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 14 February 2012

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

Series on Testing & Assessment
No. 166

The complete document is available in pdf format only.

JT03316628

Complete document available on OLIS in its original format
This document and any map included herein are without prejudice to the status of or sovereignty over any territory, to the delimitation of international frontiers and boundaries and to the name of any territory, city or area.

ENV/JM/MONO(2012)4/PART4
Unclassified

English - Or. English

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

Environment Directorate

ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT

Paris 2012

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 34 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in ten different series: Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides and Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; and Safety of Manufactured Nanomaterials. More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/ehs/).

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

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

This publication is available electronically, at no charge.

Also published in the Series on Testing and Assessment (link):

For this and many other Environment, Health and Safety publications, consult the OECD's World Wide Web site (www.oecd.org/ehs/)

or contact:

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

© OECD 2012

Applications for permission to reproduce or translate all or part of this material should be made to: Head of Publications Service, RIGHTS@oecd.org. OECD, 2 rue André-Pascal, 75775 Paris Cedex 16, France

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).

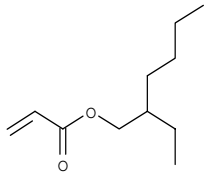
The collection of SIAPs has been divided in six parts, following a chronological order, to keep individual parts to a manageable size. For each part of the document, the corresponding SIDS Initial Assessment Meeting (SIAM) number and the year of the meeting have been indicated below.

		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.	103-11-7
Chemical Name	2-Ethylhexylacrylate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

2-Ethylhexyl acrylate (2-EHA) is rapidly and extensively absorbed, distributed and eliminated after oral administration. There are no specific toxicokinetic studies available using dermal administration or inhalation exposure. Studies on rats have indicated that short-chain acrylates such as 2-EHA undergo carboxylesterase-catalyzed hydrolysis to acrylic acid and 2-ethylhexanol.

Human data on the acute toxicity of 2-EHA are not available. In animal tests, single oral or dermal administration or inhalation of saturated atmospheres of 2-EHA demonstrated only low toxicity. Acute oral toxicity in rats is characterised by LD50 values of 4000 - 6000 mg/kg with slight toxic effects (scant droppings, wet yellow stained anogenital area, decreased spontaneous motoric activity and ataxia). For rabbits, a dermal LD50 value >10000 mg/kg is reported. Valid data on acute inhalation toxicity tests are not available. In a test with rats, after an 8-hours inhalation of an atmosphere saturated with EHA at 20°C no mortality and no clinical signs were observed.

Human data on the local irritant/corrosive properties of the substance are not available. 2-EHA caused severe irritation near corrosion after application to the skin of rabbits. Eye irritation was less severe in animal experiments. Considerations on the general irritation potential of 2-EHA with nasal and ocular irritations in a test on acute inhalation toxicity with rats warrants classification and labelling for respiratory irritation. Based on the observation on eye and skin irritation 2-EHA is considered to be a respiratory irritant.

Positive patch-tests are reported for humans. In various test models involving guinea pigs, 2-EHA proved sensitizing, with and without adjuvants. 2-EHA has a moderate sensitizing potential in experimental animals.

The relevant toxic effect after 90-day inhalation exposure of rats to 2-EHA was dose-related increased degeneration of the olfactory epithelium at concentrations from 30 ppm and higher (0.225 mg/l). The NOAEC for local effects on the respiratory tract was 10 ppm (0.075 mg/l). Animals exposed to 2-EHA concentrations of 30 ppm or higher showed poor health condition (lethargy, ptosis) during exposure period and reduced body weight gain, but no toxic effect on internal organs was identified (NOAEC for systemic effects). Minimal liver damage was indicated by elevated liver enzyme activities at a concentration of 100 ppm (0.75 mg/l). Valid studies with dermal or oral application routes are not available. Cancer studies and less documented subchronic studies with dermal application revealed that 2-EHA causes skin irritation at concentrations > 2.5% (LOAEL).

2-EHA is negative in bacterial mutation tests. Data from mammalian cells give no relevant evidence for clastogenicity; however, a fully reliable *in vitro* study is lacking. 2-EHA seems to have a low potential for induction of gene mutations in mammalian cells. Since this effect is limited to doses with strong cytotoxicity, it is highly unlikely that this potential will be expressed *in vivo*. The data from *in vitro* mammalian cell indicator tests do not add

relevant information. An *in vivo* UDS assay in rats performed according to OECD Guideline 486 was negative. Cleavage products of 2-EHA - acrylic acid (SIAR, cf. finalised EU Risk Assessment) and 2-ethylhexanol - were negative in *in vivo* chromosomal aberration mutagenicity tests. From all these data there is no relevant evidence that 2-EHA might be an *in vivo* mutagen.

There are no data available to the carcinogenic effects with respect to oral or inhalation exposure routes. Findings from the dermal mouse carcinogenicity study showed that 2-EHA induces skin tumors at concentrations which were highly irritative. However, other studies on different mouse strains did not confirm this finding. Acrylic acid, the hydrolysis product, did not induce tumors in mice treated dermally and in rats administered orally. Also, there is no concern from cancer data on 2-ethylhexanol. It is concluded that equivocal results from mice painting studies give no significant evidence of carcinogenic properties of 2-EHA.

From animal testing screening information on reproductive toxicity is available from a developmental toxicity study supplemented with data from a 3 month inhalation study indicating no effects on male and female reproductive organs investigated histologically. In both tests exposure up to and including 100 ppm (appr. 0.75 mg/l) was investigated. Evaluation of the available screening information so far does not provide evidence for significant reproductive toxicity of 2-EHA.

Environment

The environmental behaviour of 2-ethylhexyl acrylate is determined by the following characteristics:

The liquid substance (melting point = -90 °C; boiling point = 216 °C) has a water solubility of 9.6 mg/l and a vapour pressure of 12 Pa. With a Henry´s law constant of H = 230 $Pa \cdot m^3/mol$ evaporation from surface water is rapid and therefore an important fate process.

Based on the physical chemical properties of 2-ethylhexyl acrylate, the atmosphere is the main target compartment for distribution and only small amounts remain in the hydrosphere. Using the fugacity model of Mackay (level 1) about 97% are expected to be distributed to the atmosphere, about 1% remain in the surface water and less than 1% are expected to end up in each soil and sediment.

The estimated atmospheric half-life is approximately 19 hours. Hydrolysis and photolysis in water are not relevant degradation processes in the environment, but 2-ethylhexyl acrylate can be classified as readily biodegradable.

From the log Pow of 3.9 BCF- and Koc-values can be calculated indicating a moderate potential for bioaccumulation and geoaccumulation.

The valid ecotoxicological studies in fish, invertebrates and plants where the effect concentrations are based on analytical monitoring are compiled below:

Rainbow trout, *Oncorhynchus mykiss* , 96 h-LC50 = 1.8 mg/l
Crustacean, *Daphnia magna*, 48 h- EC50 = 1.3 mg/l (swimming ability)
Green algae, *Desmodesmus subspicatus*, 72 h-E_RC50 = 1.71 mg/l (growth)
Protozoa, *Chilomonas paramaecium* , 48 h-TGK (EC5) = 2.3 mg/l (growth, nominal concentration)

For aquatic organisms a Predicted No Effect Concentration (PNEC) of 1.3 µg/l can be calculated from the lowest reported acute test result for *Daphnia magna* (48 h- EC50 = 1.3 mg/l) applying an assessment factor of 1000.

For microorganisms in waste water treatment plants a PNEC of 2.3 mg/l can be derived based on the 48 h-TGK (EC5) reported for protozoan using an assessment factor of 1.

Data on biotic or abiotic effects in the air compartment are not available. Because of the short half-life of 2-ethylhexyl acrylate in the atmosphere (about 19 hours) adverse effects are not expected.

Exposure

Six companies are known to produce or import 2-ethylhexyl acrylate within the European Union. In 1999 the total EU production volume was 70,000 t/a, the import volume was approximately 30,000 t/a and 10,000 t/a were exported.

From the actual figures available for 1999, a total amount of 90,000 t/a is estimated to be available on the European market, 32,000 tonnes of that are used as an internal intermediate and 58,000 tonnes are sold to external processing sites. Recent information obtained from industry confirmed that no significant changes of the tonnages have to be expected for 2000 and 2001.

2-Ethylhexyl acrylate is used as a monomer in the chemical industry for the production of polymers and copolymers, which are mainly processed further to aqueous polymer dispersions. The polymers and polymer dispersions are used in adhesives and as binders for paints. Other applications include coatings raw materials and uses in the plastics and textiles industries.

In addition, 2-ethylhexyl acrylate is used as a monomer in construction-industry chemicals (e.g. floor coatings, road-marking substances) in concentrations between 0.1 - 21 %.

Releases of 2-ethylhexyl acrylate into the environment are expected to occur mainly during production and processing with waste water and exhaust gases.

Further releases are expected through residual monomeric acrylate-contents in the polymeric products. According to the producer, the aqueous polymer dispersions, as the main products, contain less than 200 mg monomeric 2-ethylhexyl acrylate per kg. Through storage of the polymeric products the residual monomers may partly polymerise and quantification of the releases into the environment from polymeric products can be performed only roughly.

RECOMMENDATION

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

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. Hazardous properties have been identified for this substance (local effects after repeated inhalation, irritation, sensitisation). In an assessment performed in the European Union in the context of the EU Existing Substances Regulation, exposure leading to concern has been identified during formulation of preparations, production and polymerisation and the use of formulations containing monomeric 2-EHA in the building trade. Other member countries may wish to perform an exposure assessment for humans and if necessary a risk assessment.

Environment:
2-Ethylhexyl acrylate possesses properties indicating a hazard for the environment. Based on data present 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.

A comprehensive risk assessment has been performed in the European Union in the context of the EU Existing Substances Regulation. From the comparison between estimated exposure levels from all life cycle steps with the

Predicted No Effect Concentrations it is deduced, that 2-ethylhexyl acrylate represents, based on the present data configuration, no risk to the environment. There is therefore at present no need for further testing or gathering of exposure information.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	115-07-1
Chemical Name	Propylene or 1-Propene
Structural Formula	CH2=CH-CH3

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

A small fraction of the inhaled propylene is metabolised to propylene oxide (OECD SIDS Cas No. 75-56-9) in both animals and humans; the majority of propylene is immediately exhaled unchanged. The formation of propylene oxide from propylene exhibits saturation kinetics. Studies in rodents have shown that saturation of metabolism occurs at concentrations > 500 ppm (>860 mg/m^3; 1ppm = 1.72 mg/m^3) propylene. The highest possible body burden of propylene oxide in rats, resulting from inhalation exposures to 10,000 ppm propylene at steady state, is limited by the saturation of propylene metabolism to a calculated maximum of 71 nl propylene oxide gas/ml tissue. This value is about 2-fold less than the estimated body burden of propylene oxide resulting from chronic exposure to 100 ppm propylene oxide. Preliminary data from inhalation exposures at 25 ppm propylene with one human volunteer indicate that about 35% of the inhaled propylene is taken up into the body and only about 20% of this is metabolized; from these data, it can be calculated that about 7% of the inhaled propylene is metabolized, with the rest exhaled unchanged.

Propylene has a low order of acute toxicity by the inhalation route of exposure. The lower flammability limit for propylene is 2% or 20,000 ppm. The threshold for narcosis in humans is 46,000 ppm. Thus, the explosive range of airborne concentrations for propylene is reached before any acute narcotic effects can be manifested.

In the gaseous state propylene is not irritating to the skin or eyes based on limited human studies. However, should skin or eye contact occur to this chemical in its liquid state, tissue freezing, severe cold burn, and/or frostbite may result.

No adverse effects were observed in repeated dose inhalation toxicity studies in rodents at concentrations up to 10,000 ppm propylene, for 14 weeks. Furthermore, there was no evidence of carcinogenicity in rats or mice exposed to propylene concentrations as high as 10,000 ppm for up to 103 weeks. Inflammation of the nasal cavity was the only indication of toxicity observed following exposure of male rats to 5,000 and 10,000 ppm propylene and female rats exposed to 10,000 propylene for 103 weeks. These effects were not observed when rats were exposed to similar concentrations for 14 weeks. To further investigate this finding, a recent repeated dose inhalation study indicated no propylene-specific nasal lesions were microscopically detected in any of the male or female rats exposed to 200, 2000, or 10,000 ppm for 3 or 20 days. No exposure-related inflammation (rhinitis) or alterations (e.g. degeneration, necrosis, hyperplasia, metaplasia) in the squamous, transitional, respiratory or olfactory epithelium lining the nasal airways were found in any of the sections examined from these propylene-exposed rats. In addition, there were no apparent exposure-related changes, compared to that of controls, in the density of BrdU-labelling in the four specific nasal epithelial populations. These studies demonstrate that propylene produced no toxic effects in rodents exposed to concentrations up to 10,000 ppm, one-half of the lower flammability limit, for up to 14 weeks. However, based on the lifetime repeated dose study in which increased squamous metaplasia and inflammation of the nasal cavities were observed in rats the NOAEL is <5,000 ppm.

The overall weight of the experimental evidence indicates that propylene is not likely to be mutagenic in humans. Mutagenic activity was observed in a single bacterial strain in the Ames assay in the presence of S9 suggesting that

metabolites are positive in this strain. Propylene was without activity in the other bacterial strains tested with and without metabolic activation. A negative result was seen in an *in vitro* study in mouse lymphoma cells. Propylene did not induce any increase in micronucleated polychromatic erythrocytes in male rat bone marrow or an increase in Hprt mutant frequencies when evaluated after a total of 20 exposures at exposure levels up to 10,000 ppm. Therefore, propylene is not an *in vivo* mutagen based on the available evidence.

Data from two competent bioassays in rat and mouse conducted by the NTP are negative. Consequently, propylene does not give any indication of being a carcinogen.

Inhalation exposure of pregnant Wistar rats to propylene from implantation to one day prior to the expected day of parturition (days 6-19 p.c.) elicited no maternal toxicity, prenatal or developmental toxicity, or teratogenicity at all tested concentrations up to 10,000 ppm. These findings, along with the with findings of no biologically significant effects on male or female reproductive organs attributed to propylene exposure in repeated dose inhalation studies, which included histopathological examination of the gonads, in rats (NTP, 104 weeks) and mice (NTP, 14 weeks), leads to a conclusion of low concern for reproductive toxicity.

Environment

Propylene is a gas of vapour pressure 11,586 hPa (25 degrees C), water solubility 200 mg/l (25 degrees C) and Log Kow 1.77.

Results of distribution modelling show that propylene will partition predominantly to the air compartment (99.998%), with negligible amounts partitioning to water (0.002%). Propylene has the potential to rapidly volatilise from surface waters, based on a calculated Henry's Law constant of 2.438×10^5 $Pa \cdot m^3$/mole. In spite of its water solubility, wet deposition of propylene is not likely to play a significant role in its atmospheric fate. Volatilisation to the air will contribute to the rapid loss of propylene from aqueous and terrestrial habitats. In the air, propylene has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals with a calculated degradation half-life of approximately 5 hours. Aqueous photolysis and hydrolysis will not contribute to the transformation of propylene in aquatic environments because it is either poorly or not susceptible to these reactions.

Propylene concentrations have been reported to range in rural air samples from 0.1 to 4.8 ppb, in urban air samples from 4 to 10.5 ppb, and in industrial air samples from 7 to 260 ppb.

The photochemical ozone creation potential (POCP) for propylene is cited as 107.9. Because of the relatively short half-life of propylene in the atmosphere and the low environmental concentrations typically found, its contribution to potential global warming can be considered minor. The ozone depletion potential of this substance is negligible.

Studies to evaluate the microbial metabolism of propylene indicate that it can be degraded in the environment. These data also suggest that propylene can be degraded in wastewater treatment plants, although its primary route of removal will be through volatilisation. Propylene is not expected to sorb significantly to organic matter in soil, sediment, and wastewater solids based on a log Koc of 1.38.

Due to the fact that propylene is a gas at ambient temperature and pressure and is expected to partition predominantly to the atmosphere, no aquatic toxicity testing has been conducted. The ECOSAR model was used to predict aquatic toxicity using the equation for neutral organics, a reliable estimation method for this class of substance. Calculated acute toxicity values for fish and invertebrates are 51.3 and 54.1 mg/L, respectively. For algae, the calculated 96-hr EC50 is 33.4 mg/L. Chronic toxicity values of 6.4, and 2.9 mg/L are calculated for fish and algae, respectively. Propylene has a low potential to bioaccumulate in aquatic species based on a calculated bioconcentration factor of 13.18.

A 14-day LC50 value of 304.7 mg/kg soil has been calculated for an earthworm. Ambient air concentrations of propylene are not expected to achieve levels that could cause effects to plants.

Exposure

Propylene is a gas that is produced in two grades, 95 to 100% for a polymer grade and 90 to 99.8% for a chemical grade. In 2001, 38,500 kilotonnes were produced in Asia, Western Europe and North America. Propylene is used in the manufacture of plastics and the synthesis of a wide range of industrial chemicals. Because propylene is a gas, releases will partition rapidly to the air, which is expected to provide the main route of potential exposure in the environment.

The primary human exposure to propylene is in the occupational setting. Established OELs for propylene are 500 ppm. Consumer exposure to propylene is only likely from the low levels in heating gases and some anthropogenic sources such as combustion product of organic matter, motor vehicle exhaust, and cigarette smoke.

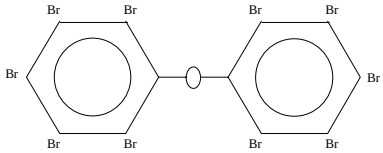
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties suggesting a hazard for the environment. Although this does not warrant further work (as it is related to acute aquatic toxicity which may become evident only at very high exposure levels), it should nevertheless be noted by chemical safety professionals and other users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1163-19-5
Chemical Name	Bis(pentabromophenyl) ether (Decabromodiphenyl ether)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Decabromodiphenyl ether (DBDPE) can be absorbed through the gastro-intestinal tract (approximately 6-9.5%) and is distributed to the blood, the liver and the adipose tissue. Given the low rate of oral absorption in rats, a low bioaccumulation potential might be anticipated. Some DBDPE is absorbed intact from the intestine and excreted intact or in the form of metabolites (e.g. debrominated hydroxylated diphenyl oxides). Only trace amount of bromine compounds was found in tissues and the brain of neonatal mice exposed on postnatal day 3, 10 or 19. However the toxicological significance of this last finding is unclear. A maximal dermal absorption of 1% may be assumed. Although pulmonary exposure may occur due to the small particle size (<5 µm), the limited available data do not allow determination of pulmonary absorption.

DBDPE has a low oral, dermal and inhalation acute toxicity in animals. Acute oral toxicity data indicate a rat LD50 greater than 5,000 mg/kg for DBDPE in corn oil. No clinical signs of toxicity were observed up to 2,000 mg/kg and no deaths were seen up to 5,000 mg/kg. A dermal LD50 greater than 2,000 mg/kg has been demonstrated in rabbits using DBDPE applied neat under occlusive wraps. No deaths were observed up to 2,000 mg/kg. Local and general signs of toxicity were not reported and necropsies were not performed in this dermal toxicity study. Following acute rat inhalation administration of DBDPE at 2 and 48.2 mg/l during one hour, no deaths were seen, only minor ocular signs and dyspnea were observed from 2 mg/l concentration. The reliability of this data is limited by the absence of information on particle size distribution.

DBDPE is not a dermal or an ocular irritant and does not exhibit a chloroacnegenic activity. There is no indication of skin sensitisation.

The lowest NOAEL of 1,120 mg/kg/day for systemic toxicity (including non neoplastic lesions exclusively) is derived from a chronic dietary study in rats. At the highest dose tested (2,240 mg/kg/day) in males, non neoplastic lesions in the liver (increased incidence of thrombosis and degeneration), spleen fibrosis and lymphoid hyperplasia of the mandibular lymph nodes were observed. In the same study, a LOAEL of 1,120 mg/kg/day is determined for local effects based on the slight increase of the forestomach acanthosis observed from 1,120 mg/kg/day. No effects on thyroid homeostasis were found in either sex of two species after 13 weeks treatment with DBDPE up to approximately 7,000 and 11,000 mg/kg/day in mice and 2,800 and 3,800 mg/kg/day in rats and only mild effects (follicular cell hyperplasia and marginally increased incidence of thyroid follicular cell adenomas or carcinomas) were found in one species after a life time exposure from 3,200 mg/kg/day in male mice.

With regard to mutagenesis, DBDPE is considered as a non *in-vitro/in-vivo* genotoxic.

With regard to carcinogenesis, a LOAEL for carcinogenicity of 1,120 mg/kg/day is stated based on the increased incidence of liver neoplastic nodules from the lowest tested dose (1,120 mg/kg/day) in a dietary study in rats. On thyroid, marginal increase in incidence of thyroid tumours in mice but not in rats, supported by an increased incidence of follicular cell hyperplasia is observed. It is recognized that there are marked species differences in thyroid gland biochemistry and physiology and that the rodent thyroid gland is markedly more active and operates at a considerably higher level with respect to thyroid hormone turnover as compared to primate. Finally, it should be reminded that DBDPE presents a non-genotoxic profile as well as other polybrominated congeners such as OBDPE and PeBDPE and is devoid of alert-structure for genotoxicity.

With regard to reproductive toxicity, no effects on fertility were seen in a 1-generation reproduction oral study in rats up to 100 mg/kg/day administered in the diet, though the absence of parental toxicity indicates higher dose levels could have been tested. However, no histological changes were seen in the reproductive organs in rats and mice treated for 2 years in a dietary study with up to 50,000 ppm DBDPE (equivalent to approximately 2,240-2,550 and 6,650-7,780 mg/kg/day respectively).

For developmental effects, no adverse treatment related effect was observed such as external or internal malformations or variations, foetal weight, sex ratio, total resorption and late resorption up to 1,000 mg/kg/day.

With regard to breast feeding, following pregnancy, HxBDPE and other PBDPEs such as TeBDPE and PeBDPEs have been identified in breast milk but such measurements were not carried out on DBDPE neither on OBDPE. However, considering the toxicokinetic profile of DBDPE, a rather low excretion in breast milk might be anticipated.

With regard to neurotoxicity, DBDPE caused behavioural disturbances on post-natal day 3 in neonatal mice exposed to DBDPE in a single dose of 2.22 to 20.1mg/kg/bw. This effect was not seen in mice exposed on post-natal day 10 or 19. The authors indicate that PCBs have been shown to induce this type of behavioural profile when administered on post-natal day 3, but this response is always accompanied by a response in animals exposed to the toxic compound on post-natal day 10. The study has certain limitations compared with regulatory guidelines and thus uncertainty as regards interpretation of the results remains. Moreover only an abstract of this study and a personal communication from the authors are available with limited details. Therefore**,** no firm conclusion can be drawn from this end-point.

