is an important macronutrient for the normal function of cells and is the fourth most abundant anion in human plasma (300 μM). Sulfate is absorbed from the intestine by an active transport system. All cells have sulfate transporters for the influx/efflux of sulfate. Sulfate is also used for detoxification of compounds to sulfate esters, which can be excreted in the urine. Sulfate is eliminated by the kidney and levels are regulated by the kidney through a reabsorption mechanism.

The acute oral LD_{50} values for potassium magnesium sulfate is $>2,000$ mg/kg bw (OECD TG 423/425). No adverse clinical signs were observed. Although only reliability 4 studies were available for calcium sulfate and potassium sulfate, reported LD_{50} s for these substances were consistent with that reported for potassium magnesium sulfate. No reliable acute dermal or inhalation toxicity data in animals are available. There are no reliable skin/eye irritation or sensitization studies for the sulfates. The category/analogue, calcium sulfate dihydrate is not a skin irritant or a skin sensitizer in experiments performed to OECD TG 404 and 406, respectively. Dust of anhydrous calcium sulfate has an irritant effect on the respiratory tract and eyes in humans in occupational settings, which may be related to its desiccant properties. The irritating effects of anhydrous calcium sulfate cannot be applied to the category as a whole.

In a combined repeated-dose/reproductive/developmental toxicity screening study (OECD TG 422) rats were treated with 0, 50, 750 and 1,500 mg/kg bw/day potassium sulfate by oral gavage for 28 days. The NOAEL was 1,500 mg/kg bw/day based on the absence of treatment related adverse effects at the highest dose tested. In a combined repeated-dose/reproductive/developmental screening study (OECD TG 422), rats were treated by oral gavage with 0, 100, 300 and 1000 mg/kg bw/day of the category analogue calcium sulfate, dihydrate. Male rats showed changes in clinical chemistry (decreased levels of total protein, albumin, blood urea nitrogen, and creatinine) at 300 mg/kg bw/day. Female rats showed no treatment related effects at the highest dose tested. The overall NOAEL was 100 mg/kg bw/day. As the clinical chemistry effects observed were only seen for calcium sulfate and not for potassium sulfate the effects can be ascribed to the calcium ion. No repeated-dose studies for calcium sulphate and potassium magnesium sulphate are available.

Potassium sulfate and calcium sulfate were negative with and without metabolic activation in Ames tests (OECD TG 471) and *in vitro* chromosomal aberrations tests (OECD TG 473). No *in vitro* genotoxicity studies were available for potassium magnesium sulphate. Calcium sulfate dihydrate tested negative in the micronucleus test *in vivo* up to the test concentration of 5000 mg/kg bw (OECD TG 474). The members of the sulfate category are not considered to be mutagenic or genotoxic. No reliable data are available for carcinogenicity.

In a reproductive/developmental toxicity screening study (OECD TG 422), rats were treated with 0, 50, 750 and 1500 mg/kg bw/day potassium sulfate by oral gavage. The NOAEL for reproduction and developmental toxicity was 1,500 mg/kg bw/day based on the absence of treatment related adverse effects at the highest dose tested. In a reproductive/developmental toxicity screening study (OECD TG 422) with calcium sulfate dihydrate, rats treated up to 1000 mg/kg bw/day by oral gavage showed no treatment-related effects on reproduction and development. The NOAEL for reproductive and developmental toxicity was 1000 mg/kg bw/day. Based on the available data, members of the sulfates category are not expected to be reproductive or developmental toxicants.

Environment

The sulfate category members are solid compounds with melting points ranging from 972 to 1450°C and a relative density ranging from 2.31 to 2.97. Physico-chemical properties such as partition coefficient are not applicable for inorganic salts. Vapor pressure for these inorganic salts is expected to be negligible. All substances from the sulfate category are soluble in water (2.09-240 g/L) and dissociate upon release into aqueous environments. The pKa of sulfuric acid describes the behavior of the sulfate ion in aqueous solution; the equilibrium hydrogen sulfate/sulfate is 1.92 at 25°C, which indicates that the sulfate dianion is present at pH 7. The cations are not expected to play a significant toxicological role at low doses.

Any sulfate released into the environment will be distributed between water and soil. Sulfate is constantly replenished by means of the sulfur cycle (sulfate/sulfide oxidation and reduction), and is ubiquitous in the environment because of the abundance of sulfur on earth. Terrestrial evaporite minerals and the ocean are the largest reservoirs of planetary sulfate. The fate and behavior of sulfates, such as bioaccumulation, are also closely related to the sulfur cycle in air, soil and water. Living organisms assimilate sulfate and reduce it to organic sulfur, an essential constituent of some amino acids and polysaccharides. The reduction of sulfate by sulfate-reducing bacteria may produce hydrogen sulfide under anaerobic conditions.

LC₅₀ values for the sulfate salts ranged from >63.6 mg/L for potassium magnesium sulfate to 3,550 mg/L for potassium sulfate for fish toxicity (*Oncorhynchus mykiss*, *Pimephales promelas* and *Lepomis macrochirus*) and >100 mg/L for calcium sulfate dihydrate to >1970 mg/L for calcium sulfate for aquatic invertebrates (*Daphnia magna* and *Ceriodaphnia dubia*). For calcium sulfate dihydrate a growth rate EC₅₀ for algae (*Pseudokirchneriella subcapitata*) of >100 mg/L was reported.

Exposure

This document may only be reproduced integrally. The conclusions and recommendations (and their rationale) in this document are intended to be mutually supportive, and should be understood and interpreted together.

According to the latest figures (2004) the production volume for the sulfate category was estimated to be approximately 6,100 ktonnes for Japan and the Nordic countries. Worldwide production of potassium sulfate in 2006 was 5.12 Mtonnes. Potassium magnesium sulfate and potassium sulfate are mainly used as fertilizers. In 2005-2006, 149,892 tonnes of potassium magnesium sulfate were consumed in the United States. Calcium sulfate (identified as phosphogypsum) is used as a fertilizer. Purified calcium sulfate is also used in construction materials, as filler in paint, paper and toothpaste, and as a food additive (to coagulate soy milk, production of tofu, as a nutrient, dietary supplement, yeast food, dough conditioner, firming agent, and sequestrant).

Occupational exposure may occur in general during production, transport and processing of the substances. Field exposure of workers is possible during use as a fertilizer. The dermal and inhalation routes will be the most important routes of exposure. In the United States, the Occupational Safety and Health Administration has set permissible exposure limits (PEL) of 15 mg/m³ (as total dust) and 5 mg/m³ PEL (as respirable fraction) (8 hour Time Weighted Average). Consumer exposure may occur when using fertilizers. In the Sponsor country, calcium sulfate and potassium sulfate are used as food additives and are generally recognized as safe (GRAS) by the Food and Drug Administration.

Environmental exposure is mainly limited to soil and water after use as a fertilizer.

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

Human health: The chemicals are currently of low priority for further work. The chemicals do not possess hazards for human health with the exception of irritation caused by anhydrous calcium sulfate. This hazard does not warrant further work as it is related to transient effects. It should nevertheless be noted by chemical safety professionals and users.

Environment: The chemicals are currently of low priority for further work for the environment due to their low hazard profile.

It is recommended that the use of the chemicals as fertilizers be taken into account when assessing environmental exposure.