Environment

The environmental effects database does not formally meet the requirements of the SIDS data package as there is no information on the toxicity to invertebrates. Based on the available data for fish and algae, the substance appears to have a very low toxicity in short-term tests, with no effects being seen up to the water solubility of the substance. Similarly, no effects would be expected with *Daphnia* based on the lack of effects seen with the closely related octabromodiphenyl ether. Due to the lack of effects seen in the aquatic toxicity tests, it is not possible to derive a PNEC for this compartment.

For microorganisms, no effects were seen in a 3 hour activated sludge respiration inhibition test at a concentration of 15 mg/l. A $PNEC_{microorganisms}$ for waste water treatment plants of $\geq$ 1.5 mg/l was derived from this value using an assessment factor of 10.

Toxicity data are available for the sediment and the terrestrial compartment. For sediment, no effects were seen with the worm *Lumbriculus variegatus* in a prolonged toxicity test (28 days) using two different sediment types. The lowest NOEC from these studies was $\geq$ 3,841 mg/kg dry weight and a PNEC for sediment of $\geq$ 384 mg/kg dry weight basis (or $\geq$ 148 mg/kg on a wet weight basis) was derived from the data using an assessment factor of 10 (a factor of 10 is used as this species was the most sensitive species found for another related substance, pentabromodiphenyl ether).

For the terrestrial compartment, studies on the toxicity to plants and earthworms (*Eisenia fetida*) have been carried out. No effects were seen on germination and growth six species of plant (*Zea mays*, *Allium cepa*, *Lolium perenne*, *Cucumis sativa*, *Glycine max* and *Lycopersicon esculentum*) at concentrations up to 5,349 mg/kg dry weight. For *Eisenia fetida* no effects were seen at concentrations up to 4,910 mg/kg dry weight in a 56 day reproduction test. Based on a NOEC of $\geq$ 4,910 mg/kg dry weight, a PNEC for this end point of $\geq$ 98 mg/kg dry weight (or $\geq$ 87 mg/kg

on a wet weight basis) can be derived using an assessment factor of 50.

No data are available to allow a PNEC to be derived for the atmospheric compartment. However, the atmospheric concentrations of decabromodiphenyl ether are very low and so adverse effects are unlikely.

For secondary poisoning, based on the available standard mammalian toxicity tests, a PNEC of 2,500 mg/kg food can be derived. However, although decabromodiphenyl ether has generally shown a low level of toxicity in standard tests, there is some evidence from non-standard behavioural tests on mice that these standard tests may not detect more subtle effects that might be occurring with this substance at lower doses with sensitive life stages or over prolonged exposure.

Based on the available laboratory data, decabromodiphenyl ether appears to have a low bioaccumulation potential. However, the substance has recently been found at low but measurable concentrations in fish, marine mammals and predatory birds' eggs (Peregrine Falcons and Common Terns), which indicates that the substance is able to cross biological membranes and possibly that it is being accumulated in the food chain. The mere presence of a chemical in biota is not necessarily a cause for concern, and there is no evidence at this point in time of biomagnification taking place or actual environmental harm arising from this substance. However, these findings, when coupled with the uncertainties over the effects of this substance, mean that further work should be considered. In addition, the possibility that the substance may photodegrade in the environment to give more toxic and accumulative products should be investigated further.

Exposure

The world-wide demand for decabromodiphenyl ether was reported to be 54,800 tonnes in 1999. The substance is imported into the EU and the 1999 EU consumption was 7,500 tonnes. The substance is used in the plastics and textile industries as a flame retardant. In the plastics industry, it is used as an additive flame retardant in a wide range of plastic types. In the textile industry, the substance is generally backcoated onto the textile in a latex binder. The commercially supplied decabromodiphenyl ether is a mixture of congeners, consisting of mainly decabromodiphenyl ether (≥97%), with small amounts of other brominated diphenyl ethers such as nonabromodiphenyl ether.

The substance is a white solid with a melting point in the range 300^{o}C to 310^{o}C and a vapour pressure of 4.63×10^{-6} Pa at 21^{o}C. The substance does not have a distinct boiling point as it decomposes at >320^{o}C. It has a very low solubility in water (<0.1 µg/l at 25^{o}C), and shows limited solubility in common organic solvents. The n-octanol water partition coefficient (log Kow) has been measured as 6.27.

Emissions to the environment can occur both to the atmosphere (as vapour and as dust) and waste water. Sources of release include production sites, polymer processing sites and textile processing sites. In addition emissions to the environment could also occur from finished articles (e.g. plastic components, treated textiles) during their use and at disposal.

The substance does not appear to biodegrade under either aerobic or anaerobic conditions but can be degraded photolytically. The products formed from this direct photolysis reaction, and also the rate and extent of the reaction, in the environment are uncertain but may include small amounts of toxic and accumulative brominated diphenyl ethers that contain lower numbers of bromine. It is also expected to degrade in the atmosphere by reaction with hydroxyl radicals and a rate constant for this reaction of around 1.7×10^{-13} cm^{3} molecule^{-1} s^{-1} has been estimated.

The low vapour pressure, water solubility and high log Kow value indicate that the substance has a high potential for adsorption onto soil, sediment or suspended sediment.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The SIDS requirements are met. Further work is needed to address the concerns over the possible accumulation in, and effects on, top predators and also the possible formation of more accumulative and toxic congeners from photolytic processes in the environment. These areas are difficult to address with standard tests. In this respect, industry has volunteered to carry out, as part of the EU risk assessment:

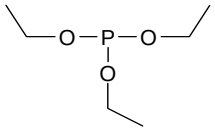
a) a more widespread monitoring project to determine whether the finding in predatory birds (including birds' eggs) is a widespread or localised phenomenon and to identify any possible trends,

b) a more detailed investigation of the rate of formation of photodegradation products under environmentally relevant conditions, and

In addition, consideration is being given to carrying out a further developmental neurotoxicological test (OECD 426 or similar).

No further work is required for the human health assessment, however, as stated above, a neurotoxicity study may voluntarily be carried out for the environmental part and the results from this study could be useful to better assess the neurotoxicity properties of this substance.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	122-52-1
Chemical Name	Triethyl phosphite
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No experimental data are available regarding the toxicokinetic behavior and metabolism of triethyl phosphite.

The acute toxicity after oral, dermal, and inhalation exposure is relatively low. The oral LD50s in rats ranged between 1840 mg/kg bw (females) and 2470 mg/kg bw (males). Symptoms of rapid breathing and tremors were observed prior to death. In mice LD50 values above 3700 mg/kg bw were recorded. The 6-hour inhalation LC50 with an aerosol of 1.6-3.5 µm MMAD in rats was between 11,100 mg/m^3 (females) and 11,600 mg/m^3 (males). Clinical signs included eye and upper respiratory irritation, salivation and rapid, shallow breathing. The dermal LD50 in rabbits was between 2800 mg/kg bw (males) and > 3000 mg/kg bw (females).

Neat triethyl phosphite was slightly irritating to the skin and the eyes of rabbits (OECD TG 404, 405). It was sensitizing to the skin of guinea pigs (OECD TG 406).

The NOAEL in rats was 150 mg/kg bw/day in a 4-week gavage study. At the higher dose (750 mg/kg bw/day), mortality (3 out of 10 animals), a stimulation of the haematopoietic system and inflammatory changes, fibrosis and hyperplasia of the bronchial epithelium in the lungs were found.

Triethyl phosphite was not mutagenic in the Ames test both with and without a metabolic activation system, and including cytotoxic concentrations. *In vivo*, triethyl phosphite did not induce micronuclei after a single intraperitoneal injection of 1500 mg/kg bw in mice (OECD TG 474).

No data are available regarding the tumorigenic potential of triethyl phosphite.

In a screening study in rats according to OECD TG 421, developmental toxicity was found at dose levels ≥ 320 mg/kg bw/day as evidenced by severely reduced pup survival and reduced pup birth weights (NOAEL: 80 mg/kg bw/day). Effects on fertility were seen in females at 320 mg/kg bw/day in the presence of general toxicity as an increase in time to insemination, severely reduced gestation rate, and an increase in stillbirths and dead pups. Male rats showed changes in the testes at the clearly toxic dose of 640 mg/kg bw/day (NOAEL females: 80 mg/kg bw/day; NOAEL males: 320 mg/kg bw/day).

Environment

Triethyl phosphite is a colourless liquid with a melting point of -112 °C, boiling point of 158°C, density of 0.96 g/cm^3 and a vapour pressure of 2.6 hPa at 20°C. Due to rapid hydrolysis the determination of water solubility and log Kow of triethyl phosphite is not appropriate. A log Kow of 0.74 and a water solubility of 15 g/l was calculated. The

estimated Henry's law constant of 2.9 Pa·m³/mol indicates moderate volatility from aqueous solution.

The main degradation process in water is hydrolysis. In acid solution (pH= 4) triethyl phosphite reacts immediately with water to form diethyl phosphite and ethanol. At pH 7 triethyl phosphite hydrolyses completely within 20 minutes, after 3 hours 89.3% diethyl phosphite and 10.7 % monoethyl phosphite are formed. At pH 9 triethyl phosphite is more stable ($t_{1/2water}$: ca. 5.1 hours), 70 % of the substance remains unhydrolyzed after 3 hours. In 2 tests on ready biodegradation triethyl phosphite was degraded by 49 - 69 %. Therefore, it did not reach the criteria for ready biodegradability. However, it can be assumed that triethyl phsophite is inherently biodegradable. From two studies on the ready biodegradation of diethyl phosphite it can be concluded that diethyl phosphite is not readily biodegradable but can also be regarded as inherently biodegradable. From the degradation curve it can be assumed that hydrolysis was the prerequisite for biodegradation. It is expected that in the atmosphere a degradation of triethyl phosphite occurs due to indirect photolysis ($t_{1/2air}$: ca. 6.6 hours). As the substance hydrolyses under environmental conditions the calculation of a Mackay distribution model is also not appropriate. Due to rapid hydrolysis bioaccumulation of triethyl phosphite is not expected. The calculated log Kow value for diethyl phosphite (log Kow = -0.2) indicates no bioaccumulation potential of the hydrolysis product.

Concerning the toxicity of triethyl phosphite towards aquatic species, reliable experimental results of short term tests with fish, daphnia, and algae are available. The following concentrations are given for triethyl phosphite and are estimations based on the reported results for diethyl phosphite. The acute toxicity determined for fish (*Brachydanio rerio*) was 251.66 mg/l (96 h LC50) and for daphnia (*Daphnia magna*) 94.1 mg/l (24 h-EC50). In the growth inhibition test (72 h) with algae (*Scenedesmus subspicatus)* an EC50 > 73.6 mg/l was determined for both growth rate and biomass.

From the lowest effect value available a PNECaqua of 73.6 µg/l was derived applying an assessment factor of 1000 according to the EU Technical Guidance Document. This factor is justified as short-term effect values from each of the three trophic levels are available.

Tests on terrestrial species are not available.

Exposure

In Europe there is only one producer of triethyl phospite with a production volume between 1000 and 5000 t/a. The world wide production volume is estimated as 10,000 to 20,000 t/a. Triethyl phosphite is exclusively used as an intermediate for the production of flame retardants, optical brighteners, pesticides, antioxidants, and pharmaceuticals. At production sites effective control techniques are used to minimize exposure of workers. No direct use is known, and no consumer products containing triethyl phosphite were located in the Sponsor country. Triethyl phosphite is not listed in European product registers.

Methyl and ethyl esters of phosphorous acid can be converted by chemical synthesis to nerve gases. Therefore, the production and export of triethyl phosphite is stringently controlled under the International Chemical Weapons Convention.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health. Based on data presented by the Sponsor country, exposure is well controlled in occupational settings and is negligible for consumers. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: Triethyl phosphite possesses properties indicating a hazard for the environment. 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

CAS No.	150-90-3
Chemical Name	Disodium succinate
Structural Formula	$NaOOCCH_2CH_2COONa$

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

Disodium succinate is stable as a hexahydrate and has been produced as disodium succinate hexahydrate (CAS No.: 6106-21-4) in Japan. Many toxicity studies were conducted using disodium succinate hexahydrate as the test substance, because there should be no difference between disodium suucinate and disodium succinate hexahydrate in terms of environmental behavior, aquatic toxicity, and mammalian toxicity.

Human Health

There is no available information on toxicokinetics and metabolism.

An oral acute toxicity study [OECD TG 401] of disodium succinate hexahydrate showed that this chemical did not cause any changes even at 2,000 mg/kg. The oral LD50 value was considered to be greater than 2,000 mg (equivalent to 1,200 mg of disodium succinate)/kg bw in male and female rats.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], Crj: CD (SD) IGS rats were given disodium succinate hexahydrate by gavage at 0, 100, 300, or 1,000 mg/kg bw/day. Males were dosed for 52 days from day 14 before mating and females were dosed from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. Blood urea nitrogen levels were increased in females at 1,000 mg/kg bw/day. Higher levels of urinary protein were found in one and two of the five males at 300 and 1,000 mg/kg bw/day, respectively, whereas no animals with these high levels were found in the control and 100 mg/kg bw/day groups. These findings suggest adverse effects of this compound on the kidney. Therefore, the NOAEL of disodium succinate hexahydrate for repeated dose toxicity was considered to be 100 mg (equivalent to 60 mg of disodium succinate)/kg bw/day for male rats and 300 mg (equivalent to 180 mg of disodium succinate)/kg bw/day for female rats.

In a reverse gene mutation assay [OECD TG 471], disodium succinate hexahydrate was not mutagenic in *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537, and *Escherichia coli* WP2 *uvr*A with and without an exogenous metabolic activation. In a chromosomal aberration test [OECD TG 473], disodium succinate hexahydrate did not induce structural chromosomal aberrations or polyploidy with and without an exogenous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells.

There is no data available on the carcinogenicity.

The above-mentioned combined study [OECD TG 422] showed that the reproduction/developmental parameters, i.e., mating, pregnancy, delivery, lactation, and viability and body weight of pups, were not affected by disodium succinate hexahydrate at up to 1,000 mg/kg bw/day. The NOAEL of disodium succinate hexahydrate for reproduction/developmental toxicity was considered to be 1,000 mg (highest dose tested, equivalent to 600 mg of disodium succinate)/kg bw/day in rats.

There is no available information on eye and skin irritation and sensitization.

Environment

Disodium succinate is a white powder with a melting point of more than 400 degree C, a water solubility of more than 100 g/L. This chemical is stable at pH 4, 7 and 9 at 50 degree C for 5 days, and readily biodegradable. A vapour pressure of 1.16×10^{-5} Pa is calculated. A Log Pow of < -0.59 is estimated and the bioaccumulation potential of disodium succinate is expected to be low.

The toxicity of disodium succinate on aquatic organisms has been studied in three freshwater species belonging to three trophic levels. The toxicity tests were conducted using disodium succinate hexahydrate instead of the test substance because disodium succinate hexahydrate is not different to the test substance in aqueous solution and disodium succinate is stable as hexahydrate.

In an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum*, open system), the 72 h ErC50 and the 72 h EbC50 were >998 mg/L. For daphnids, a 48 h EC0 of 997 mg/L and a 48 h EC50 > 997 mg/L were reported (OECD TG 202, *Daphnia magna*, static). For fish (OECD TG 203, *Oryzias latipes*, flow-through) a 96 h LC0 of 47.0 mg/L, 96 h LC50 >95.4 mg/L and 96 h LC100 > 95.4 mg/L were determined.

Regarding chronic toxicity to algae, a 72 h NOErC of 998 mg/L and a NOEbC 998 mg/L (OECD TG 201, *Selenastrum capricornutum*, open system) were reported. For daphnids, the 21 d EC50 was more than 95.2 mg and a 21 d NOEC of 95.2 mg/L on reproduction and a 21 d LC50 >95.2 mg/L for parent daphnids were reported (OECD TG 211, *Daphnia magna*, semi-static).

There is no information available on toxicity to terrestrial or other organisms.

Exposure

Disodium succinate anhydrate and hexahydrate is used as a seasoning agent and raw material for plating reagent. This chemical is permitted for use as a food additive and no limit value for food additives exists in Japan. This chemical is naturally contained in shellfish. In Japan disodium succinate is being produced in its hexahydrate form and the annual production volume in Japan is ca. 3,000 tonnes.

The main target environmental compartment of this chemical is water and once it is released into the aquatic phase, partitioning to other compartments is unlikely to occur.

Occupational exposure to this chemical through inhalation and dermal routes is possible. Consumer exposure to this chemical through ingestion is possible.

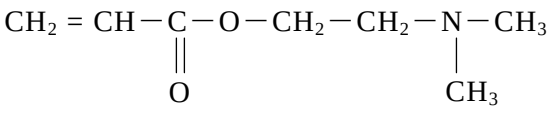
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical is currently of low priority for further work based on its low hazard potential.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2439-35-2
Chemical Name	2-Dimethylaminoethyl acrylate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no metabolism data specific to 2-dimethylaminoethyl acrylate. However, based on the fact that the structurally related compound 2-dimethylaminoethyl methacrylate hydrolyzes in simulated saliva and simulated intestinal fluid to methacrylic acid and dimethylaminoethanol, it can be assumed that this substance hydrolyzes to acrylic acid and dimethylaminoethanol in the same circumstances. This is supported by the comparison of acute toxicities between acrylic acid with methacrylic acid and this substance with 2-dimethylaminoethyl methacrylate.

The acute oral LD50, dermal LD50, and inhalation LC50 in rats are 455 mg/kg, 419 mg/kg, and 0.066 mg/L, respectively, therefore this substance is considered to be toxic by inhalation, and slightly toxic by oral and dermal route.

This substance is considered to be severely irritating or corrosive to skin, eye and respiratory tract, and does have a sensitizing potential in animal studies.

A repeated dose 90-day oral toxicity study in rodents [OECD TG 408] was conducted with SD (Crl: CD) rats at 0, 2, 10 and 50 mg/kg/day administered by gavage. At 50 mg/kg/day, the macroscopic lesions were limited to sporadic lung damage that was caused by reflux of stomach content. Judging from the hyperplasia/keratosis or other irritation changes found in forestomach, the reflux is a result of incontinence in the gastro-intestinal tract. This substance was not toxic at 2 and 10 mg/kg/day. At the latter dose-level, treatment-related lesions were found in the forestomach of 4 males, however, these findings were almost of minimal grade which were not regarded to be adverse effects. A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] was also available with SD (Crj: CD) rats at doses of 0, 4, 20 and 100 mg/kg/day administered by gavage. The toxicity revealed is common in the two studies. At 100 mg/kg/day, similar changes compared to those seen at 50 mg/kg/day in the former study was observed. At 20 mg/kg/day, similar changes in the forestomach were observed in 2 males. However, these changes were not statistically significant, and considered to be not toxicologic by the authors. This substance was not toxic at 20 mg/kg/day in both sexes in the combined study. Nevertheless, the NOAEL was considered to be 10 mg/kg/day in the 90-day study, by the author.

This substance did not induce gene mutations in 3 strains of *Salmonella typhimurium* and in *Escherichia coli* but did induce gene mutations in the TA98 strain with metabolic activation in one out of two studies. *In vitro*, this substance was only weakly positive in the highest dose tested in CHL lung cells and human lymphocytes with and without metabolic activation. However, *in vivo*, this substance was negative when administered i.p. at the MTD in a single dose study. Based on the present results, and taking into account data on structurally related substances, it is unlikely that this substance is mutagenic *in vivo*.

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] (0, 4, 20, 100 mg/kg/day) was conducted with SD (Crj: CD) rats. There was no sign of reproductive or developmental toxicity up to 100 mg/kg/day, but maternal toxicity was overt and included death. Furthermore, a teratogenicity study [OECD TG 414] (0, 10, 30, 100 mg/kg/day) were conducted with SD (Crl: CD) rats. At 100 mg/kg/day, 27/299 fetuses showed anomalies (dwarf, adactyly) in external examination and 2/144 fetuses showed anomalies (cleft palate, hydrocephaly, testicular ectopia) in internal examination. The absence of ossification of various bones (vertebrae, sternebrae) was found in many individuals. Maternal toxicity including death was evident. At 30 mg/kg/day, no teratogenic effects were observed, two females, however, died and this substance was found to be maternally toxic. Fetuses with reduced ossification were found at this dose. At 10 mg/kg, no adverse effect was evident. In the teratology study, the NOAEL for maternal toxicity in rats was 10 mg/kg. Prenatal developmental toxicity was only observed at doses (100 mg/kg) which produced signs of maternal toxicity and mortality. The NOAEL for reproduction/developmental toxicity and teratogenicity are considered to be 10 and 30 mg/kg/day respectively.

Environment

Abiotically 2-dimethylaminoethyl acrylate is hydrolyzed at pH 7 and at pH 9 at 25°C with a half-life of 12.5 hours and 1.21 hours, respectively, whereas it is supposed to be stable at pH 4 at 25°C. Melting point, boiling point, and vapour pressure are -80 °C, 172.5 °C, and 68 Pa (20 °C), respectively. Water solubility is ca. 24 g/100 mL at 20 °C, although it is not precisely measurable due to hydrolysis. Indirect photo-oxidation in the atmosphere by hydroxyl radicals is predicted to occur with a half-life estimated at 1.4 hours. This substance is readily biodegradable and has a low bioaccumulation potential based on its log Kow of 0.68. Fugacity modeling (Mackay level III) predicts that this substance if released to water is unlikely to migrate into other compartments. When this substance is released to air, 88.1 % stays in air and 11.9 % is transported into water and soil.

This substance has been tested in a limited number of aquatic species including algae, daphnids and fish. The toxicity results (growth inhibition: [OECD TG 201]) for algae (*Selenastrum capricornutum*) were 0.201 mg/L (72 h-EC50) and 0.01 mg/L (72 h-NOEC). A 72 h-EC50 of 0.23 mg/L and a NOEC of 0.039 mg/L was found in another green algae study (*Scenedesmus suspicatus*). The acute (immobility, OECD TG 202) and chronic (reproduction, OECD TG 211) toxicity results for daphnids (*Daphnia magna*) are 9.92 mg/L (48h-EC50), <5.00 mg/L (48h-NOEC), 3.94 mg/L (21d-LC50), 6.27 mg/L (21d-EC50), and 3.00 mg/L (21d-NOEC), respectively. The acute LC50 (96 hr, OECD TG 203) and prolonged LC50 (14 d, OECD TG 204) for fish (Medaka: *Oryzias latipes*) were 8.49 mg/L and 5.66 mg/L, respectively. Although this substance was hydrolyzed in these test conditions to acrylic acid and 2-dimethylaminoethanol readily, these results are, however, consistent with the aquatic toxicity of the metabolites reported in the respective SIARs. Toxicity of acrylic acid contributed to these results predominantly.

Exposure

The production volume of 2-dimethylaminoethyl acrylate was estimated at approximately 80,000 t/year world-wide in 2002 (6,000 t/year in Japan, 40,000 t/year in the USA, 34,000 t/year in the EU). This substance is produced in a closed system. Most of this substance is industrially converted to the quaternary ammonium salts. All of these salts are converted to the copolymers for flocculants to be used in water treatment and for paper industries (world-wide 95-97%). The remainder is used to produce other copolymers. The use of these polymers is almost exclusively limited to non-dispersive use and exposure to workers is low and the exposure to the general population is extremely unlikely.

During production and use of this substance, occupational exposure is possible by the inhalation and dermal route. The workplace exposures during those conversion processes are controlled by a closed equipment, ventilation and by personal protective equipments. Consumer exposure is controlled because the use of the substance is non-dispersive.

Because this substance hydrolyzes to acrylic acid and 2-dimethyaminoethanol in neutral or alkaline aquatic media, it can be assumed to hydrolyze in water under environmental exposure circumstances.
Migration of residual monomer from the polymer matrix is expected to be low.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possess properties indicating a potential hazard for human health 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2837-89-0
Chemical Name	1-chloro-1,2,2,2-tetrafluoroethane (HCFC-124)
Structural Formula	ClFHC-CF_3

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

The analogs HCFC-141b (1,1-dichloro-1-fluoroethane; CAS No. 1717-00-6) and HCFC-142b (1-chloro-1,1-difluoroethane; CAS No. 75-68-3) were used to supplement the SAR estimations for aquatic toxicity. These analogs were chosen based on similar functional groups (both analogs are two-carbon alkanes with chlorine and fluorine), similar molecular weights, and similar Log Kows.

Human Health

Metabolism/kinetic studies in animals indicate HCFC-124 is metabolised to a slight extent, primarily by cytochrome P450 IIE1 with consequent urinary excretion of trifluoroacetic acid and fluoride. It has been postulated that the intermediate metabolite (trifluoracetaldehyde) could result in covalently-bound protein adducts, but no toxic effects have been observed that support this hypothesis.

In rats, the 4-hr ALC was 230,000-300,000 ppm (1.3×10^6 - 1.7×10^6 mg/m^3). No rats died at the lower dose, and all rats died at 300,000 ppm (1,671,847 mg/m^3). The 6-hr LC50 was >360,000 ppm (2×10^6 mg/m^3). Exposure of dogs to concentrations of 2.5% (139,500 mg/m^3) or greater resulted in cardiac sensitisation to epinephrine. No studies specifically designed to identify eye or dermal irritation have been performed.

Repeated-dose studies via inhalation have been conducted in rodents for 4 weeks, 13 weeks, and 2 years (6 hrs/day, 5 days/wk). The highest tested concentration in all studies was 50,000 ppm (279,140 mg/m^3). Several clinical signs/symptoms were observed at this highest dose, including lethargy, uncoordinated movements and/or reduced noise stimuli responsiveness. A variety of clinical chemistry and some other parameters were affected at different time intervals and doses between 10,000 and 50,000 ppm. Specifically, effects observed in the 13-week study at higher doses included decreased arousal times in males at 15,000 and 50,000 ppm (55,838 and 279,140 mg/m^3) as well as decreased triglyceride levels at these doses. Increased alkaline phosphatase was observed in females at 50,000 ppm (279,140 mg/m^3). Based on effects observed at 50,000 ppm in the 4-week rat study, a NOAEL of 10,000 ppm (55,828 mg/m^3) was determined and the 13-week sub-chronic studies resulted in a NOAEL of 15,000 ppm (83,700 mg/m^3) in mice and female rats and 5,000 ppm (27,900 mg/m^3) in male rats. The toxicological significance of the effects observed in the chronic 2-year study were unclear.

In *in vitro* and *in vivo* genotoxicity studies, HCFC-124 has shown no mutagenic or clastogenic activity.

No effects were seen in reproductive organs in the repeated-exposure studies. HCFC-124 showed no developmental effects in pregnant rats and rabbits exposed to up to 50,000 ppm (279,000 mg/m^3) for 6 hours per day. In the dams, there was a transient decrease in food consumption (8% decrease in rats) and reduced noise stimuli responsiveness (rabbits) during exposure. The NOAELs for maternal effects were 5,000 ppm (28,000 mg/m^3) in rabbits and 15,000 ppm (83,700 mg/m^3) in rats. The NOAEL for developmental effects was 50,000 ppm (279,000 mg/m^3).

Environment

HCFC-124 (1-chloro-1,2,2,2-tetrafluoroethane, CAS no 2837-89-0) is a colorless gas with a faint ethereal odour at room temperature and atmospheric pressure. It has a melting point of -199ºC and a boiling point of -12ºC at 1013 hPa. It is soluble in water, has a log Kow of 1.94 and a vapour pressure of 3850 hPa.

Degradation of HCFC-124 will occur predominantly in the air by reaction with hydroxyl radicals. Breakdown is expected to proceed via intermediates resulting in formation of HCl and CF_3COF, which would be removed from the atmosphere within a few days to a few months by uptake into clouds, rain and the oceans. The CF_3COF will then rapidly hydrolyse to trifluoroacetic acid and hydrofluoric acid. The atmospheric half-life of HCFC-124 is estimated to be 6 years. Its ozone depleting potential (ODP), relative to CFC-11 (=1.0), has been estimated, giving results in the range 02-0.04. Global warming potential values range from 470 to 620. The value of 470 was adopted by the Kyoto Protocol.

According to the Model River and Lake Program (in EPIWIN), any HCFC-124 present in aqueous waste streams discharged directly into rivers ($t_{1/2}$ = 1.2 h) and lakes ($t_{1/2}$ = 4.6 d) is likely to evaporate rapidly. Results from Level I MacKay modelling also suggest that HCFC-124 would partition mostly to the atmosphere (99.986%), with approximately 0.013% in water and 0.001% in soil. The substance is not readily biodegradable. Its relatively low measured Log Kow (1.94) and estimated bioconcentration factor (6.22) indicate a low potential to bioaccumulate.

Due to the chemical's specific physicochemical properties and distribution in the environment, aquatic and terrestrial testing has not been performed. Using QSAR, a 96-hr LC50 for fish (137 mg/L), a 48-hr LC50 for daphnids (145 mg/L), a 96-hr LC50 for green algae (90 mg/L), and a 14-day LC50 for earthworm (927 mg/L) have been estimated. Measured data for analogs of HCFC-124 (HCFC 141b and HCFC 142b) show low to moderate aquatic toxicity and support the SAR data of HCFC-124.

Because of its ODP, the production and consumption of HCFC-124 will be phased out by the Montreal Protocol. In the case of developed countries, a phase-out of HCFC 124 and other hydrochlorofluorocarbons (HCFCs) is scheduled as follows: 35% in 2004, 65% in 2010, 90% in 2015, 99.5% in 2020. A total phase-out is scheduled in 2030. For developing countries, a freeze of the production is scheduled in 2016 and a total phase-out in 2040. In the European Union, the phase-out of ozone depleting substances is scheduled more rapidly than that required by the Montreal Protocol. The total ban of hydrochlorofluorocarbons is required on January 1, 2010.

Exposure

In the U.S., HCFC-124 is produced in closed systems. The world-wide production volume in 2001 was approximately 2,277 metric tonnes. Its use is limited to foam blowing agents and as a blend in refrigerants. The population exposed either directly or indirectly to HCFC-124 is expected to be limited. Occupational exposure is expected to be the primary exposure. Possible emissions during production are likely to be small. Because HCFC-124 is a gas and is used in anhydrous conditions, release of HCFC-124 to water systems is not expected. In cases of accidental emissions, it is expected to partition almost exclusively to the air.

RECOMMENDATION

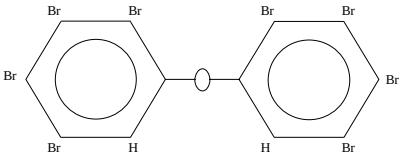
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

This chemical possesses properties indicating the potential for low to moderate hazard to aquatic organisms and low hazard for human health. Based on data presented by the Sponsor country, exposures are anticipated to be low. In

addition, the chemical is being phased out under the Montreal Protocol due to its ozone depletion potential. Ozone depletion may have human health effect consequences. 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.	32536-52-0
Chemical Name	Diphenyl ether, octabromo derivative
Structural Formula	e.g. 

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Animal data show an absorption of Octabromodiphenyl ether (OBDPE) by oral or inhalation route with an accumulation of the parent compound or its metabolites in the liver and also in the adipose tissue and the lung following inhalation administration. The extent of absorption and elimination cannot be assessed from the data available. No information on the metabolism of OBDPE is available. Following oral administration, OBDPE is an inducer of xenobiotic metabolism. There are no measured data on OBDPE dermal absorption. However based on OBDPE physicochemical properties and analogy with PCBs, a dermal absorption of 4.5% may be estimated.

Evidence from humans indicates that OBDPE, HxBDPE, HpBDPE and NonaBDPE which are components of commercial OBDPE can be absorbed into the body and distributed into the blood. Distribution to the adipose tissue was evidenced at least for OBDPE and HxBDPE. There are no data available on the rate of elimination or on bioaccumulation of OBDPE from human adipose tissue neither for PeBDPO but given the high lipophilicity of these compounds and the adipose tissue accumulation observed in rats following oral or inhalation routes, it can be assumed that in humans OBDPE might bioaccumulate in these tissues as well. Following pregnancy HxBDPE and others PBDPEs such as TeBDPE and PeBDPEs are excreted in the breast milk. Unfortunately, such measurements were not carried out on OBDPE. However, based on the high lipophilicity of OBDPE, its potential to bioaccumulate in adipose tissues and the breast milk measured data with HxBDPE (one component of commercial OBDPE), excretion of OBDPE in the breast milk may be anticipated

OBDPE has a low acute toxicity in animals. Acute oral toxicity data indicate a rat LD50 greater than 28,000 mg/kg. No deaths, no weight changes or necropsy lesions were reported up to 5,000 mg/kg. At 10,000 mg/kg and 28,000 mg/kg, no deaths were observed but no more information on these studies are available. A dermal LD50 greater than 2,000 mg/kg has been demonstrated in rabbits using DBDPE applied neat under occlusive wraps for 24 hours. No deaths were observed up to 2,000 mg/kg. Local and general signs of toxicity were not reported and necropsies were not performed in this dermal toxicity study. An inhalation LC50 greater than 60 mg/l has been demonstrated in rats exposed with OBDPE during one hour. No deaths and no clinical signs of toxicity were observed up to 60 mg/l.

OBDPE is not a dermal or an ocular irritant. There is no indication of skin sensitisation in animals.

The only information concerning the effects of repeated oral and inhalation exposure to OBDPE comes from studies in rats involving administration of commercial OBDPE. These studies consistently indicate that the liver is the key target organ within 4 and 13 weeks of repeated oral dosing and within 14 days and 90 days of inhalation exposure. The changes in thyroid status are apparent within 4 and 13 weeks of repeated oral dosing from 1,000 ppm and within 13 weeks of repeated inhalation dosing from 16 mg/m3 (analytical concentration). The LOAEL is considered to be

100 ppm ≈ 7.2 mg/kg/day in the 90 day dietary study based on the liver changes (increase of liver weight and granular cytoplasmic changes) observed from 100 ppm ≈ 7.2 mg/kg/day. The NOAEC for systemic toxicity is considered to be 1.1 mg/m^3 in the 90 day rat study by inhalation route based on the liver and thyroid status changes observed at the concentration just above: 16 mg/m^3 .

Alterations in thyroid homeostasis were reported with organochlorine compounds for many species, including humans and a thyroid hormone like affinity for the serum transport protein transthyretin was shown for hydroxylated PCBs as well as for PBDPE congeners such as DiBDPE and TeBDPE. To our knowledge, no studies on transthyretin-T_4 competition have been carried out on OBDPE neither on DBDPE.

Following inhalation exposure, local toxicity was demonstrated with hyperplasia/hypertrophy of the goblet cells within 2 weeks of exposure and with chronic active lung inflammation and alveolar histiocytosis within 13 weeks of exposure. It is obvious that the observed effect at 1.1 mg/m^3 is minimal and reveals only a trend to a chronic inflammation however this value has been taken to set up the LOAEC for local toxicity.

Regarding mutagenicity no *in vivo* data are available. However based on the available *in vitro* data, OBDPE is considered as non-genotoxic *in vitro* and no concern for mutagenicity is assumed.

No chronic or carcinogenicity studies in animals are available.

No specific fertility study is available. A recent rat inhalation sub-chronic study, well conducted and specifically designed to investigate reproductive organs, did not demonstrate adverse effects on male reproductive organs. Therefore no concern is assumed for male fertility. Regarding female reproductive organs, absence of corpora lutea was shown in this study in 3/10 females at 202 mg/m^3 versus 0/10 in the control group. Since the absence of corpora lutea is considered to be an unusual finding in rats at 20 weeks of age, the 30% incidence in this group was considered treatment-related and therefore a NOAEC for female fertility of 16 mg/m^3 was considered.

Developmental effects are observed in rats in two studies (decrease of fetal body weight from 10 mg/kg/day, increase of post-implantation loss with late resorptions, increase in dead or resorbed conceptuses per litter at 25 mg/kg/day (33.2% versus 4.3%); decrease in the average number of live fetuses per litter (8.9 versus 14.6) and fetal malformation/variation and delayed skeletal ossification at 25 mg/kg/day. Those developmental effects do not seem to be related to maternal toxicity. However, these developmental effects are not confirmed in a third assay in rats conducted with a test article containing a lower percentage of the OBDPE component. In rabbits, the substance produces only slight foetotoxicity from 5 mg/kg/day (slight decrease of the fetal body weight and increase in delayed ossification). The lowest identified NOAEL is considered i.e. 2 mg/kg/day from the rabbit study. Since some of these results are indicative of developmental effects which are most likely unrelated to maternal toxicity, OBDPE is considered as a developmental toxicant.

With regard to neurotoxicity, recently behavioural disturbances have been reported when mice (10 day old) were exposed to a single oral dose of hexabromo-diphenyl ether (0.45, 0.9 and 9 mg/kg bw). Those effects are observed at 2, 4 but also 6 months of age. Nicotinic receptors were also affected in adult mouse in the previous conditions of exposure. The study has certain limitations compared with regulatory guidelines and thus uncertainty as regards interpretation of the results remains. Moreover only an abstract of this study is available with very few details. Therefore, no firm conclusion can be drawn from these data.

Environment

In order to take into account more fully the presence of the more accumulative hexabromodiphenyl ether congeners in the commercial product, the hazards to the environment of both the octabromodiphenyl ether product and hexabromodiphenyl ether congeners specifically have been addressed where appropriate. The environmental effects database for octabromodiphenyl ether does not formally meet the requirements of the SIDS data package as there is no information on the toxicity to algae. Based on the available data, the substance appears to have a very low toxicity to fish in short-term tests, with no effects being seen up to the water solubility of the substance. QSAR estimations for non-polar narcosis predict that all NOECs and L(E)C50s are above the water solubility limit of octabromodiphenyl ether. Similarly, no effects were seen in a longer-term reproduction study with *Daphnia*, for

which a 21 day NOEC of ≥ 2 μg/l was determined. Based on the results of the long-term *Daphnia* study a PNEC for surface water of ≥ 0.2 μg/l was derived for octabromodiphenyl ether using an assessment factor of 10. For the hexabromodiphenyl ether component a PNEC for surface water of 0.53 μg/l has been derived based on that derived for the commercial pentabromodiphenyl ether product.

For microorganisms, no effects were seen in a 3 hour activated sludge respiration inhibition test at a concentration of 15 mg/l. A $PNEC_{microorganisms}$ of ≥ 1.5 mg/l was derived for this endpoint using an assessment factor of 10.

Toxicity data are available for octabromodiphenyl ether for the sediment and terrestrial compartment. For sediment, no effects were seen with the worm *Lumbriculus variegatus* in a prolonged toxicity (28 day) test using two different sediment types. The lowest NOEC from these studies was ≥ 1,272 mg/kg dry weight and a PNEC for sediment of ≥ 127 mg/kg dry weight (or ≥ 49 mg/kg on a wet weight basis) was derived for octabromodiphenyl ether from the data using an assessment factor of 10 (a factor of 10 is used as this species was the most sensitive species found for another related substance, pentabromodiphenyl ether). Based on the same data, a PNEC for sediment of ≥ 7.0 mg/kg dry weight (or ≥ 2.7 mg/kg wet weight) was derived for hexabromodiphenyl ether component alone.

For the terrestrial compartment, studies on the toxicity to plants and earthworms (*Eisenia fetida*) have been carried out with octabromodiphenyl ether. No effects were seen on germination and growth in six species of plant (*Zea mays*, *Allium cepa*, *Lolium perenne*, *Cucumis sativa*, *Glycine max* and *Lycopersicon esculentum*) at concentrations up to 1,190 mg/kg dry weight. For *Eisenia fetida* no effects were seen at concentrations up to 1,470 mg/kg dry weight in a 56 day reproduction test. Based on a NOEC of ≥ 1,190 mg/kg dry weight from the plant tests, a PNEC for this end point of ≥ 23.8 mg/kg dry weight (or ≥20.9 mg/kg on a wet weight basis) can be derived for octabromodiphenyl ether using an assessment factor of 50. Based on the same data, a PNEC for soil of ≥ 1.3 mg/kg dry weight (or ≥ 1.2 mg/kg wet weight) has been derived for the hexabromodiphenyl ether component alone.

No data are available to allow a PNEC to be derived for the atmospheric compartment. However, the atmospheric concentrations of octabromodiphenyl ether are very low and so adverse effects are unlikely.

For secondary poisoning, based on the available standard mammalian toxicity tests, a PNEC of 6.7 mg/kg food can be derived for octabromodiphenyl ether. Based on the same data, a PNEC for secondary poisoning of 0.58 mg/kg food can be derived for the hexabromodiphenyl ether component alone. However, these PNECs are based on the results of standard tests, and there is some evidence from non-standard behavioural tests on mice that these standard tests may not detect more subtle effects that might be occurring with sensitive life stages or over prolonged exposure.

Based on the available laboratory data, octabromodiphenyl ether itself appears to have a low bioaccumulation potential. However, the main components of the commercial substance (hepta- to decabromodiphenyl ethers) have recently been found at low but measurable concentrations in fish, marine mammals and predatory birds' eggs (Peregrine Falcons and Common Terns), which indicates that these highly brominated substances are able to cross biological membranes and possibly that they are being accumulated in the food chain. The mere presence of a chemical in biota is not necessarily a cause for concern, and there is no evidence at this point in time of biomagnification taking place or actual environmental harm arising from this substance. However, these findings, when coupled with the uncertainties over the effects of this substance, means that further work should be considered. In addition, the possibility that the substance may photodegrade in the environment to give more toxic and accumulative products should be investigated further.

Exposure

Since 1998, production of octabromodiphenyl ether in the EU has ceased and all of this substance used within the EU is now imported. The reported world-wide demand for octabromodiphenyl ether was 3,825 tonnes/year in 1999.

The substance is used in the plastics industry, mainly as an additive flame retardant for acrylonitrile-butadiene-styrene (ABS) polymers. The commercially supplied product is a mixture of polybrominated diphenyl ethers typically consisting of ≤33% octabromodiphenyl ether. The other main components are hexabromodiphenyl ether (≤ 12%), heptabromodiphenyl ether (≤ 45%), nonabromodiphenyl ether (≤10%) and decabromodiphenyl ether (≤

0.7%).

The substance is an off-white powder or flaked material with a melting point in the range 70-257°C and a vapour pressure of 6.59×10^{-6} Pa at 21°C. The substance does not have a distinct boiling point as it decomposes at elevated temperatures. It has a very low solubility in water (~0.5 µg/l) and a high n-octanol-water partition coefficient (log Kow = 6.29).

Emissions to the environment can occur both to the atmosphere (as vapour and as dust) and waste water. Sources of release include production sites and polymer processing sites. In addition, emissions to the environment could also occur from finished articles (e.g. plastic components) during their use and at disposal.

The substance is not readily biodegradable, but there is evidence that at least some components of the commercial product have the potential to biodegrade slowly under anaerobic conditions. The substance can probably be degraded photolytically by analogy with other brominated diphenyl ethers. The products formed from this direct photolysis reaction, and also the rate and extent of the reaction, in the environment are uncertain but may include small amounts of more toxic and accumulative brominated diphenyl ethers that contain lower numbers of bromine. It is also expected to degrade in the atmosphere by reaction with hydroxyl radicals and a rate constant for this reaction of around 2.1×10^{-13} cm^3 $molecule^{-1}$ s^{-1} has been estimated.

The low vapour pressure, water solubility and high log Kow value indicate that the substance has a high potential for adsorption onto soil, sediment or suspended sediment. Laboratory studies indicate that the substance has a low potential for bioaccumulation in aquatic species, although some components of the commercial product (e.g. hexabromodiphenyl ether) have been shown to have a much higher potential for bioaccumulation.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The SIDS requirements are met. This substance has been discussed in the European Union Risk Assessment programme under EC Regulation 793/93, and is subject to marketing and use restrictions due to the risks identified. Other member states are therefore recommended, as a post-SIDS activity, to review the exposure situation in their countries to determine the need for similar measures. Some additional studies could be performed but in view of the marketing and use restrictions in several OECD countries, the sponsor country is unlikely to pursue these data gaps.

For the environment, the following work could be considered:

Further work is needed to address the concerns over the possible accumulation in, and effects on, top predators and also the possible formation of more accumulative and toxic congeners from photolytic processes in the environment. These areas are difficult to address with standard tests. Possibilities include:

a) Consideration of a more widespread monitoring project to determine whether the finding in top predators (including birds' eggs) is a widespread or localised phenomenon and to identify any possible trends.

b) Consideration of further toxicity testing on birds.

c) Consideration of an investigation on the rate of formation of degradation products under environmentally relevant conditions over a suitably prolonged time period (e.g. years).

d) Consideration of further toxicological work on the non-diphenyl ether degradation products to determine if they pose a hazard.

For health, the following work could be considered:

- Information is needed on transthyretin-T4 competition with OBDPE.
- Information on the effects of prolonged exposure: This may involve the conduct of a lifetime study in rodents depending upon the way in which the methodology for assessing lifetime exposure is developed and any data requirements that may be indicated for such a methodology.
- Further information is needed on food chain modelling.
- Information on the extent of excretion of commercial OBDPE into the breast milk.
- Information on the extent of excretion of commercial OBDPE into cows' milk. Depending upon the results submitted by Industry on milk excretion further information might be requested.
- There is a need for exposure information from local and regional sources on the concentration of OBDPE in cows' milk.

Consideration of national or regional exposure information gathering and, if indicated, a risk assessment may need to be considered for secondary poisoning from the hexabromodiphenyl ether component of the commercial product via the earthworm food chain. This is based on an existing regional risk assessment for Europe.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3323-53-3
Chemical Name	Adipic acid, compound with hexane-1,6-diamine (1:1)
Structural Formula	$HOOC-(CH_2)_4-COOH.H_2N-(CH_2)_6-NH_2$

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

Adipic acid, compound with hexane-1,6-diamine (1:1) (AH salt) rapidly dissociates to form adipate and 1,6-hexanediammonium in an almost neutral aqueous solution. Depending on the exposure route (stomach: pH 1 to 3, intestines pH 7, lung: pH 6.9), adipate may be protonated to yield adipic acid (pKa1: 4.3, pKa2: 5.4). Therefore, according to the equation of Henderson-Hasselbalch, regardless of whether adipic acid or AH salt is applied, in the stomach adipic acid is formed, whereas in the lung adipate is formed. The cation 1,6-hexanediammonium has pKa values of 10.0 and 11.1 and therefore is formed when AH salt or 1,6-hexanediamine is applied regardless of the exposure route. Thus, it can be expected that systemic effects of adipic acid and 1,6-hexanediamine are representative for AH salt irrespective of the exposure route. However, local effects of 1,6-hexanediamine which are due to its alkalinity have no relevance for AH salt, which is almost neutral.
Since a fertility study with adipic acid is lacking, a one-generation study with di(2-ethylhexyl) adipate (DEHA) which is rapidly metabolized to adipic acid is used to cover this endpoint.

Additionally, 13-week studies with 1,6-hexandiamine and a 2 year study with adipic acid were used to assess subchronic and chronic effects. Ames tests with 1,6-hexanediamine and adipic acid have been additionally used for the endpoint mutagenicity *in vitro*.

Toxicologically, AH salt may be evaluated based on data available from adipic acid and 1,6-hexanediamine and DEHA.

Human Health

There are no toxicokinetic studies with AH salt but with its constituents: Adipic acid or adipate are partially oxidized in the lipid metabolism pathways and excreted via the kidney or the lungs. 1,6-Hexanediamine is partially oxidized by diaminooxidases and aldehydedehydrogenases to 6-aminohexanoic acid, which is excreted via the urine to some extent after N-acetylation. A small part is also excreted unchanged.

The oral LD50 of AH salt in rats was approximately 4,900 mg/kg bw. Clinical signs at sublethal doses included stiff gait, apathy, reduced appetite, diarrhea, and rough coat. The lowest lethal dose (LDlo) after 24 hour occlusive dermal exposure in rabbits was above 7,940 mg/kg bw for AH salt. Clinical signs included reduced appetite and activity, salivation and ocular discharge. No data are available on the inhalation toxicity (LC50) of AH salt.

In limited studies, a 50% aqueous preparation of AH salt was not irritating to the skin and slightly irritating to the eyes of rabbits.

After repeated administration of AH-salt to rats by gavage for 28 days liver (hepatocytic necrosis), kidney (renal tubular degenerative changes) and stomach (gastric mucosal necrosis) were target organs after exposures to high dose levels (5000 mg/kg bw). The NOAEL was 1000 mg/kg bw/day.

No further data for AH salt were available, therefore in some studies the components of AH salt were investigated. Adipic acid (2 year study) and 1,6-hexanediamine (13 week study), gave no indication of specific target organs in dietary studies in rats. NOAELs of 500 - 1000 and 50 mg/kg bw/day, respectively, were obtained. Higher doses caused body weight retardation.

Inhalation of 1,6-hexanediamine dihydrochloride caused increased absolute and relative liver weights in male mice and no effects in female mice and Fischer rats of either sex besides local effects possibly due to the unphysiological pH. The local NOAEC was 5 mg/m^3, the systemic NOAECs were 16 mg/m^3 for mice and 160 mg/m^3 for rats. There is no inhalation toxicity information available on adipic acid, and therefore, it is not possible to predict a NOAEC for this endpoint for this substance, nor for AH salt.

On balance, sufficient data are available to assess the subchronic toxicity profile of AH salt, showing relevant effects only at very high exposure levels.

AH salt was not genotoxic in limited *in vitro* (Ames test, UDS test) and neither clastogenic nor aneugenic in a mouse micronucleus test (OECD 474) after intraperitoneal administration. Additionally, Ames tests for the two components of AH salt showed no mutagenic activity. AH salt is therefore considered to be non-genotoxic.

There are no data on carcinogenicity for AH salt.

Data for fertility and developmental toxicity are only available for the components of AH salt and for di(2-ethylhexyl) adipate, which is metabolized to adipic acid.

1,6-hexanediamine (or its dihydrochloride salt) had no effect on fertility of rats in a two-generation study after administration with the diet in doses up to 150 mg/kg bw/day and after inhalation of up to 160 mg/m^3 for 13 weeks in rats and mice. In the 2-generation study the top dose (500 mg/kg bw/day) was associated with a small reduction in litter size in the F1- and F2 generation, however, without histological changes in the sex organs of males and females and in the presence of paternal as well as maternal toxicity. With the exception of a slight reduction of the litter size reproductive parameters were not adversely influenced in rats fed with di(2-ethylhexyl) adipate up to exposure levels of 12,000 ppm in the diet (corresponding to ca. 240 480 mg adipic acid/kg bw/day). The second metabolite 2-ethylhexanol resp. its metabolite 2-ethylhexanoic acid might have contributed to the slight reduction of litter size seen at that dose. 1800 ppm (36 - 72 mg adipic acid/kg bw/day) was a clear NOAEL for fertility effects. This NOAEL corresponds to 65 -129 mg AH salt/kg bw/day.

The overall conclusion is that AH salt may present a hazard to fertility only at doses which are parentally toxic.

In various species (rat, mouse, rabbit), studies with adipic acid, one of the two constituents of AH salt, did not indicate an adverse effect on development up to the highest doses tested (gavage; 250 - 288 mg/kg bw/day). In none of these studies, signs of maternal or fetal toxicity have been observed. (NOAEL rat, mouse, rabbit (maternal/developmental toxicity) 250 - 288 mg/kg bw/day). Data on purity of adipic acid are lacking, but as no effects were observed up to the highest dose tested this is thought not to impair the validity of the results. The other constituent, 1,6-hexanediamine, caused some retardation in fetal development of rats in the presence of maternal toxicity. No teratogenic effects were found up to the highest tested dose level of 300 mg/kg bw/day, which was already associated with pronounced maternal toxicity (NOAEL maternal/developmental toxicity: 112 mg/kg bw/day). An impairment of body weight gain of rat pups in the postnatal period was shown for 1,6-hexanediamine at a dose of 500 mg/kg bw/day in the absence of maternal toxicity. The NOAEL for this effect is 150 mg/kg bw/day. These doses correspond to 1130 mg and 338 mg AH-salt/kg bw/day, resp. However, as no adverse effects on pup body weights occurred on the day of birth (day 0) and on the day 4 after birth, but only on day 21 after birth (less than 10 %; no data presented on days 7/14 after birth) it cannot be excluded that the effect on pup body weight data are a consequence of the food intake rather than lactation of the pups, particularly between days 14-21 after birth.

Therefore, there is insufficient evidence that AH salt may act as developmental toxicant by impairment of body weight gain of progeny during lactation found at non maternally toxic but high doses of 1,6-hexanediamine.

Environment

AH salt is a white solid, with a solubility in water of 468 g/l at 21 °C, a melting point of 202 °C, a density of 1201 kg/m^3, and a measured log Kow of –4.4. The vapor pressure is expected to be very low due to the salt character of the substance.

In a Zahn-Wellens test (OECD 302 B) conducted with industrial activated sludge a biodegradation of 96 % after 3 days was found. From this test result it can be concluded that AH salt is inherently biodegradable. There is no study available that indicates ready biodegradation of AH-salt. A BOD5/COD ratio of 0.61 was obtained using effluent from an industrial sewage treatment plant as inoculum. One component of AH-salt, adipic acid, is readily biodegradable while for the second component, 1,6-hexanediamine, no adequate test is available to determine whether the chemical is readily biodegradable.

Due to the salt character of the substance the calculation of a fugacity model is not appropriate. Based on the physico-chemical properties, water is expected to be the main target compartment. Due to its salt character and physico-chemical properties, volatilization from surface waters and sewage treatment plants is not expected. The substance is also not expected to bioaccumulate based on its log Kow. The mobility in soil is expected to be high based on the log Kow. However, the soil absorption can be only roughly estimated because of possible ionic interactions of the cations with negatively charged particles in the soil that may reduce their mobility. Photochemical degradation in water with estimated half-lives of 10 – 67 days for the 2 components of AH- salt does not appear to be a relevant mechanism of elimination.

Static short-term tests have been conducted with species from three trophic levels. The following effect values were found:

Fish*:*	*Leuciscus idus:*	96h-LC50 = 10,000 mg/l;
	Salmo gairdneri, Lepomis macrochirus:	96h-LC50 > 470 mg/l;
Daphnids:	*Daphnia magna*:	48h-EC50 = 90 mg/l;
Algae*:*	*Scenedesmus subspicatus*:	72h-EC50 = 394.5 mg/l.

To derive the PNECaqua the EC50 from the test with *Daphnia magna* is used: PNECaqua = 90 mg/l / 1000 = 90 µg/l (for the derivation of the PNECaqua an assessment factor of 1000 is used according to the EU Technical Guidance Document as only short-term effect values are available).

Exposure

AH salt is the basic raw material for the production of nylon 66 polymers and copolymers, that are used in fibres and yarns for textiles, carpets, apparel, tire cord, and industrial applications, or in engineering resins, used for automotive parts, electrical and electronic applications, machine parts, films, and wire coatings.

The world-wide production capacity for AH salt is estimated to be 3,400,000 tonnes/year (1,000,000 tonnes/year in Western Europe, 1,900,000 tonnes/year in North & South America and 500,000 tonnes/year in Asia).

AH salt is not registered in the product registers of Denmark, Finland, Norway and Sweden. The Swiss product register contains 3 products: 1 industrial (100 % AH salt, chemical intermediate) and 2 consumer products (up to 1 % AH salt, detergents and soaps) without mentioning any quantities processed or used.

Releases into the environment may occur during production and processing. According to measurements in a German chemical plant releases are low. Releases to the environment from the use of end products containing AH salt are considered negligible, since AH salt is present in these products only in small amounts. Occupational exposure may occur during production and processing of AH salt. Workplace measurements are available from a European production plant and gave a 95 % percentile of 0.83 mg/m^3 (total dust: personal sampling). No exposure

information is available with regard to processing sites.

One of the components, adipic acid, is approved as food additive.

AH salt is used in the production of numerous consumer end products. In these products, AH salt is generally bound into the polymer matrix and hence is not expected to be present above trace concentrations.

RECOMMENDATION

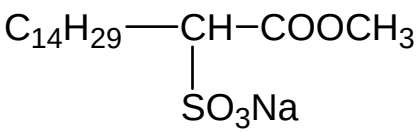
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The components of the substance possess hazards concerning reproductive toxicity but only at high doses. 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: AH-salt possesses properties indicating a hazard for the aquatic environment. 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

CAS No.	4016-24-4
Chemical Name	Hexadecanoic acid, 2-sulfo-, 1-methylester, sodium salt
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information on toxicokinetics and metabolism.

In an acute toxicity study [OECD TG 401] with hexadecanoic acid, 2-sulfo, 1-methylester, sodium salt in rats, compound-related changes including death, decrease in the body weight and locomotor activity, ptosis, and piloerection were observed. The oral LD50 values were considered to be 2,142 mg/kg bw in male rats and 1,819 mg/kg bw in female rats. No information on inhalation toxicity is available.

A skin irritation test in guinea pigs showed slightly positive reactions. Dermal exposure to this chemical for 28 days caused primary irritation in rats. There is no available information on eye irritation. This chemical was not sensitizing in a mouse Local Lymph Node Assay.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], Crj:CD (SD) IGS rats (10 animals/sex/dose) were given this compound by gavage at 0, 5, 20, 80, or 300 mg/kg bw/day. Males were dosed for 47 days from day 14 before mating and females were dosed for 42-45 days from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. An increase in the GPT levels and decrease in the triglyceride levels were found in males at 300 mg/kg bw/day. At necropsy, thickening of the forestomach mucosa was observed in six males and nine females at 80 mg/kg bw/day and in 10 males and females at 300 mg/kg bw/day. In histopathological examinations, squamous hyperplasia, erosion, and edema of lamina propria and/or submucosa and inflammatory cell infiltration were observed in the forestomach of both sexes at 80 and 300 mg/kg bw/day. Based on the pathological findings in the forestomach at 80 mg/kg bw/day, the NOAEL for repeated dose toxicity was considered to be 20 mg/kg bw/day in male and female rats.

In a reverse gene mutation assay [OECD TG 471], this chemical was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA1537, TA 98 and *Escherichia coli* WP2 *urv*A with and without an exogenous metabolic activation. In a chromosomal aberration test [OECD TG 473], this compound did not cause structural chromosomal aberrations or polyploidy with and without an exogenous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells.

There is no available information on carcinogenicity.

The above-mentioned combined study [OECD TG 422] showed that the reproduction/developmental parameters, i.e. mating, pregnancy, delivery, lactation, and viability and body weight of pups, were not affected by this compound up to 300 mg/kg bw/day. The NOAEL for reproduction/developmental toxicity was considered to be 300 mg/kg bw/day in rats.

Environment

Hexadecanoic acid, 2-sulfo-, 1-methylester, sodium salt has a melting point of 178.2 – 181.9 degree C and this chemical is estimated to be stable of pH 4, 7 and 9 at 25 degree C for 1 year, and it is readily biodegradable. A critical micelle concentration (CMC) of 0.73 mM (271.9 mg/L) is reported. A vapor pressure of 5.12^{-13} Pa at 25 degree C and a Log Pow of 4.06 (for the ionized form) are calculated. This chemical exists primarily in the ionized form under the environmental pHs. Due to the ionizing properties of this chemical and based on data from analogues, it can be assumed that bioaccumulation is not likely to be significant. This chemical on the market contains 20 to 30% (w/w) of tetradecanoic acid, 2-sulfo-, 1-methylester, sodium salt.

In an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum*, open system), the 72 h ErC50 and the 72 h EbC50 were >9.00 mg/L. For daphnids, a 48 h EC50 of 1.24 mg/L was reported (OECD TG 202, *Daphnia magna*, static). For fish (OECD TG 203, *Oryzias latipes*, semi-static) a 96 h LC50 of 1.50 mg/L was available.

Regarding chronic toxicity to algae, a 72 h NOErC of 9.0 mg/L and a NOEbC of 1.48 mg/L (OECD TG 201, *Selenastrum capricornutum*, open system) were reported. In daphnids, a 21 d EC50 of 0.70 mg and a 21 d NOEC of 0.24 mg/L were reported (OECD TG 211, *Daphnia magna*, semi-static).

There is no available information on toxicity to neither terrestrial nor other organisms.

Exposure

Hexadecanoic acid, 2-sulfo-, 1-methylester, sodium salt is used as detergent of clothing. In Japan only one company produces this chemical with a production volume of 10,000 to 100,000 tonnes/year (containing up to 30% of tetradecanoic acid, 2-sulfo-, 1-methylester, sodium salt). For 2001, a production volume of 13,400 tonnes is reported.

This chemical is mainly released to the aquatic compartment and it can be expected that the partitioning to other compartments is unlikely but adsorption onto sludge is possible due to the surface active properties.

Occupational exposure to this chemical through inhalation and dermal routes is possible.

Some low level direct exposure to general public is possible during washing cloths by hands via the dermal route and via inhalation of particles.

RECOMMENDATION

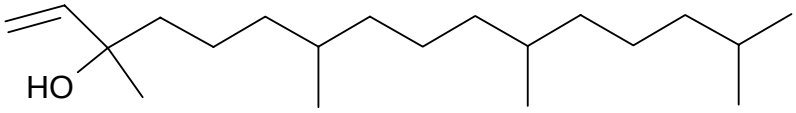
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work based on a low hazard potential.

Environment: The chemical possessed properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure levels and also this chemical is readily biodegradable, they should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	505-32-8
Chemical Name	Isophytol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Isophytol has a low acute oral and dermal toxicity: oral mammalian LD50 above 5000 mg/kg bw, with most values greater than 8000 mg/kg bw. The acute dermal LD50 is above 5000 mg/kg bw in rabbits. One intraperitoneal LD50 in mouse is 169 mg/kg bw. Inhalative tests over 8 hours in rodents show no effect of a non-aerosol isophytol-enriched atmosphere (NOEC ≈ 0.3 mg/m^3 based on vapour pressure).

Isophytol is irritating to the skin, based on animal studies, but a 10% solution in petrolatum was not irritating to human volunteers. Isophytol is a slight eye irritator. In rabbit transient irritant reactions of the eyes were produced, which all resolved within 8 days. In two sensitisation tests the reactions were judged to be of an irritant rather than a sensitising nature, a maximisation test with 10% isophytol in human volunteers was negative.

The 28-day subchronic oral NOEL is 250 mg/kg bw/d, with only minor and reversible effects (including kidney weight changes) at the LOAEL of 1000 mg/kg bw/d. Based on histopathological data from a one-generation study with an average exposure of 64 days for females and of 98 days for males, the NOEL and NOAEL for parental systemic toxicity was below 250 mg/kg bw/d.

Isophytol was not mutagenic in two bacterial tests, whereas one bacterial test was predominantly negative with a few ambiguous results. In an *in vivo* micronucleus test no clastogenic effects were seen. Thus isophytol is considered to be not mutagenic. There are no proper carcinogenicity data.

In a one-generation reprotoxicity study, 250 mg/kg bw/d was the LOAEL for parental toxicity based on effects in kidney (dilated renal tubules; renal mineralization). 500 mg/kg bw/d was the NOAEL for maternal reprotoxic effects based on a slightly increased mean pre-coital time, a decreased fertility index and conception rate. Postnatal loss was observed at low and medium dose (2% in controls, 7% at 250, 8% at 500 mg/kg bw/d) an increase of 39% at 1000 mg/kg bw/d was observed where also clinical signs in the mothers appeared. A NOAEL of 500 mg/kg bw/d was derived for developmental toxicity of the pups based on clinical signs and decreased body weight during the lactation period.

In conclusion, the overall mammalian toxicity of isophytol is considered to be low but, based on animal data, there is a potential for irritation.

Environment

Water solubility = 5.8 mg/l (25°C); vapour pressure = 0.00003 hPa (20 °C); logP_{OW} ≈ 8.1. Isophytol preferentially partitions to soil and sediment while water and atmosphere are clearly less important compartments. Based on two out of three tests, isophytol was readily biodegradable. It is not significantly biodegradable under anaerobic conditions. No experimental bioaccumulation data have been located but in view of the high log P_{OW} a potential for

bioaccumulation may reasonably be expected. In both aerobic and anaerobic sediments, however, isophytol has been shown to be a relatively short-lived intermediate in the diagenetic chemical conversion of the chlorophyll phytol side chain to kerogen, high-molecular-weight lipophilic organic matter bound in sediment and rocks.

Isophytol was not acutely toxic to fish and algae at loadings (nominal concentrations) far higher than the water solubility in older studies which were not optimised as regards investigations of chemicals with low solubility. Some older daphnid EC50 values vary widely, from 0.11 to 20.3 mg/l, due to nominal concentrations reported and different ways of preparing test solutions. A recent semi-static OECD 202 test under GLP with analytical monitoring resulted in an acute EC50 of 0.130 mg/l (based on average measured concentrations, because the concentration of the substance significantly diminished during each of the two days of the semi-static test). Entrapment of daphnids to the surface of the test media was noted at all test concentrations, but not in the controls. Isophytol had low toxicity to microorganisms, from activated sludge to various species of bacteria and yeasts, with all reported NOECs at least 100 mg/l (nominal concentration). Based on the lowest acute EC50 with measured concentrations, an aquatic PNEC of 0.13 µg/l is proposed for freshwater using an assessment factor of 1000. Nonstandard tests with marine crustaceans resulted in not otherwise specified "weak" effects at 500 mg/l (nominal concentration) in one case, respectively in a minimal inhibitory concentration for the attachment of larvae to surfaces of ≤ 1 µg/cm^2 in the other.

In a chronic and reproductive test with the ubiquitous soil and sediment nematode *Caenorhabditis elegans* the NOEC was high (15,000 mg/kg sediment dry weight). No proper data for effects on terrestrial plants have been located, but isophytol was not toxic in nonstandard *in vitro* tests with maize leaves and safflower cell cultures. Isophytol may work as a semiochemical for certain rice moths, but there are no reports on proper insect toxicity. No avian data have been located.

In conclusion, isophytol showed no acute toxicity towards fish and algae, but seemed to have effects at low concentrations to daphnia after short time exposure. Interpretation of the effects on the daphnids are however complicated because of the disappearance of the substance during the test, and because the effects may have been caused by physical entrapment of the daphnids and not because of toxicity of isophytol. Isophytol is barely toxic for microorganisms and for a common soil and sediment dweller. There is no indication for toxicity against terrestrial plants and insects.

Exposure

Worldwide, approximately 35,000–40,000 tonnes isophytol *per annum* are estimated by industry to be produced. In addition, there is some natural biosynthesis by plants as evidenced by analytical determinations, however, the ubiquitous formation of isophytol from chlorophyll, as postulated in the Merck Index, is not supported by the original literature consulted. More than 99% of synthetic isophytol is used as an intermediate in the synthesis of vitamins E and K_1 and of further terpenoid compounds, while clearly less than 1% is used in fragrance mixtures and less than 0.1% is estimated to be added to food and beverages for flavouring. The initial formulators of isophytol produced at the Swiss plant have comparable emission controls and waste treatment facilities as the manufacturer, hence only minor losses to the environment are expected. Some isophytol is released to the atmosphere, where it is expected to be rapidly degraded abiotically with an estimated half-life below 30 minutes. In the aquatic compartment, isophytol is rapidly biodegraded under aerobic conditions, while anaerobic biodegradation is negligible. In sediment there is evidence for the formation of isophytol as a relatively short-lived intermediate in the abiotic transformation of chlorophyll-derived phytol to high-molecular-weight organic compounds locked in sediment respectively rock. No measured environmental concentrations have been located.

Chemical production workers are rarely exposed to isophytol, due to closed synthesis; where direct contact is possible, standard occupational hygiene measures limit exposure. There may be some limited exposure on filling transport containers. The public is exposed to isophytol as an ingredient of perfumes and cosmetics, however, concentrations in the final products are clearly $< 0.2\%$. Isophytol is listed as a food ingredient in the European Union, but not in the United States; while no quantitative data have been located the actual use in food must be minimal.

RECOMMENDATION

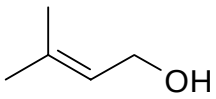
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human health: The only hazard identified is irritation to skin and slight irritation to eyes. Given the main use as a chemical intermediate and the low content of the substance in consumer products in the Sponsor country, the substance is considered to be 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 a hazard for the environment. These hazards do not warrant further work (but they should nevertheless be noted by chemical safety professionals and users). Based on data presented by the Sponsor country, exposure to the environment is anticipated to be low.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	556-82-1
Chemical Name	3-Methylbut-2-en-1-ol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The LD50 for the rat after oral administration of 3-methylbut-2-en-1-ol was 1591 mg/kg bw. The main symptoms described were apathy, dyspnea and reddened eyes and ears. A dose response was observed, with symptoms getting progressively worse with increasing dose and recovery occurred within 7 days in the two lowest doses tested (172 and 1376 mg/kg bw). After inhalation of vapors of the substance, a LC50 of > 16.8 mg/l/4 hrs can be estimated for rats using Haber's rule. A dermal LD50 in rats was found to be > 4000 mg/kg bw. In rabbits the substance was corrosive to the skin and highly irritant to the eyes.

In a maximization test in humans, the substance (10 % in petrolatum) caused no skin sensitization.

In a 90 days study (OECD guideline 408) with administration of the test substance in the drinking water up to concentrations of 5000 ppm (243.8 and 307.2 mg/kg bw/day for males and females), the only treatment related findings were reduction in food and water consumption at the high and mid dose which was accompanied by a decrease in body weight and body weight gain at the high dose. There were no other treatment related significant changes in clinical examinations, functional observational battery, opthalmoscopy, clinical chemistry, hematolgy, urinalyses, organ weights, pathology and histopathology. The no observed adverse effect level (NOAEL) was 1000 ppm for both sexes (65.4 and 82.1 mg/kg bw/day for males and females)

No mutagenic effect was found in the Ames Test (preincubation test and liquid suspension assay) and *in vivo* in the mouse micronucleus test.

Based on the results of the well conducted 90 days study in rats with administration of the test substance in the drinking water, 3-methylbut-2-en-1-ol does not have potential to damage the reproductive organs at least up to the highest tested concentration of 5000 ppm (243.8 and 307.2 mg/kg bw/day).

3-Methylbut-2-en-1-ol showed no evidence of developmental toxicity (including no teratogenicity) in an OECD TG 414 study when administered by gavage (up to 600 mg/kg bw/day) to pregnant rats from implantation to one day prior the expected day of parturition (days 6-19 after conception). The NOAEL for maternal toxicity was 200 mg/kg bw/day while the NOAEL for prenatal developmental toxicity was > 600 mg/kg bw/day.

Environment

3-Methylbut-2-en-1-ol is a colorless liquid, with high solubility in water (170 g/l at 20°C) and high vapor pressure (3.17 hPa at 25°C). The substance has a flash point at 51.5 °C and is flammable. The density of the substance (0.85 g/cm^3 at 20°C) is slightly lower than that of water. The boiling point of the substance is about 142 °C, the calculated melting point at –59.3 °C. The measured partition coefficient n-octanol water (log K_{OW}) is 0.91.

Distribution modelling using Mackay level I indicates water to be the main target compartment (95 %). The calculated Henry´s constant in the range of 0.73 to 1.4 Pa*m^3/mole suggests a moderate volatilisation from water. According to OECD-criteria the substance is readily biodegradable (OECD 301F, 82 % after 28 d, 10d-window fulfilled). Hydrolysis is not expected according to the structure. In the atmosphere 3-methylbut-2-en-1-ol will be indirectly photodegraded by reaction with hydroxyl radicals (calculated half-life 4.25 hours) or ozone (calculated half-life 38 min). Calculations based on the log K_{OW} = 0.91 do not indicate a potential for bio- and geoaccumulation.

Acute aquatic toxicity has been determined for fish (*Leuciscus idus*: LC50 (96 h) 46 mg/l), for aquatic invertebrates (*Daphnia magna*: EC50 (48h) = 144 mg/l) and for green algae (*Scenedesmus subspicatus*: E_bC50 (72 h) > 500 mg/l). According to the EU Technical Guidance Document, the PNEC aqua can be calculated to 0.046 mg/l by applying an assessment factor of 1000 on the most sensitive species.

Exposure

The world-wide production of 3-methylbut-2-en-1-ol for the year 2001 was in the range of 6,000 to 13,000 tonnes, thereof 5,000 to 10,000 tonnes in Europe. It is produced in Europe and Asia by two producers, in the NAFTA it is processed at a range of 1,000 to 5,000 tonnes per year.

3-Methylbut-2-en-1-ol is mainly used as intermediate in the chemical industry for the synthesis of active ingredients (pharmaceuticals, aroma chemicals). A minor fraction, estimated to a maximum of 50 tons, is used as flavoring agent (1 - 10 ppm in final products) and in cosmetics at a maximum level of 0.1 %. There are no products containing the substance in the Swedish, Danish, Swiss and Norwegian product registers.

3-Methylbut-2-en-1-ol naturally occurs in citrus fruits, cranberry, bilberry, currants, grapes, raspberry, black berry, tomato, white bread, hop oil, coffee, Arctic bramble, cloudberry and passion fruit.

Releases into the environment may occur during production and processing of 3-methylbut-2-en-1-ol as an intermediate, as well as from the use of the substance as an ingredient in cosmetic products.

Exposure to workers is adequately controlled in the industry of the sponsor country (Germany).

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The substance is corrosive. Given the main use as a chemical intermediate in closed systems and the low content of the substance in consumer products in the Sponsor country, the substance is considered to be of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The substance possesses properties indicating a hazard for the environment. 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

CAS No.	7782-50-5
Chemical Name	Chlorine
Structural Formula	Cl-Cl

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Chlorine is a gas which when dissolved in water is in a fast equilibrium with hypochlorous acid (HOCl) which is in equilibrium with hypochlorite ion (ClO^{-}). The latter is predominant at alkaline pH values, while Cl_2 is mainly present at pH below 4. Therefore the concentration of chlorine in an aqueous solution is generally expressed as available chlorine which is the sum of Cl_2+HOCl+ ClO^-, regardless whether these species stem from dissolved gaseous chlorine or from dissolved sodium hypochlorite.

Although the ingestion of chlorine gas is unlikely, solutions of chlorine may pose hazard by this route of exposure.

Most of data for chlorine toxicity by oral route come from studies performed with sodium hypochlorite. In biological systems, characterised by pH values in the range 6-8, the most abundant active chemical species is HOCl, in equilibrium with ClO.

Available chlorine is readily absorbed via oral route and distributed into plasma, bone marrow, testis, skin, kidney and lung. Only ca. 50% is excreted mainly with the urine followed by excretion with feces. HOCl is not enzymatically metabolised and its (bio) tranformation readily occurs through direct reactions with organic compounds or with other chemicals present in the cellular environment, leading to the formation of chlorinated organic compounds possessing their own inherent toxicity.

Irrespective of the mode of breathing (either through the nose or the mouth) and respiratory flow rate, > 95% of the inspired Cl_2 was absorbed in the upper airways, whereas the dose delivered to the lower airways was < 5% when a micro-bolus of 3 ppm in air is injected into an airstream. No data are available for a continuous exposure to 3 ppm or more of chlorine.

A large number of studies on acute inhalation toxicity of chlorine have been performed. The results from these studies show that acute inhalation toxicity is high and LC50 values ranges from 250 ppm (900 mg/m^3 /30 min) for mice to 400 ppm (1200 mg/m^3 /30 min) for rats. Asthma-like symptoms following acute inhalation of high-dose irritant gases have also been related to acute chlorine exposure in humans.

No information is available on any potential systemic toxicity that can be caused by dermal route as no dermal acute toxicity studies are available for both chlorine or hypochlorite salts solutions. It can be expected to be low considering the low acute systemic toxicity by the oral route.

Chlorine is corrosive to the skin and severe effects can be expected from exposure to the eyes. Moderate to severe lesions in the respiratory tract after exposure to 9 ppm (27 mg/m^3) chlorine for 6 h/d at 1, 3 and 5 days were reported in rats and mice, mainly in the nasal passage, epithelial necrosis, cellular exfoliation, erosion, ulceration and squamous metaplasia. Skin sensitization studies are not available. No case reports were found showing a sensitization potential in humans.

For repeated dose toxicity, in a two year study, the LOAEL for respiratory irritation has been determined to be 0.4 ppm (1.2 mg/m^3) for rats and mice: an NOAEL for inhalation route could not be established. In none of the available studies any systemic effect was observed.

A NOAEL of 950 ppm available chlorine (59.5 mg/kg bw/day) can be derived from a 13-week rat study with sodium hypochlorite in drinking water. A NOAEL of 14 mg/kg bw/day for rats and a NOAEL of 22.5 mg/kg bw/day for mice can be derived from a two year study with sodium hypochlorite in drinking water.

There are many detailed studies reported for human exposure. An inhalation acute NOEL of 0.5 ppm (1.5 mg/m^3) which excludes tissue lesions and impairment of the pulmonary function can be derived by human experience and control studies in volunteers.

For genetic toxicity the majority of the *in vitro* assays have shown positive or ambiguous responses, suggesting that sodium hypochlorite may be mutagenic *in vitro*, however genotoxic effects were not seen *in vivo* probably due to the cytotoxic properties of chlorine.

No evidence of treatment related carcinogenicity was observed in mice and rats exposed by inhalation to chlorine and orally to sodium hypochlorite, but some equivocal results were reported for female rats by oral route. For human cancer no association between chlorine exposure and tumor incidence was observed.

The absence of reproductive toxic effects was clearly shown up to 5 mg/kg (maximum dose tested) in a one generation oral study in rats. Although limited data are available in animals, there is no evidence of adverse developmental effects. Moreover, epidemiological studies in humans did not show evidence of toxic effects on foetal development.

Environment

Chlorine is a greenish-yellow gas with a pungent odour at ambient temperatures and pressures. Density is 2.5 times higher than air. Its vapour pressure is 6.39 10^6 Pa at 20 °C. Molecular chlorine is a strong oxidiser and a chlorinating agent. Chlorine is moderately soluble in water (~6.5 g/ l). The total amount of chlorine dissolved in water and the relative amounts of the components in equilibrium (Cl_2+HOCl+ ClO^- = free available chlorine) are dependent on ionic strength and pH. Diluted aqueous solution of hypochloric acid will decompose, very slowly in the dark, but more rapidly in the presence of light, particularly rapidly in full sun light, by producing hydrogen chloride and oxygen. Some chlorine and chloric acid may also develop. The physico-chemical properties indicate that chlorine released into the environment is distributed into water and preferably air.

In water and in atmosphere chlorine/hypochlorite undergoes photolysis with an estimated half-life of 1-4 hours, depending on the time of the day. In natural water, in the presence of organic or inorganic compounds, the free available chlorine immediately reacts forming various chlorinated by-products e.g. chloramines and chloromethanes which are mainly distributed to the hydrosphere, but are also able to transfer to some extent to the atmosphere depending on their intrinsic properties. A potential for bioaccumulation or bioconcentration of active chlorine species can be disregarded, because of their water solubility and their high reactivity.

Valid freshwater short-term toxicity data are available only for invertebrates: the LC50 for *Ceriodaphnia dubia* is 5 µg FAC/l (FAC=Free available chlorine). Adequate standard acute tests with fish are not available, but from many reliable studies performed under intermittent exposure conditions a 96h LC50 of 60 µg TRC/l and a 168h LC50 of 33 µg TRC/l can be derived (TRC= total residual chlorine= the sum of combined end free residual available chlorine). Due to the intermittent regime (three 40 minutes pulses per day) a 96h LC50 << 60µg TRC/l can be expected for fish in a standard test.

For freshwater long-term toxicity, no valid NOEC values from standard long-term tests are available, but data can be derived by some microcosm and field studies: 7d -NOEC for algae 3 µg TRC/l, corresponding to 2.1 µg FAC.

For salt water short-term toxicity valid data are available for molluscs (48h EC50 = 26 µg TRC/l) and for fish (*Oncorhynchus kisutch* 96 h LC50 = 32 µg TRO/l) (TRO = Total Residual Oxidant) showing comparable sensitivity.

For long term toxicity the molluscs are more sensible than fish showing a 15d NOEC = 7 µg TRO/l, while a NOEC of 40 µg CPO/l was calculated for fish fry survival (CPO = Chlorine Produced Oxidants).

Exposure

Total annual world-wide chlorine production capacity was 46.5 million metric tonnes in 1999. Chlorine is produced from sodium chloride by three different processes: diaphragm, mercury and membrane. Chlorine is mainly used as a chemical intermediate to produce raw materials for chemical, pharmaceutical and crop protection industries. There are also wide dispersive use applications of elemental chlorine in water such as drinking water, pulp and paper, swimming pool, sewage treatment, cooling water and textile industry. It can be estimated that less than 1.8‰ of the production volume was released into the environment in the year 1999 and the world wide total antropogenic chlorine release can be estimated to be 71,000 metric tonnes.

Gaseous compounds such as hydrogen chloride (HCl), molecular chlorine (Cl_2), hypochlorous acid (HOCl), and nitryl chloride ($ClNO_2$) occur in nature in sea-salt aerosols arising from the oceans. Volcano eruptions release 400,000-11,000,000 tonnes/year hydrogen chloride into the atmosphere.

All systems for production of chlorine as well as the loading and unloading systems are closed systems. Chlorine is supplied in gaseous form to the destination plants mainly by pipeline. To a minor extent, it is distributed in liquefied form in bottles or tank cars (road and railway). Exposure to chlorine can occur through accidental events in industry (e.g. during filling operations of chlorine gas, in the pulp and paper industry using chlorine, HCl or chlorine dioxide as bleaching agents), in transport and storage, in professional water purification and disinfection measures for swimming-pools.

For workers an indicative limit of 0.5 ppm for short term exposure (15 minutes) to chlorine is proposed in a draft of European Directive on occupational exposure limits.

Since chlorine/ hypochlorite can be irritating or corrosive depending on the concentrations, exposure control should be provided and protective equipment for eyes and skin, masks with filters or self contained breathing apparatus should be worn during specific situations (filling operations, sampling for laboratory purposes) and kept always ready to use.

For consumers exposure to chlorine can occur through accidental events during the use of chlorine for disinfection of swimming-pools and the use of hypochlorite-containing cleaning products, e.g. through mixing of household cleaning agents, such as hypochlorite and acids eventually associated with chlorine release and inhalation.

General population can be exposed by indirect exposure via drinking water and by inhalation of natural occurring sources in the atmosphere.

RECOMMENDATION

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

Environment: The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses corrosive properties and is an acute respiratory toxicant, indicating a hazard for human health. Based on data presented by the Sponsor country 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

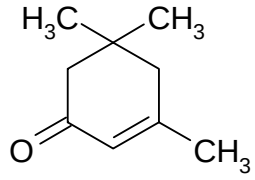
measures beyond those which are being applied.

Environment: The substance has hazardous properties for the environments. As there are some open uses of the substance (e.g. cooling water disinfection) an exposure assessment and if necessary risk assessment should be performed for these uses. The formation of chlorinated by-products should be taken into account.

Work to that effect is being or has been performed in many countries and also within the framework of the EU Existing Substances Regulation.

The substance is under risk assessment following the EU Existing Substances Regulation EC No.793/93.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-59-1
Chemical Name	3,5,5-trimethylcyclohex-2-enone (Isophorone)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Upon oral and inhalative administration, isophorone is well absorbed and rapidly distributed through the body of rats and rabbits. While part of the absorbed isophorone is excreted unchanged via urine and exhaled air, metabolites are mainly excreted as glucuronides. The tendency of isophorone to bioaccumulate is very low, since within 24 hours after administration more than 93% of orally administred isophorone was excreted by rats.

The acute toxicity in laboratory animals is low to moderate (oral LD50 $\geq$ 1500 mg/kg bw; dermal LD50 $\geq$ 1200 mg/kg bw; inhalative LC50 = 7000 mg/m^3). Isophorone is an eye irritant and a respiratory irritant but does not irritate the skin. It is not sensitizing in animal studies.

In subchronic studies, oral administration of high doses of isophorone (NOAEL (male rat, 90 days) = 102.5 mg/kg bw/day, NOAEL (female rat, 13 weeks) = 500 mg/kg bw/day; NOAEL (male mouse, 16 days) = 500 mg/kg bw/day, NOAEL (female mouse, 16 days) = 125 mg/kg bw/day; NOAEL (dog, 90 days) $\geq$ 150 mg/kg bw/day) caused no significant toxic effects (all NOAELs are based on slight (< 14%) reductions in body weight gain). After inhalational administration nose and eye irritation and blood and liver changes were observed (NOAEL (rat, 28 days) < 208 mg/m^3).

Although in one mouse lymphoma assay a positive result was observed, the majority of *in vitro* genotoxicity studies revealed clearly negative results. Together with the negative *in vivo* results and the negative DNA binding assay, the overall conclusion is that isophorone is not mutagenic.

There was some evidence of carcinogenicity of isophorone in male rats (kidney tumors, preputial gland carcinomas). The kidney tumors can be attributed to an α2u-globulin associated mechanism. The observed nephropathy in male rats is therefore irrelevant to other species. As the preputium is only investigated histopathologically when gross lesions are found, neither true tumor incidences from this study nor from historical controls are available. Therefore, the higher incidence of preputial gland tumors in high dose male rats cannot be put into perspective. There was equivocal evidence of carcinogenicity for male mice (liver tumors, mesenchymal tumors of the integumentary system). There was no evidence of carcinogenicity of isophorone in female rats and mice.

There is no evidence indicating that isophorone interferes adversely with the reproduction. No changes were observed in pregnancy rates, litter sizes, pups abnormalities or in histopathological examinations of the reproduction organs after long-term studies. In an inhalation teratogenicity study, the NOAEL for maternal toxicity was 289 mg/m³ (based on a reduction in body weight gain of less than 7%).

Isophorone was neither embryotoxic nor teratogenic up to the highest test concentration of 664 mg/m³ isophorone.

Environment

Isophorone has a melting point of –8.1 °C, a solubility in water of 14.5 g/l at 20 °C, and a vapour pressure of 40 Pa at 20 °C. The measured log Kow is 1.67.

According to a Mackay Level I model calculation the main target compartments for isophorone will be the hydrosphere (87.6 %) and atmosphere (11.7 %). The calculated Henrys' law constant of 0.38 $Pa.m^3/mol$ indicates evaporation from surface waters within several days. With a calculated Koc of 77 l/kg the sorption potential to soil or sediment organic matter is expected to be low.

In the atmosphere, isophorone is rapidly removed by reaction with ozone with an estimated half-life of 23 minutes. The calculated half-life for photodegradation by reaction with OH radicals is 16 h. Isophorone can be considered to be readily biodegradable. In surface waters, the main removal mechanisms are expected to be biodegradation and volatilization. Photolytical degradation in surface waters is expected to be of minor importance. Furthermore, hydrolytic degradation is not to be expected. Experimentally determined BCF values below 10 l/kg indicate a low bioaccumulation potential.

The lowest valid acute test results of aquatic testing determined for fish, daphnia, algae and bacteria were as following:

Cyprinodon variegatus:	96h-LC50 = 140 mg/l
Daphnia magna:	48h-EC50 = 120 mg/l
Scenedesmus subspicatus:	72h-EbC50 = 475 mg/l; 72h-EbC10 = 64 mg/l
Activated sludge:	3h-EC50 = 100 mg/l

In 3 fish early-life-stage tests with *Pimephales promelas* NOEC-values of 4.2 mg/l (32 d), 15.6 mg/l (32 d) and 11 mg/l (35 d) were obtained for the endpoint growth (measured as weight). The geometric mean of these 3 NOEC is 8.9 mg/l. Based on this value, a PNEC of 0.178 mg/l is calculated using an assessment factor of 50.

For the terrestrial compartment, a PNEC could not be calculated. Isophorone spiked into soils is expected to be rapidly removed by biodegradation, thus the test substance concentration will be unstable during the test period.

Exposure

The production volume of Isophorone is approx. 100,000 t/y world wide. Isophorone is widely used as a solvent for a number of synthetic resins and polymers, as well as in special application paints and printing inks. It is a chemical intermediate and an important solvent in certain herbicide formulations.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical is currently of low priority for further work based on its low hazard potential. The substance is an eye irritant. Although this does not warrant further work, this property should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-00-5
Chemical Name	1,1,2-Trichloroethane
Structural Formula	$Cl_2CH\text{-}CH_2Cl$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute toxicity (LD50) of 1,1,2-trichloroethane is 837 mg/kg by oral administration in rats, 9 g/m^3 /6 hr by inhalation in rats and 5.38 g/kg by dermal administration in rabbits. This chemical is considered to be irritating to skin, eyes, the upper respiratory tract and the stomach. There is no available information on skin sensitisation.

In a 90 days drinking water study of mice at the concentration of 0, 20, 200, or 2,000 mg/l, a reduction of P-450 contents in liver were observed and the NOEL was considered to be 3.9 mg/kg/day. Repeated inhalation exposure (7 hours/day, 5 days/week) to 83 mg/m^3 air for 6 months did not lead to any chemical-related changes in the rat, guinea pig and rabbit. The daily intake is equivalent to roughly 11 mg/kg/day in rats, 7.4 mg/kg/day in guinea pigs, and 25 mg/kg/day in rabbits. In humans, this chemical was reported to act as a narcotic at low concentrations, and to irritate the conjunctiva, the mucosa of the respiratory tract and the external skin. Moreover, gastrointestinal tract complaints, fatty degeneration of the kidneys and lung damage by prolonged exposure were reported.

A carcinogenicity study with this chemical by gavage showed hepatocellular carcinomas and pheochromocytomas in mice but the chemical was not carcinogenic in rats. Initiation/promotion screening studies on male rat liver demonstrated that this chemical has neither initiation nor promotion activity. A carcinogenicity study in skin of rats given 0, 2.05 or 6.24 mg by subcutaneous injection once a week for two years indicated no chemical related changes.

A bacterial mutagenicity study showed negative results in all strains of *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100 with and without metabolic activation. Unscheduled DNA synthesis was not observed in livers of treated mice. On the other hand, a mutation study in *Saccharomyces cerevisiae* and an *in vitro* micronucleus test with human lymphocytes was positive. However, the latest micronucleus test in mice *in vivo* showed negative results. Therefore the weight of evidence suggests that this chemical is not genotoxic *in vivo*.

In a developmental toxicity study, the chemical was administered by gavage to mice on days 8 through 12 of gestation at dose of only 350 mg/kg/day. Any changes including teratogenicity and embryo/fetal viability, and/or postnatal growth and viability were not observed. Therefore, the NOEL for developmental toxicity was considered to be 350 mg/kg/day.

Environment

1,1,2-Trichloroethane is a stable liquid and is not readily biodegradable (OECD TG 301C). Its measured bioconcentration factor is 0.7 – 4.0 (OECD TG 305C).

As the lowest acute toxicity test results for algae, zooplankton and fish, a 96 h-EC50 for *Phaeodactylum tricornutum* (60 mg/l), a 48 h EC50 for *Daphnia magna* (18 mg/l) and a 7 d LC50 for *Poecilia reticulata* (40 mg/l) were selected. As the lowest chronic toxicity test results for algae, zooplankton and fish, a 72 h NOEC (growth) for *Selenastrum capricornutum* (51.4 mg/l), a 21d NOEC (reproduction) for *Daphnia magna* (32 mg/l) and a 56d NOEC (mortality during early life stage) for *Pleuronectes platessa* (3.0 mg/l) were selected. An assessment factor of 10 was used on

the chronic toxicity data to determine a PNEC, which is 0.3 mg/l in the present report.

Exposure

The production volume of this chemical was ca. 153,000 tonnes/year in 1996 in Japan. This chemical is used as an intermediate for the production of vinylidene chloride and is not included in consumer products in the Sponsor country. The potential environmental distribution of 1,1,2-trichloroethane obtained from a generic fugacity model (Mackey level III) showed that this chemical would be distributed mainly to air and water. The main route of human exposure is inhalation with a limited number of workers potentially exposed during sampling, subsequent analysis, tank filling and maintenance operations.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

As the original recommendation was "An i*n vivo* genotoxicity study such as an *in vivo* micronucleus test is recommended because an *in vitro* chromosomal aberration test indicates clear positive results", an *in vivo* micronucleus test was conducted as post-SIDS work. Based on the negative result, this chemical is currently of low priority for further work.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-38-9
Chemical Name	Chlorotrifluoroethylene (CTFE)
Structural Formula	ClFC=CF2

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

Two tetrahalotehylenes, tetrafluoroethylene (TFE; CAS No. 116-14-3) and tetrachloroethylene (TCE; CAS No. 127-18-4), are used as analogues for CTFE. TCE data are used for aquatic toxicity endpoints and TFE is used to supplement the genetic toxicity endpoint.

All three chemicals have similar structures, physicochemical properties and fate characteristics. They have high vapor pressures indicating that they will reside in the atmosphere. The distribution is further supported by fugacity modeling. These chemicals also are not subject to hydrolysis or photolysis. However, the major metabolic pathways of TCE and CTFE differ and therefore, human-health related endpoints are addressed only with TFE data. TFE data are considered appropriate because the kidney is a common target organ of both CTFE and TFE.

Human Health

CTFE is metabolized via glutathione and cysteine conjugation pathways, as demonstrated *in vitro* in rat liver hemogenate. Isolated rabbit renal tubule suspensions also show biotransformation of CTFE to the glutathione conjugate.

Most recent (1981) acute inhalation toxicity data indicate a rat LC50 of greater than 540 ppm. Degeneration of the renal tubules was seen at 220 and 345 ppm (1,048 and 1,644 mg/m^3) and diuresis at 100 ppm (476 mg/m^3) following 4 hour exposures. Clinical signs include proximal tubular necrosis, increase in serum BUN/creatinine, urinary fluoride, and urinary LDH activity. These effects were reversible. Older data show a 3-hr LC50 of 8000 ppm (38,109 mg/m^3) in mice, a 4-hr LC50 of 1000 ppm (4,764 mg/m^3) in rats, and a 2-hr LC50 of 5040 ppm (24,009 mg/m^3) in rats and rabbits. An oral LD50 of 268 mg/kg bw has been demonstrated in mice using a CTFE solution in olive oil. No data are available for skin and eye irritation or dermal sensitization.

In repeated-dose inhalation studies in the rat with CTFE exposure durations of 6 hours/day, 5days/week for periods from 2 to 13 weeks, the no-observable-adverse-effect-level was 29 ppm (138 mg/m^3). The higher exposure levels of 62 and 121 ppm (295 and 576 mg/m^3) induced dilated tubules in the kidneys. The effects seen at 62 ppm were reversible 2 weeks after exposure. In a study conducted in the mid 1950's, dogs, rats, guinea pigs, and rabbits were exposed to up to 18 4-hour exposures of CTFE at 300 ppm (1,429 mg/m^3). The following effects were observed: mortality (guinea pigs and rabbits), degenerative changes in renal tubules (rats) loss of body weight (guinea pigs) and encephalopathy, intermittent leucopenia and granulocytopenia (dogs). In a subsequent study which lasted 14 months, rats, rabbits, guinea pigs, and dogs were exposed for 6 hours/day, 5days/week to progressively higher levels of CTFE (15, 30, 50, 100, and 150 ppm; 72, 143, 238, 476, and 715 mg/m^3). Neither the guinea pigs nor the rabbits were adversely affected. The rats developed degenerative changes in the renal tubules. In the dog, exposure at 100 ppm (476 mg/m^3) (and possibly 50 ppm – 238 mg/m3), resulted in significant

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.

hematological changes. Neurological disturbances and degenerative changes in the nervous system were observed at 150 ppm (715 mg/m^3).

Overall CTFE did not present toxicologically significant genotoxic activity *in vitro* and *in vivo*. It was not active in an Ames test with exposure levels up to 50% in the air above the cultures. It also was not active in two *in vivo* sister chromatid exchange studies, one with rabbits and the other with rats. Both used an exposure level of 204 ppm (972 mg/m^3). TFE data were also used as supplemental information. TFE showed no toxicity in a gene mutation study at the HPRT locus in Chinese hamster ovary (CHO) cells without activation but was inconclusive in a study with activation; negative results were obtained after conducting a subsequent study with metabolic activation. In a study of structural chromosomal aberrations using TFE in CHO cells, no increase in frequency of aberrations was observed at any dose up to 100% nominal concentration in air either with or without metabolic activation. In an *in vivo* micronucleus assay conducted using peripheral blood erythrocytes from mice exposed to 0, 1250, 2500 or 5000 ppm via inhalation for 90 days; no increases in micronuclei were observed.

Reproductive organs were evaluated in the 13-week inhalation study of CTFE. No adverse effects were observed after full histopathological examination of the tissues from the testes, epididymides, ovaries, and uterus at exposures up to 121 ppm (576 mg/m^3) for 6 hours/day for 5 days/week. Other subchronic studies also did not result in adverse effects on reproductive organs.

In a limited developmental study, pregnant rats were exposed to 33, 61, 119, or 241 ppm (157, 291, 567, or 1,148 mg/m^3) of CTFE. At 119 ppm (567 mg/m^3) and above, slight reductions in maternal body weight gain were seen. No effects were seen at or below 61 ppm (291 mg/m^3). There was no evidence of developmental toxicity at any exposure level. In a subsequent developmental toxicity study, groups of 25 time-mated female rats were exposed to levels of 0 (control), 31, 89 or 187 ppm (148, 424, 891 mg/m^3). The NOAEL for the dams was 31 ppm. At 89 ppm the dams showed body weight gain depressions. At 187 ppm the exposures were terminated after 7 exposures due to dam body weight loss. The NOAEL for the pups was 89 ppm. At 187 ppm, reduced pup weight and reduced ossification were observed. There were no other test material increases in variations or abnormalities in the offspring.

Environment

CTFE is a gas with a melting point of -157.5 °C, a boiling point of - 27.9 °C, a water solubility of 804 mg/L, and vapor pressure of 537 kPa. It exhibits slow indirect photolysis that is primarily attributed to hydroxyl radicals (with a half-life of approximately 50 days), and very slow direct photolysis. The compound does not have hydrolysable groups, and therefore, will not undergo hydrolysis in water. The low octanol/water partition coefficient (log K_{ow} = 1.65) indicates a low potential for bioaccumulation. Most estimates available from EPIWIN indicate that CTFE generally does not rapidly (or readily) biodegrade. Studies using the analog TCE generally showed no biodegradation under aerobic conditions but suggest biodegradation under anaerobic conditions.

Estimates for the toxicity of CTFE have been calculated with the ECOSAR program in the EPIWIN model. For fish, the 96-hr LC_{50} was estimated to be 4.123 mg/L; for daphnids, the 48-hr EC_{50} was estimated to be 242 mg/L; and for green algae, the 96-hr EC_{50} was estimated to be 44 mg/L. To supplement these results, data using the analog TCE show that in fish, the lowest 96-hr LC_{50} is 4.8 mg/L (measured in rainbow trout). The lowest 48-hr EC_{50} in the invertebrate *Daphnia magna* is 8.5 mg/L. In algae, the 72-hr EC50 is 3.64 mg/L.

Exposure

CTFE has been produced for over 25 years and the estimated worldwide production in 2000 was estimated to be 1,000 to 5,000 tonnes. There is one production site in the U.S. and there are two sites that use CTFE in the U.S. CTFE is one of a series of halogenated ethylenes used as a monomer for the production of chlorofluorocarbon polymers. It is also used as a starting material in the manufacture of fire suppressants and pharmaceuticals such as Halothane. Since it is a gas (BP –27.9°C) at room temperature, it is used in

sealed systems. Exposure levels have been determined from workplace monitoring studies. Eighty-two percent of air samples from employee breathing zones during maintenance operations were below the threshold limit value of 5 ppm (25 mg/m^3) in one U.S. plant; all personal air samples were below 5 ppm in another U.S. plant. Less than 0.5% of samples were above 5 ppm when sampling areas from all parts of the plant in 2003. No adverse effects have been reported.

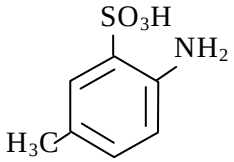
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a possible hazard for the environment (aquatic toxicity between 1 and 100 mg/L based on data for CTFE and for the supporting substance TCE) and human health (acute, repeated-dose and developmental toxicity). Data presented by the Sponsor country indicate that CTFE is an industrial intermediate, that workplace exposures are controlled, that CTFE has no consumer uses, and that the chemical will partition to the atmosphere. These data indicate that exposure to humans and the aquatic 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 in the Sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-44-8
Chemical Name	4-Aminotoluene-3-sulfonic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

From the outcome of a single dose administration reported in a preliminary examination of a 28-Day Repeat Dose Toxicity study [OECD TG407], the oral LD50 in rats is considered to be greater than 2000 mg/kg in both sexes. This substance was not corrosive or irritant to human skin.

In the 28-Day Repeated Dose Toxicity study [OECD TG407], this substance was administrated to male and female rats at 0, 100, 300, 1000 mg/kg/day dose by gavage. At 1000 mg/kg/day in males, a decrease of white blood cell count, total cholesterol and urine pH, also an enlargement of cecum were observed. At 1000 mg/kg in females, an increase of GPT and a decrease of glucose, also an enlargement of cecum were observed. All of those changes recovered within 14 days after cessation of the treatment. No other dose-dependent histopathological changes were observed in any dose groups. No changes in mortality, behavior or toxic effects on the body weight and food consumption were observed in any dose levels and in any sexes. The NOAEL for both sexes is considered to be 300 mg/kg/day.

This substance was not mutagenic in bacteria up to 5,000 ug/plate [OECD TG471, TG472] and 10,000 ug/plate. A chromosomal aberration test tested up to 1.9 mg/mL (10mM) [OECD TG473] was negative except in the 6hr short-term test in the presence of an exogenous metabolic activation system. The positive response in the 6 hr short term test was based on the low pH, because the induction of chromosomal aberration was diminished after adjustment of the pH to a neutral range. The result of an unscheduled DNA synthesis up to 187 mg/L was negative. Furthermore, an *in vivo* micronucleus test was negative. Overall, this substance can be considered to be not genotoxic *in vitro* and *in vivo*.

In a Preliminary Reproduction Toxicity Screening Test [OECD TG421], this substance was administrated to male and female rats at 0, 100, 300, 1000 mg/kg/day dose by gavage for 48 days in males and 41 – 46 days (from 14 days before mating to 3 days after parturition) in females. No compound-related dose effects were observed in the copulation index, fertility index, gestation length, number of corpora lutea or implantations, implantation index, gestation index and maternal behavior. As for pups, there were no significant differences in number of offspring or live offspring, sex ratio, the live birth index, the viability index or the body weight. No pups with malformations were found in any groups. No changes in clinical signs and necropsy findings were observed in offspring. From those results, the NOAEL for reproductive and developmental toxicity is considered to be 1000 mg/kg/day.

Environment

This substance is soluble in water (6.0 g/L at 20°C) and the vapor pressure is low (< 0.00052 Pa at 100°C) [OECD TG104]. This substance was not readily biodegradable (0% after 14 days on BOD) [OECD TG301C] and is stable to

hydrolysis in water at pH 4, 7 and 9 [OECD TG111]. The bioconcentration potential is low (BCF < 4 (0.2 mg/L) and < 0.4 (2 mg/L)) [OECD TG305C]. The log Pow is –0.67 at 25°C [OECD TG107]. This substance, if released into the atmosphere, will react with photochemically produced hydroxyl radical and decrease with a half-life of 4.5 hours. The pKa value of this substance is 3.28. It is present as a zwitterion under environmental condition. The behavior of this substance in the environment is considered to be similar to a weak acid.

The fugacity model (Mackay level III) suggests that if released to water, the majority of the substance would remain in the water compartment and, if released into air or soil, ca.50% would distribute to both water and the soil compartment.

In an acute toxicity test to fish, the LC50 was greater than 10 mg/L (*Oryzias latipes*, 96hr limit test) [OECD TG203].
In an acute toxicity test to daphnia, the EC50 was greater than 10 mg/L (*Daphnia magna*, 48hr limit test) [OECD TG202].
In an acute toxicity test to algae, the EC50 was greater than 10 mg/L (*Selenastrum capricornutum*: 0 – 72 hr biomass, and 24 – 72 hr growth rate) [OECD TG201].
In a chronic toxicity test to daphnia, the NOEC was 3.2 mg/L (*Daphnia magna*, 21 days reproduction) [OECD TG211] and in a chronic toxicity test to algae, the NOEC was 10 mg/L (*Selenastrum capricornutum*: 0 – 72 hr biomass, and 24 – 72 hr growth rate) [OECD TG201].

Exposure

The production volume of this substance in 2001 is estimated to be 2,000 - 3,000 metric tonnes/year in Japan and ca.18,000 metric tonnes/year in the world. The production countries are Japan, Korea, P.R. China, United Kingdom and U.S.A. In total there are about 20 manufacturing sites and about 55 use sites in the world.

This substance is produced in closed systems, and the packing process is performed in semi-closed or open systems. The user may use it in semi-closed systems. The only recognized use is as an industrial intermediate in the synthesis of organic pigments (Pigment Red 57 and its metal salts). These pigments are utilized in ink, paint, stationery goods, cosmetic goods and for the coloring of resin, fiber, leather, paper, rubber, etc. The concentration of the non-reacted parent substance in pigments is not known, but the consumer exposure is thought to be insignificant. There are no known direct uses of this substance in any consumer product. In the case of cosmetic goods (lip stick, etc.), regulations are in place in each region, for example the content of the substance in the colouring agent must be less than 0.2 % in the USA. Therefore, the possibility of consumer exposure from cosmetic goods is considered to be low.

Because of its use limited to the pigment industry and its low vapor pressure, the release of this substance into air and soil is very low. The concentration of this substance in effluent water from waste water treatment plant of manufacturer in Japan is less than 0.009 mg/L. The total emission from manufacturer's site through water in Japan is calculated to be less than 5 kg/year.

Based on the use and the properties of the substance, only occupational exposure by inhalation and dermal routes need to be considered.

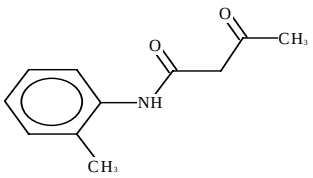
RECOMMENDATION

The chemical is currently of low priority for further work.

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 potential.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	93-68-5
Chemical Name	o-Acetoacetotoluidide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The oral LD50 of o-Acetoacetotoluidide (AAOT) in rats was 1854 mg/kg in males and 1945 mg/kg in females [OECD TG401]. Toxicological effects such as decreased locomotor activity, adoption of a prone position, hypotonia, ptosis, deep respiration, piloerection, hypothermia, lacrimation and pale skin were observed at 819 mg/kg and higher in both sexes in a dose dependent manner.

In addition, the following data was available, although they were insufficient for adequate assessment. AAOT caused slight irritation to the rabbit eyes, and caused slight to moderate irritation to the guinea pig skin. There was a potential for it to induce contact sensitization to guinea pig. Erythema was found in one of ten guinea pigs.

In a Combined Repeat Dose and Reproduction/Developmental Toxicity Screening Test in rats [OECD TG422], AAOT was administered by gavage at the dose levels of 0, 8, 25, 80 and 250 mg/kg/day.
The blood findings in males in the 250 mg/kg/day group were: decreases of erythrocyte count, hemoglobin concentration and hematocrit value, also increases of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), reticulocyte count, methemoglobin concentration, bilirubin and potassium. Other findings in the 250 mg/kg/day group were: increase of pituitary weight in males; increases of weight of spleen, weight of liver, extramedullary hematopoiesis and congestion in spleen, also blackening of spleen and hemosiderin deposit in liver and spleen in both sexes.
The blood findings in males in the 80 mg/kg/day group were: decrease of erythrocyte count and increase of MCV and bilirubin. Other findings in the 80 mg/kg/day group were: increase of congestion in spleen in females, blackening of spleen and hemosiderin deposit in liver and spleen in both sexes.
In all dose groups up to 250 mg/kg/day, no changes in mortality, behavior or toxic effects on the body weight and food consumption were observed in any sexes. No toxic effects were observed in any dose groups up to 25 mg/kg/day.
Based on these results, the NOAEL for repeat dose toxicity is considered to be 25 mg/kg/day in both sexes.

AAOT was not mutagenic in bacteria up to 5,000 ug/plate [OECD TG471, 472]. Although AAOT showed marginal response in induction of chromosomal aberrations in CHL/IU cells at 2.5 or 5.0 mg/mL, the response was observed only at concentration levels higher than 10 mM (1.91 mg/mL) [OECD TG473]. Therefore, the response was regarded as a biologically irrelevant phenomenon under unphysiological (high osmolality) culture condition. Both the unscheduled DNA synthesis test in rat CD-1 cells and HGPRT assay in CHO cells were negative. Considering all of the *in vitro* studies available, AAOT is not genotoxic.

For reproduction/developmental toxicity, AAOT was administered in the above described screening test [OECD TG422] for 44 days in males and 41 – 45 days (from 14 days before mating to 3 days after parturition) in females. No toxic effects were observed in the following test parameters in parental animals; copulation index, fertility index, gestation index, number of corpora lutea or implantations, implantation index, gestation index and maternal behavior, at up to 250 mg/kg/day.
As for pups; no compound-related effects on the number of pups, delivery index, sex ratio, body weight and viability index were observed in any dose groups. No pups with malformations were found in any groups. No changes in histopathological findings were observed in offspring.
Based on these results, the NOAEL for reproduction/developmental toxicity is considered to be 250 mg/kg/day.

Environment

AAOT is soluble in water (3.0 g/L at 25°C) and the vapour pressure is low (0.00066 Pa at 20°C by calculation) [MPBPWIN v1.40]. AAOT is inherently biodegradable with pre-adapted inoculum (78.5% on DOC after 7 days incubation) [OECD TG302B]. AAOT is stable to hydrolysis in water at pH 4, 7 and 9 [OECD TG111]. The bioaccumulation potential is estimated to be low (BCF = 3.2: calculated from log Pow = 0.85 [OECD TG107]). If AAOT is released into the atmosphere, it will react with photo-chemically produced hydroxyl radicals and will be decreased with a half-life of 8.0 hours. The Fugacity Model [Mackey level III] suggests that if released to water, the majority of the substance would remain in the water compartment, if released into air, 41 % would distribute to water and 58 % distribute to soil compartment, and if released to soil, 36 % would distribute to water and 64 % remain in soil compartment.

In acute toxicity tests with algae, daphnids and fish [OECD TG201, 202, 203 and other methods], the EC50 for algae (*Selenastrum capricornutum*) was 383 mg/L (0 - 72hr biomass) and 654 mg/L (24 - 72hr growth rate), the EC50 for daphnids was 931 mg/L (*Daphnia magna*, 48hr) and the LC50s for fish were > 100 mg/L (*Oryzias latipes*, 96hr limit test), 316.2 mg/L (*Pimephales promelas*, 96hr) and > 500 mg/L (*Brachydanio rerio*, 96hr).

In chronic toxicity tests with daphnids and algae [OECD TG211, 201], the NOEC for daphnids was 10 mg/L (*Daphnia magna*, 21 days reproduction), and the NOEC for algae (*Selenastrum capricornutum*) was 95.3 mg/L (0 - 72hr biomass) and 171 mg/L (24 - 72hr growth rate).

Exposure

The production volume of AAOT in 2001 is estimated to be 1,000 - 1,500 tons/year in Japan and ca. 4,000 tonnes/year in the world. The production countries are Germany, India, Japan, P.R. China, Switzerland, U.S.A and maybe in Eastern Europe. In total there are about 15 manufacturing sites and about 55 use sites in the world.

AAOT is produced in closed systems, and the packing process is performed in semi-closed or open systems. The user may use it in semi-closed systems. The only recognized use is an industrial intermediate in the synthesis of organic pigments. These pigments are utilized in ink, paint and coloring of various materials. There are no known direct uses of AAOT in any consumer product.

The concentration of non-reacted AAOT in the pigments is unknown. However, migration of the pigments is expected to be very limited and there are no adverse health reports from such exposure. Therefore, significant consumer exposure is not expected.

Because of its use limited to the pigment industry, the releases to the environment are estimated to be low.

A survey of users and producers show that the chemical is usually used in well controlled processes and therefore worker exposure is likely to be low.

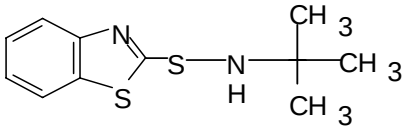
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a potential hazard for human health. 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-31-8
Chemical Name	N-tert-butylbenzothiazole-2-sulphenamide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information on toxicokinetics. Based on the available data, it can be concluded that the chemical or its hydrolysis products can be absorbed by oral dermal or inhalation routes. Toxicity may be via the hydrolysis products. Hepatic metabolism of the parent material or the hydrolysis products is likely. Excretion is most likely via the kidney.

The oral LD50 (rat) was greater than 2000 mg/kg [OECD TG 423]. The dermal LD50 (rabbit) was greater than 7940 mg/kg. The substance shows signs of mild irritation in the skin and eyes of rabbits but is not considered to be a skin or eye irritant. A hydrolysis product, mercaptobenzothiazole, is a strong skin sensitiser. This is further supported by animal testing (Buehler assay) and human patch tests with the parent chemical reported in the secondary literature.

In a combined oral repeat dose reproductive/developmental toxicity screening test [OECD TG 422] rats were dosed by gavage at 40, 200 and 1000 mg/kg bw/day. Toxicologically significant effects were identified in liver (hepatocyte hypertrophy), kidneys (vacuolar degeneration) and erythrocytes (haemolytic anaemia).The LOAEL was 40 mg/kg/day for males, based on anaemia (female data unavailable). In a 90 day oral toxicity study, which cannot be validated, females showed increased liver and kidney weight at 1000 mg/kg/day together with increased cholesterol and urine specific gravity. Bodyweight was reduced in males at 300 mg/kg/day and 1000 mg/kg/day. The NOAEL was 100 mg/kg/day. A 28 day repeated exposure inhalation study (5 days per week exposure) has been conducted but cannot be validated. The highest exposure level, 0.084 mg/L, produced a decrease in bodyweight and effects to liver and lymph nodes. The NOAEL was 0.029 mg/L.

Based on these studies the LOAEL for repeated dose toxicity (oral) is considered to be 40 mg/kg/day for males, based on anaemia (female data unavailable). The NOAEL for repeated dose toxicity (inhalation) is 0.029 mg/L (non-validated data).

The chemical was not mutagenic in bacteria [OECD TG 471 and 472] and in several *in vitro* mammalian gene mutation assays. Positive responses, however, were seen in several mouse lymphoma assays in the presence of exogenous metabolic activation. It also induced chromosomal aberrations in mammalian cells *in vitro* in the presence of an exogenous metabolic activation system [OECD TG 473]. Because the chemical was non-mutagenic in bacteria and mammalian cells and clastogenic in mammalian cells, the positive response in the mouse lymphoma assays seemed to be derived from chromosomal aberrations. The chemical was negative in the mouse micronucleus assay [OECD TG 474] tested up to 2000 mg/kg. Accordingly this chemical was clastogenic *in vitro* but not *in vivo*.

For the above mentioned reproduction/developmental toxicity screening test [OECD TG 422], the chemical was given for 42 days in males and from 14 days before pregnancy to day 3 of lactation in females. No adverse effects were observed in terms of fertility, delivery and nursing in parent animals. The viability and body weight of offspring were unaffected and no malformations were detected. Both male and female reproductive tissues were well examined and

no abnormalities were observed. Changes in fertility index were observed at 40 and 1000 mg/kg bw/day, but not at 200 mg/kg bw/day.

In a developmental toxicity study reported in the secondary literature, female rats were dosed with the chemical at up to 500 mg/kg bw/day between days 6-15 of gestation. No effects were seen, either in females or offspring, at any dose level and under the conditions of the test the chemical was considered to have no effect on reproduction. No further details of the study could be obtained. The NOAEL for developmental toxicity was 500 mg/kg bw/day.

Environment

The chemical has a log Pow of 3.9 at room temperature, a vapour pressure of less than 0.0000021 hPa at 25°C and a water solubility of 0.345 mg/L at 20°C. Fugacity model Mackay level III calculations suggest that the majority of the chemical would distribute to soil if released to the air or soil compartments and to water if released to the water compartment. The chemical is not ionised at environmental pHs ($pKa_{(1)}$ 1.75, $pKa_{(2)}$ –3.43, conjugate acid). The chemical is not readily biodegradable (0%) but it does hydrolyse in less than 1 day at pH 9 or less (t1/2 = 1.7h at pH 4, 1.8h at pH 7 and 21.5h at pH 9). The identified hydrolysis products are mercaptobenzothiazole, di(benzothiazoyl-2)disulfide, t-butylamine, and benzothiazole. These hydrolysis products have been tested and shown to have a low potential for bioaccumulation. Based on these findings, the chemical is judged to have low potential for bioaccumulation also. Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 2.8 hours. The substance does not inhibit the action of wastewater treatment microorganisms EC50 (3h) > 10000 mg/L. The hydrolysis products, such as mercaptobenzothiazole, di(benzothiazoyl-2)disulfide and benzothiazole, are non-volatile and not readily biodegradable in the environment.

In an acute fish toxicity study (OECD TG 203, *Oryzias latipes*, 96h) a LC50 = 0.345 mg/L (limit of water solubility) was reported. In Daphnia magna, an acute toxicity value of 48h EC50 = 0.345 mg/L (limit of water solubility) was reported. The results in algae (OECD TG 201) were an E_rC50 = 0.071 mg/L, a $NOEC_b$ (0 to 72 h, biomass) = 0.011 mg/L and a $NOEC_r$ (24 to 72 h, growth rate) = 0.023 mg/L (measured concentrations). In a prolonged fish toxicity study (OECD TG 204, *Oryzias latipes*) a 14d LC50 = 0.345 mg/L (limit of water solubility) and a 14d NOEC = 0.15 mg/L were presented. The chronic toxicity to *Daphnia magna* (OECD TG 211) was a NOEC (14d, reproduction) = 0.042 mg/L (measured) and NOEC (21d, parental) = 0.068 mg/L (measured).

Some of the degradation products of N-tert-butylbenzothiazole-2-sulfenamide, and especially mercapto-benzothiazole, show similar levels of aquatic toxicity compared to the parent compound.

Exposure

The production volume of the chemical in 2000 is 16,000 – 20,000 t/y worldwide, with production in Japan being 4,000 – 4,500 t/y. The chemical is an accelerator for the vulcanization of rubber. Due to the chemical transformation processes involved in vulcanization, the finished rubber products only contain small amounts of the chemical in addition to substances produced from the synthesis, such as benzothiazole, 2-mercaptbenzothiazole and 2-mercaptobenzothiazole disulfide. The substance and its degradation products may be released to the environment during the use of rubber products, such as tyres.

Occupational hygiene measurements suggest that occupational exposure is 0.64 mg/m^3. Personal Protective equipment (dust masks, goggles, protective clothing, gloves) is worn during operations. Consumer exposure is minimal.

RECOMMENDATION

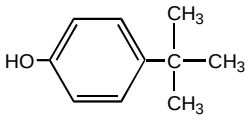
The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for the environment. Also some of the degradation products show similar hazards to the environment. The substance and its degradation products are present in many rubber products and a release to the environment is possible. An exposure assessment, and if necessary a risk assessment for the environment of the chemical and its degradation products should be performed. The currently on-going assessment of di(benzothiazoyl-2)disulfide (CAS No 120-78-5) and of N-cyclohexylbenzothiazole-2-sulfenamide (CAS No 95-33-0) should be taken into account.

The chemical also possesses properties indicating a hazard for human health (sensitisation and anaemia). An exposure assessment and, if necessary, a risk assessment for human health should be performed.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-54-4
Chemical Name	p-tert-Butylphenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acute toxicity of p-t-butylphenol is low via any route of administration. This chemical is considered to be an irritant to skin, eyes and the respiratory tract. The possibility of skin sensitization in human still remains because of negative results in an animal experiment (OECD TG 406) but some positive results in human patch tests. Depigmentation was observed on the skin of various animals and humans exposed to this chemical. This change was likely induced by exposure to this chemical not only via direct contact but also via inhalation or ingestion.

In a combined repeat dose and reproductive/developmental screening toxicity test (OECD TG 422) with rats exposed by gavage at doses of 20, 60 and 200 mg/kg/day for 46 days, this chemical showed neither systemic toxicity nor reproductive toxicity even at the highest dose of 200 mg/kg/day. Although a noisy respiratory sound was induced in a few females at 200 mg/kg/day, it is considered to be due to irritation of this chemical to the respiratory tract. In a dose-finding study (14 days), this change led to respiratory difficulty, especially at 1,000 mg/kg/day. In other studies with longer and higher exposure through the diet (approx. 1 g/kg b.w./day, for 20 or 51 weeks), forestomach hyperplasia was induced.

This chemical showed clear negative results in gene mutation tests. However, one chromosomal aberration study indicated structural chromosome aberration and polyploidy with metabolic activation in CHL/IU cells (OECD TG 473) although other studies in rat lymphocytes (OECD TG 473) and in rat liver epithelial-type cells were negative. A micronucleus test *in vivo* (OECD TG 474) showed negative results. The weight of evidence suggests that this chemical is not genotoxic *in vivo*.

There was no sufficient carcinogenicity study and no evidence of carcinogenesis in manufacturing workers, however, a two-stage carcinogenicity study indicated that this chemical has a promoting activity regarding forestomach carcinogenesis (papilloma and squamous carcinoma) in rats treated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Furthermore, since a structurally related chemical, BHA, (2(3)-tert-butyl-methoxylphenol) is a clear carcinogen, it is considered that this chemical might be a non-genotoxic carcinogen.

Environment

p-t-Butylphenol is a stable solid and is readily biodegradable (OECD TG 301). Its measured bioaccumulation factor is 34-120.

The lowest acute and chronic toxicity data were a 48h EC50 (3.4 mg/l) and a 21d NOEC (0.73 mg/l) for *Daphnia magna*. An assessment factor of 100 was chosen to be applied to the chronic toxicity data (NOEC), because only two NOEC values (algae and *Daphnia*) are available. Thus, the PNEC of p-t-butylphenol is 7.3×10^{-3} mg/l in this report. p-t-Butylphenol may have potential chronic toxicity to aquatic organisms, because the NOEC for *Daphnia* is

relatively low and the chemical has a moderate bioaccumulative potential.

Exposure

The production volume of this chemical was ca. 5,000 tonnes/year in 1993 in Japan. This chemical is used as an intermediate for phenol resins and polycarbonate resins. It is also used as a raw material for construction elements and floors in buildings. The potential environmental distribution of p-t-butylphenol obtained from a generic fugacity model (Mackey level III) shows that it will be mainly distributed to water. The main route of human exposure is inhalation with a limited number of workers potentially exposed during sampling and bag or tank filling operations.

RECOMMENDATION

The chemical is currently of low priority for further work.

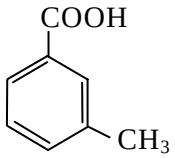
RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

As the original recommendation was "An i*n vivo* genotoxicity study such as *in vivo* micronucleus test is recommended because *in vitro* chromosomal aberration test indicates clear positive results", an *in vivo* micronucleus test was conducted as post-SIDS work. Based on the negative result, no further work is recommended in the SIDS context.

NOTE

The present SIDS Profile is already an update of the SIDS Profile published by UNEP Chemicals (2002, Volume 8, part I). An *in vivo* micronucleus test was conducted by Japan, and the results are integrated in the conclusions above. Further post-SIDS work is currently on-going in the context of the EU Existing Substances Regulation (Sponsor country: Norway), to further investigate the potential of the substance for endocrine disruption and reproductive toxicity. Once the additional post-SIDS work planned by Norway is available, addenda to the SIDS Dossier and the SIDS Initial Assessment Report will be elaborated and published together with a revised SIDS Profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	99-04-7
Chemical Name	*m*-Toluic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

m-Toluic acid is metabolized to methylhippuric acid and rapidly excreted in the urine.

The acute oral toxicity of the substance is relatively low. The oral LD_{50} in rats is greater than 2,000 mg/kg bw. At 2,000 mg/kg no animals died, no clinical signs, no effect on body weight gain, and no macroscopical changes were observed.

This substance is considered to be not irritating to skin. The sensitizing effect of *m*-toluic acid is not clear due to the lack of reliable data, but this substance might potentially be a sensitizer.

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] was conducted in rats at the doses of 0 (vehicle), 30, 100, 300 and 1,000 mg/kg/day administered by gavage. For males, the adverse effects, such as a decrease in locomotor activity, extension of prothrombin time, decrease in platelet, increase in GOT and increase in relative weight of the pituitary were observed at 1,000 mg/kg/day. For females, an increase in relative and absolute liver weight associated with periportal hepatocellular vacuolar degeneration (7/10) were observed at 1,000 mg/kg/day. Histological changes were observed (3/10) in the 300 mg/kg/day group. The NOAEL for the repeat dose toxicity is considered to be 300 mg/kg/day for males, and 100 mg/kg/day for females based on the adverse effects in the liver.

Two independent bacterial gene mutation tests [OECD TG 471 and 472] gave negative result with and without metabolic activation. In a chromosomal aberration test with Chinese hamster cultured cells (CHL/IU) [OECD TG 473], a little higher incidence of cells with chromosomal aberrations was observed, and this test gave equivocal results. Moreover, an *in vivo* micronucleus assay using rats [OECD TG 474], tested up to 2000 mg/kg, gave negative results. Considering these points, the chromosomal aberrations observed *in vitro* seems not to occur in the animal body.

In the above-described combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], there were no signs of reproduction/developmental toxicity on the gestation index, numbers, sex ratio, or viability of pups up to 1,000 mg/kg/day. The NOAEL of the reproduction/developmental toxicity is considered to be 1,000 mg/kg/day.

Environment

m-Toluic acid is white to yellowish crystal, which is soluble in water (1 g/L at 25 °C). Melting point, boiling point, and vapour pressure are 111.7 °C, 263 °C, and 0.00019 hPa (25 °C), respectively. *m*-Toluic acid is readily

biodegradable [OECD TG 301C: BOD = 91 % after 28 days] and its bioaccumulation potential seems to be low based on its log Kow (2.37 at 25 °C). Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 63 hours. Hydrolysis is not expected to occur. Fugacity modeling (Mackay level III) predicts that if *m*-toluic acid is released to water and soil, it is unlikely to distribute into other compartments. When *m*-toluic acid is released to air, 2.1% stays in air and 15.6 % is transported to water and 82.2 % is transported to soil. This substance is weakly acidic (pKa = 4.27) and can be regarded as a non-dissociated molecule for the calculations with the fugacity model.

m-Toluic acid has been tested for the toxicity with species of three trophic levels. Acute toxicity tests were conducted with algae, daphnids and fish. The 72 h EC50 in algae (*Selenastrum capricornutum*) was 10 mg/L (biomass) or 15 mg/L (growth rate) [OECD TG 201]. The 48 h EC50 in daphnids (*Daphnia magna*) was 75 mg/L [OECD TG 202 part 1]. The 96 h LC50 in fish (*Oryzias latipes*) was 82 mg/L [OECD TG 203]. Two chronic toxicity results in algae (*Selenastrum capricornutum*) and daphnids (*Daphnia magna*) were available. For algae, a 72 h NOEC on growth inhibition of 2.2 mg/L (biomass) or 10 mg/L (growth rate), and for daphnids a 21 d NOEC for reproduction of 9.7 mg/L were reported. Algae are the most sensitive aquatic organisms among three trophic levels according to acute values.

Exposure

The production volume of *m*-toluic acid was estimated at approximately 250 t/year in Japan and 2,600 t/year world-wide in 2000. *m*-Toluic acid is produced in a closed system. Normal practice of production/conversion in Japan include sewage treatment to prevent environmental exposure to this substance. This chemical is used almost entirely as a chemical intermediate in the chemical industry to make an insect repellent used by humans. A very small portion of the product (c.a. 1%) is converted to a plastic stabilizer. During production and use of this substance, occupational exposure is possible by inhalation and dermal route.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for 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 Sponsor countries.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-92-6 106-31-0
Chemical Name	n-Butyric Acid (CAS No. 107-92-6) n-Butyric Anhydride (CAS No. 106-31-0)
Structural Formula	n-Butyric Acid HOC(=O)-CH2-CH2-CH3 n-Butyric Anhydride CH3-CH2-CH2-C(=O)-O-C(=O)-CH2-CH2-CH3

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The n-Butyric Acid/n-Butyric Anhydride Category consists of two sponsored chemicals: n-butyric acid (CAS No. 107-92-6), and n-butyric anhydride (CAS No. 106-31-0.) The category members are closely related since the anhydride rapidly hydrolyzes in the presence of water to form the acid. Since testing of the anhydride is in reality testing of the acid form, these materials share toxicity characteristics and form the basis of the category. As a result, the metabolic series approach can be used to address the non-acute health endpoints.

In addition, increased blood levels of n-butryic acid have been demonstrated following administration of the metabolic precursors of butyric acid (n-butyl actetate and n-butanol.) Since the increased blood levels of n-butyric acid following n-butyl acetate and n-butanol have been demonstrated experimentally, hazard identification studies using either n-butyl acetate or n-butanol exposures have been used to identify the hazards associated with systemic exposure to n-butyric acid. Therefore, data from n-butyl acetate (CAS No. 123-86-4) and/or n-butanol (71-36-3) are used as analogs to either address or supplement the respective systemic toxicity endpoints for n-butyric acid. Both the n-butyl acetate and n-butanol data sets were accepted at SIAM 13.

Based on hydrolysis data, the acute aquatic toxicity endpoints of both n-butyric acid and n-butyric anhydride have been addressed using data from structural analogs, alleviating the need for additional testing on n-butyric acid. As a result, available data from propionic (CAS No. 79-09-4), isobutyric (CAS No. 79-31-2) and pentanoic (CAS No. 109-52-4) acids have been used to assist in addressing the acute aquatic toxicity of butyric acid.

Human Health

The acute oral and dermal LD50 values for n-butyric acid are 2,940 mg/kg (rat) and 530 mg/kg (rabbit), respectively. The oral LD50 is representative of n-butyric anhydride. Data are available via the inhalation route indicating a low toxicity at saturated vapor concentration (no deaths). Both the acid and anhydride forms are considered skin and eye irritants. No data are available for dermal or respiratory sensitization. In general, some anhydrides are known respiratory sensitizers. However, butyric anhydride is not structurally similar to these anhydrides and is expected to quickly hydrolyze to the acid.

Repeated exposures to moderate to high concentrations of n-butyl acetate and n-butanol (the metabolic precursors of n-butyric acid) are well tolerated in rats. In a 90-day inhalation study, rats were exposed to n-butyl acetate at 0, 500, 1500, and 3000 ppm. Rats exposed at 1500 and 3000 ppm had minimal transient narcosis and sedation. Repeated exposures did not exacerbate these transient effects. Effects noted at these same exposure concentrations included reduced body weight gain and decreased feed consumption. There was no evidence of neurotoxicity based on

functional observational battery (FOB), quantitative motor activity, neuropathy and scheduled-controlled operant behavior endpoints. Based on decreased body weight gain, the NOAEL for systemic effects is 500 ppm and a NOAEL for post-exposure neurotoxicity is 3000 ppm (highest dose tested).

The developmental/reproductive toxicity for butyric anhydride and butyric acid has been met for the purposes of the OECD SIDS program. The various studies that support this make it difficult to choose a single hazard value for reproductive effects (see SIAR for details on acceptable repeated dose studies assessing reproductive organs and two separate studies examining reproductive effects of either males or females). No adverse developmental effects were noted in rats exposed to 3500 ppm n-butanol or rats and rabbits exposed to 1500 ppm n-butyl acetate.

N-butyric acid is not mutagenic in bacteria *(Salmonella typhimuriu*m) or cultured Chinese hamster lung (CHL) cells. An *in vivo* mouse micronucleus test conducted with n-butanol administered once orally to male and female NMRI mice at doses up to 2000 mg/kg body weight did not produce any chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis (spindle poison effect).

Environment

The preferred physical property values for n-butyric anhydride are: melting point –75 ^{0}C, boiling point 195 ^{0}C, density 0.96 g/m^3, vapor pressure 0.377 hPa, log Kow 1.39, aqueous solubility 4561 mg/L (estimated from Log Kow). The preferred physical property values for n-butyric acid are: melting point -7.9 ^{0}C, boiling point 165.5 ^{0}C, density 0.96 g/m^3, vapor pressure 2.20 hPa, log Kow 0.79, aqueous solubility 56,400 mg/L, Henry's constant 5.35E-7 atm-m^3/mol, and pKa 4.82. These compounds are liquid at 25°C and are very water soluble. Under environmental conditions, based on its pKa, the acid is expected to exist primarily in its dissociated form. Neither compound is expected to be volatile. Calculated atmospheric photo-oxidation half-lives were 3.1 to 3.2 days for butyric anhydride and 3.96 to 4.46 days for n-butyric acid. Butyric anhydride is unstable in water with half-lives of 2 - 17 minutes at environmentally relevant pH values pH 4 to 9 (22°C). n-Butyric acid is the hydrolysis by-product. Level III fugacity modeling results indicate that n-butyric acid (which is representative of n-butyric anhydride) will primarily partition to the soil (57.0%) and water (37.2%) compartments. Biodegradation testing cannot be performed for butyric anhydride. n-Butyric acid was readily biodegradable (72% in 5.8 days) in an OECD 301C modified MITI test. Fish bioconcentration factors of 2.3 to 3.16 were calculated for n-butyric acid.

Aquatic toxicity data are only available for n-butyric acid, due to the rapid hydrolysis of butyric anhydride in water. Since the duration of the butyric acid studies was either shorter or longer than current OECD guidelines and because of uncertainties in study details, data for analogous compounds are presented. The analogous compounds used were propionic acid ($C_3H_6O_2$, pKa 4.88), isobutyric acid ($C_4H_8O_2$, pKa 4.86), and pentanoic (valeric) acid ($C_5H_{10}O_2$, pKa 4.84). In fish *(Pimephales promelas*), the 96-hour LC50 values are 51.8 and 77 mg/L for propionic acid and pentanoic acid, respectively. In *Daphnia magna* the 48-hour EC50s values are 22.7 and 51.25 mg/L for propionic acid and isobutyric acid, respectively. In green algae (*Scenedesmus subspicatus*) the 96-hour EC50 value is 42.9 mg/L for propionic acid. The pH was not controlled in any study after test initiation. In all studies, at least at higher concentrations, pH in the test medium was reduced to as low as 4.4 to 5.8 during the test. However, since pH was not a controlled variable in any test, effects on toxicity attributable to pH fluctuations cannot be discerned. Furthermore, with a pKa of 4.82, the acute aquatic toxicity of butyric acid may be partly due to pH effects. The toxicity of n-butyric acid (unbuffered) to fish, invertebrates and green algae is expected to range between 22.7 and 77 mg/L based on analog data.

Exposure

Both n-butyric anhydride and n-butyric acid are manufactured in closed-systems in the sponsor country and transported in tank cars, thus releases to the environment are anticipated to be minimal. Should n-butyric acid or n-butyric anhyride become airborne, irritation of the upper respiratory tract in workers can occur. Based on the reactive nature of n-butyric anhydride, its tendency to hydrolyze in aqueous media, and the biodegradability of the breakdown products it does not accumulate in the environment. General population exposure is not anticipated, as n-butyric anhydride is not used in consumer products. Most n-butyric acid manufactured is consumed as an industrial intermediate in the production of other chemicals, such as cellulose acetate butyrate. The major consumer use of n-

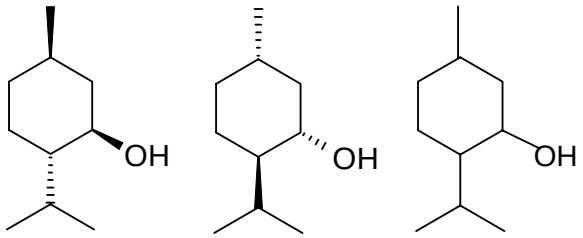
butyric acid is as an approved additive in various foods, but in terms of total pounds manufactured, this is a very low percentage use. Other uses of n-butyric acid are as a tanning agent and a fungicide, which could result in exposure. General population exposure to n-butyric acid may occur via its artificial and natural presence in foods. Environmental sources include fugitive emissions during its production and use, the exhaust of motor vehicles, and in vegetable oils and animal fluids. N-butyric acid is an important metabolite in the breakdown of carbohydrates, fats and proteins. N-butyric acid may arise from natural fermentation processes occurring in sediment and is present in butter as an ester to the extent of 4-5%. N-butyric acid is a natural component of essential oils of citronella Ceylon, eucalyptus globules, nutmeg, hops, Spanish anise and strawberry aroma.

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

Human Health: These chemicals possess properties indicating a hazard for human heath (dermal and eye irritation). Although these hazards do not warrant further work, they should nevertheless be noted by chemical safety professionals and users.

Environment: These chemicals have properties indicating a hazard for the environment (acute aquatic EC/LC50s between 1 and 100 mg/L based on analog data). However, the chemicals are of low priority for further work for the environment because of the rapid biodegradation and limited potential for bioaccumulation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2216-51-5	15356-60-2	89-78-1 (former CAS No. 15356-70-4)	1490-04-6
Chemical Name	L-Menthol	D-Menthol	D/L-Menthol	Menthol
Structural Formula	 L-Menthol D-Menthol Menthol			

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The menthols category is comprised of the isomers L-menthol, D-menthol, the racemate and menthol (unspecified isomers). The menthols can be considered as a category because of their similarity in physico-chemical, toxicological, ecotoxicological and environmental fate properties.

Human Health

L-, D/L- and the unspecified menthol isomer are well absorbed by the oral route of exposure and are mainly excreted as glucuronides. In rats an extensive enterohepatic circulation additionally leads to various hydroxylated degradation products. Glucuronides and degradation products are eliminated mainly via urine, minor quantities via the faeces.

All menthol isomers are of very low acute oral toxicity with LD50 values normally greater than 2000 mg/kg bw. Clinical signs of intoxication are unspecific, and included apathy and reduced activity. Based on old and limited studies for the racemate and the unspecified isomer, it can be assumed that the acute dermal toxicity of the menthol isomers is low.

All studied isomers of menthol are moderately irritating to the skin and slightly irritating to the eye. The skin sensitization potency of menthol isomers in animals and humans is low.

In rats given ≥ 200 mg/kg bw/d of L-menthol in soybean oil by gavage for 28 days, increased liver weights and a non dose-related vacuolization of hepatocytes were reported. The relevance of these findings remains unclear and a NOAEL could not be derived from this study. No toxicity was observed in rats receiving diets providing up to 200 mg/kg bw/d of either L- or D/L menthol for 5.5 weeks. Therefore for L-menthol and the racemate D/L-menthol a NOAEL of 200 mg/kg bw/d can be deduced from this study. Irritant effects on lungs and trachea, but no systemic effects were found in rats that were whole body exposed to L-menthol vapour for 71-79 days.

D/L-menthol administered with the diet for 13 weeks to rats (up to 937/998 mg/kg bw/d for males/females) and mice

(up to 3913/4773 mg/kg bw/d for males/females) did not induce any effects on organ weights. Microscopic examination of a comprehensive range of tissues revealed a slight increase in the severity of spontaneous interstitial nephritis in the male rats at the highest dose level. The only effect seen in mice of both sexes was a reduction in body weight gain in the highest dose group. The NOAELs derived from these studies were 937 mg/kg bw/d for the male rat, 998 mg/kg bw/d for the female rat and 1956 mg/kg bw/d for the male mouse and 2386 mg/kg bw/d for the female mouse.

In a 103-week feeding study in rats with D/L menthol (about 188 and 375 mg/kg bw/d), the only effect was a slight increase in spontaneous, chronic inflammation of the kidney in male rats of both dose groups, and a slightly reduced body weight in female rats. The NOAELs in this study were 375 mg/kg bw/d for male rats, and 188 mg/kg bw/d for female rats. In a 103-week feeding study in mice with D/L menthol (about 334 and 667 mg/kg bw/d), the NOAEL for both sexes was 667 mg/kg bw/d.

Because the racemate D/L-menthol contains the D- and L-isomers in equal proportions, the study results with the racemate are considered adequate for the evaluation of the D-isomer and of the L-isomers This view is further supported by the FAO/WHO 1999 safety evaluation on menthol, where the FAO/WHO expert committee had concluded that “the limited data that allow comparisons of metabolism and toxicity provide no indication of a difference in the toxicity of L-menthol and D/L-menthol”. Overall it can therefore be concluded that the D-, L- and D/L- menthol isomers induce no specific systemic effects and are well tolerated after repeated oral administration.

The menthol isomers are considered non-genotoxic in *in vitro* bacterial and mammalian test systems. *In vivo*, L- and D/L-menthol have demonstrated no mutagenic potential in adequately performed dominant lethal and cytogenetic tests and in a bone marrow micronucleus test in mice.

D/L-Menthol showed no evidence of carcinogenic activity in 2-year studies performed in accordance with current standards in rats and mice (highest tested dose levels in rats approx. 375 mg/kg bw/d, in mice approx. 667 mg/kg bw/d).

There is no fertility study available. Histopathological examinations of the reproduction organs of rats and mice showed no changes in repeated dose toxicity studies with D/L-menthol and also in carcinogenicity studies with D/L-menthol. Hence there is no indication of a potential of D/L-menthol to interfere adversely with reproduction.

L-Menthol was not embryo- or fetotoxic and had no teratogenic properties in well performed gavage studies in various species (rat, mouse, rabbit, hamster) at not maternally toxic doses (185-425 mg/kg bw/d). No maternally toxic dose levels were used in these studies.

In summary, the available toxicity data indicate very similar toxicity profiles for all of the menthol isomers investigated.

Environment

Menthols have a melting point of ca. 40 °C, a density of about 0.9 g/cm³ (20 - 25 °C). A vapor pressure of 8.5 Pa (25 °C) was measured for L-menthol and an unspecified isomer mixture. This value was also used for the other two category members. The measured water solubilities were in the range of 420 - 500 mg/l (20 °C), The log Kow is measured to 3.4 for L-menthol and D/L-menthol. This value can be read-across to the other two category members.

According to a Mackay Level I model calculation, the main target compartments for menthols are air (39.5 - 44.2%) and water (40.5 – 43.8 %). In the atmosphere menthols are indirectly photodegradable by hydroxyl radicals with $t_{1/2}$ = 16 hours. The calculated Henrys’ law constant of 2.6 - 3.2 Pa·m³/mol indicates the menthol isomers to be volatile from aqueous solution. Under environmental conditions, neither hydrolysis nor direct photolysis of menthols is to be expected. The ready biodegradability of menthols was shown in two recently performed Closed Bottle Tests for L- and D-menthol (L-menthol: 79-92 % after 28 d, D-menthol: 76-92 % after 28 d, 10d-window for both isomers was fulfilled). Experimentally determined BCF values in the range of <0.5-15 l/kg indicate no significant bioaccumulation potential of menthols.

For the toxicity of menthols on aquatic species experimental results from tests with fish, daphnids and algae are available for L-menthol and D/L-menthol. The data for the two category members within each trophic level are in the same order of magnitude. D/L-menthol contains the D- and L- isomers, thus effect values obtained with this mixture should cover the toxicity of D-menthol and the unspecific isomer mixture. Therefore, all available effect values can be regarded together for the assessment of this category. In acute toxicity tests the following results were obtained:

fish (3 species):	48- 96h LC50 = 15.6 – 26 mg/l;
invertebrates (*Daphnia magna*):	24h LC50 =37.7 - 71 mg/l; 48h LC50 = 26.6 mg/l
algae (*Scenedesmus subspicatus*):	72h ErC50 = 16.2 – 21.4 mg/l, 72h NOEC = 5 - 9.65 mg/l.

Applying an assessment factor of 1000 to the lowest ErC50for algae, a PNECaqua of 16.2 µg/l is calculated. This PNEC is valid for the whole category. Tests on long-term toxicity on aquatic species as well as on terrestrial species are not available. Two tests on sludge respiration are available with EC10 values of 117 and 51 mg/l.

Exposure

About 13,600 tonnes of menthols were produced worldwide in 2001. About 75 % of the menthol output is of biotic and 25 % of synthetic origin L-Menthol, D/L-menthol and menthol liquid are widely used in oral care products, pharmaceuticals, flavors, tobacco and others. D-menthol is not commonly distributed and only used for scientific purposes. The major route of occupational exposure to menthol isomers is supposed to be inhalation. The most significant routes of consumer exposure are likely to be dermal and oral.

RECOMMENDATION

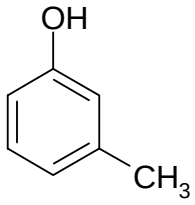
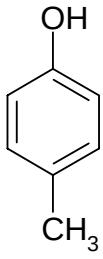
The chemicals in the Menthols category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals in the menthols category are currently of low priority for further work because of their low hazard potential. However, skin and eye irritation is noted.

Environment: The chemicals in the menthols category are currently of low priority for further work. The chemicals possess properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure levels, they should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-39-4	106-44-5	15831-10-4
Chemical Name	m-Cresol	p-Cresol	m/p-Cresol mixtures
Structural Formula	 m-Cresol	 p-Cresol	

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

m-Cresol, p-cresol and mixtures of both isomers can be considered as a single category because of their similarity in physico-chemical properties, distribution between environmental compartments, degradation, ecotoxicity, and toxicology.

Human Health

m-Cresol, p-cresol and m/p-cresol mixtures are absorbed across the respiratory and gastrointestinal tracts and through the skin, and are distributed throughout the body. The primary metabolic pathway for all cresol isomers is conjugation with glucuronic acid and inorganic sulfates. All isomers are mainly eliminated by renal excretion in form of conjugates. For p-cresol, oxidation to a reactive quinone methide intermediate was found in rat liver *in vitro*. The oral LD50 of undiluted m-cresol in rats was 242 mg/kg bw; and the LD50 of undiluted p-cresol was 207 mg/kg bw. Thus, it can be assumed that the LD50 of m/p-cresol mixtures is slightly above 200 mg/kg bw. Clinical signs included hypoactivity, salivation, tremors, and convulsions. No mortality nor clinical signs of toxicity were seen following exposure to saturated vapour concentration of either m-cresol or p-cresol. Inhalation of aerosols may however cause death, and mean lethal concentrations in rats were reported to be 29 mg/m³ for p-cresol and 58 mg/m³ for m-cresol. Clinical signs included irritation of mucous membranes, excitation and convulsions. Haematuria was reported at very high concentrations. Following dermal application in rabbits the LD50 of undiluted m-cresol was 2050 mg/kg bw and the LD50 of p-cresol was 300 mg/kg bw. It can be assumed that the LD50 of m/p-cresol mixtures is between 300 and 2000 mg/kg bw.

m-Cresol, p-cresol and m/p-cresol mixtures are corrosive to the skin and may cause serious damage to the eyes. There is no indication of a sensitizing effect of p-cresol and m/p-cresol from a limited guinea pig study and a limited human study. No sensitization test was available for m-cresol. In a survey article hypersensitivity reactions of some individuals to cresol (isomer unspecified) have been mentioned.

In 28-day and 13-week feeding studies, m-cresol, p-cresol and m/p-cresol (60:40) had a very similar pattern of toxicity in rats and mice with minimal effect levels of 1000 – 3000 ppm in the diet for increases in liver weight (rat, mouse) and kidney weight (mouse, p-cresol). No increase in relative kidney weight was found for m-cresol. Atrophy and regenerative changes in the nasal epithelia and forestomach were seen after exposure to p-cresol and m/p-cresol, presumably as direct result of the irritant effects of the chemicals. The no observed adverse effect levels (NOAELs)

for m-cresol, p-cresol and m/p-cresol were generally ≥ 50 mg/kg bw/day in rats and mice.

In vitro, m-cresol and p-cresol did not induce gene mutations in bacterial and mammalian cell systems and m/p-cresol mixture did not induce gene mutations in bacteria. m-Cresol was negative for clastogenic activity *in vitro*, and *in vivo*. p-Cresol was clastogenic *in vitro*, but has not been adequately tested in somatic cells *in vivo*. p-Cresol was, however, negative for dominant lethal mutations in germ cells in male mice at clearly toxic exposure levels. A 60:40 m/p-cresol mixture did not increase the frequency of micronucleated erythrocytes in the peripheral blood erythrocytes of mice. *In vitro*, it is possible that m- and p-cresol and m/p-cresol mixture have the potential to interact with DNA either directly or indirectly via metabolites.

As for o-cresol, there are no adequate data available to assess the carcinogenic potential of m-cresol, p-cresol or m/p-cresol mixtures. From tumour promotion studies in mice there are some indications that cresols may act as promoters. Currently, the U.S. National Cancer Institute is performing a carcinogenicity feeding study on mice and rats with cresols (mixture of ortho-, meta- and para-) within the National Toxicological Program (NTP).

Despite general toxicity (hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, perioral wetness) fertility was not affected by treatment with m-cresol or p-cresol (NOAEL, rat: 450 mg/kg bw/day). The NOAELs for general toxicity were determined as 30 mg/kg bw/day. Fertility effects including a 20% reduction in pup survival as well as reductions in the weights of male reproductive organs were found following treatment of mice with m/p-cresol mixture in a continuous breeding study at systemically toxic dose levels (reduced food consumption and reduced body weights, increases in liver and kidney weights) (NOAEL, fertility and general toxicity: 0.25 % in feed (ca. 375 mg/kg bw/day).

In developmental toxicity studies with m-cresol in rats and rabbits, no toxic effects on the developing organism could be found despite of the toxic effects on the dams as evidenced by hypoactivity, ataxia, tremor, twitches, prone positioning, audible respiration, perioral wetness, and a reduction in food consumption in rats, and audible respiration, and ocular discharge in rabbits (NOAELs: 175 mg/kg bw (maternal toxicity) and 450 mg/kg bw (developmental toxicity) for rats, and 5 mg/kg bw (maternal toxicity) and 100 mg/kg bw (developmental toxicity) for rabbits, respectively. p-Cresol caused fetotoxicity (delayed ossification, decreased fetal body weight) at maternally toxic dose levels in rats, but not in rabbits (NOAEL, rat, maternal toxicity, developmental toxicty: 175 mg/kg bw/day). Based on the available data, it can be assumed that m/p-cresol mixtures may have the potential to induce fetotoxicity in the presence of maternal toxicity.

In humans, the accidental oral uptake of cresols can induced irritation of mouth and throat, abdominal pains, vomiting, haemolytic anemia, increased heart rate, liver and kidney damage, headaches, facial paralysis, drowsiness, cramps, coma and death. Skin contact with cresols can result in corrosion, skin depigmentation, effects on the nervous system, liver and kidneys, gastrointestinal bleeding, and can cause human fatalities.

There are some case reports about tumour development in connection with probable exposure against cresol isomers. Since co-exposures to other substances cannot be excluded, no conclusion on a carcinogenic potential can be deduced from these case reports.

Environment

m-Cresol, p-cresol and m/p-cresol mixtures have a melting point of ca. 10 - 35°C, a water solubility in the range of 21.5 - 24.4 g/l (25°C), a density of about 1.03 g/cm³ (20°C), and a vapour pressure of 0.147 Pa (25°C). The experimentally determined log Kow are in the range of 1.94 - 1.96.

According to a Mackay Level I model calculation, the main target compartment for m-cresol and p-cresol is the hydrosphere (96.3%). In the atmosphere m-cresol and p-cresol are indirectly photodegradable by hydroxyl radicals with half–lives $t_{1/2}$ = 6.0 – 8.2 hours (OH concentration $5 \cdot 10^5$ molecules/cm³). The measured Henrys' law constants of 0.09 Pa·m³/mol (m-cresol) and 0.1 Pa·m³/mol (p-cresol) indicate slow volatilization from surface waters. Adsorption onto soils and sediments are low, according to experimentally determined Koc values of 34.58 for m-cresol and 48.66 for p-cresol.

With regard to the chemical structure m-cresol and p-cresol are not expected to hydrolyse under environmental conditions. Aerobic biodegradation is considered to be the major removal mechanism in the hydrosphere, leading to complete mineralization. From the available test results, m-cresol and p-cresol can be considered as being readily biodegradable under aerobic conditions. In surface waters and sediments half-lives in the range of some hours to a few days are expected. Photolytical degradation in surface waters as well as anaerobic degradation in lower sediment layers are expected to be of minor importance.

For m-cresol, a BCF of 20 was obtained in a laboratory tests on fish, indicating a low bioaccumulation potential. Because of the similarity of the log Kow the accumulation potential of m-cresol, p-cresol and m/p-cresol mixtures is assumed to be low.

For the acute toxicity of cresols on aquatic species experimental results with m-cresol and p-cresol from tests with fish, daphnids and algae are available. Long-term tests were conducted for p-cresol with fish, algae and invertebrates. Effect values with the same tested species indicate toxicity in the same order of magnitude, with p-cresol being slightly more toxic. Therefore, it is assumed that the long-term toxicity of both isomers is similar as well. No ecotoxicity tests are available for the isomeric mixture m/p-cresol. However, it is expected that the toxicity of the isomeric mixture is covered by the data for m- and p-cresol.

In acute toxicity tests the following results were obtained with either m-or p-cresol:

fish (15 species):	48 - 96 h LC_{50} = 4.4 - 57.5mg/l;
invertebrates (4 species):	24 - 48 h LC_{50} = 4.9 - > 99.5 mg/l;
algae (2 species):	48 – 72 h EC_{50} = 21 - 127mg/l.

Results from long-term tests for p-cresol are available for fish, invertebrates and algae, the most sensitive species being *Pimephales promelas* (NOEC = 1.35 mg/l), *Daphnia magna* (NOEC = 1 mg/l) and *Scenedesmus subspicatus* (ErC10 = 4.6 mg/l, EbC10 = 2.3 mg/l). Applying an assessment factor of 10 to the lower value, a Predicted No Effect Concentration (PNEC) for the aquatic compartment of 0.1 mg/l is determined for m- and p- cresol and the isomeric mixture m/p-cresol.

Exposure

Cresols (mixed isomers) are widespread in nature, occurring, for instance, in many plants, petroleum, coal tar, crude oil and, volcanic actions. They are emitted from municipal incinerators, during coal and wood combustion, with vehicle exhaust, from oil refineries and cigarette smoke. Cresols are also products of the photooxidation of toluene. p-Cresol is an endogenous metabolite of the amino acid tyrosine in humans and warm-blooded animals.

The world production figures amounts of about 28,500 tonnes for m-, 59,500 tonnes for p-, and 128,000 tonnes for the m/p-cresol isomeric mixture. The largest part of cresols are used as intermediates in chemical processes for the production of e.g. antioxidants, arylphosphates, synthetic Vitamin E and pesticides. m/p-Cresol isomeric mixture is used as a process solvent for the production of wire enamels.

Direct uses of cresols are as bactericide in biotechnological processing, pesticide and other minor, wide dispersive uses (< 1 % of worldwide production).

Information on releases into the environment from direct uses of cresols are not readily available.

RECOMMENDATION

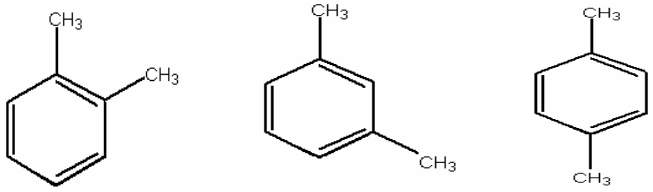
The chemicals in this category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: m-Cresol, p-cresol and m/p-cresol mixtures possess properties indicating a hazard for human health. 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 measures beyond those which are being applied already. Cresols (mixed isomers of ortho-, meta- and para-) are being tested in carcinogenicity studies under the U.S. National Toxicology Program (NTP).

Environment: The chemicals possess properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure level, they should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-47-6 106-42-3 108-38-3 1330-20-7
Chemical Name	Xylenes Category: o-xylene, m-xylene, p-xylene, and xylene (mixed isomers)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Evaluation Criteria

The data presented below are based on data presented in the IPCS (1997) Environmental Health Criteria 190 "Xylenes" as well as any further data that are relevant to the assessment of xylenes. Literature searches were performed on publicly available and company consortia data. The last literature search was conducted in January 2003.

Category Rationale

Ortho- meta- and para-xylene are chemical isomers, with the only difference being the position of the methyl group on the benzene ring. Mixed xylene is a mixture of the three isomers and in addition, typically contains 15-20% ethylbenzene. The xylene isomers have similar physicochemical properties with the exception perhaps of the higher melting point of p-xylene. In addition, the toxicity of the three individual isomers and mixed xylene is qualitatively similar.

Human Health

The human health effects of xylene by inhalation have been studied to the greatest extent because this is the most likely route of exposure, though under certain circumstances absorption through skin may contribute to exposure. Approximately 64 % of xylene is absorbed after inhalation. Xylene readily passes the placenta and is secreted into maternal milk. Approximately 72% to 95% of absorbed xylene is biotransformed and excreted in the urine within 18 hours. Around 4-6 % of retained xylene is eliminated via the expired air.

The primary metabolic pathway of xylene is the cytochrome P450-dependent monooxygenase system. Xylene is metabolised by oxidation of a methyl group to the corresponding o-, m-, or p-toluic acid, which are then excreted in the form of a glycine conjugate as o-, m-, or p-methyl hippuric acid in the urine.

Results from acute oral, dermal or inhalation toxicity studies in rats and mice indicate that the acute toxicity of xylene isomers and mixed xylenes is very low. Acute toxicity was typically characterized by central nervous system

depression. Animals exposed to xylene became uncoordinated, prostrate and comatose at doses that produced mortality within the dose group. The reported 6-hour LC50 values for xylene isomers ranged from 18.8 to 25.9 mg/L (4,330-5,984 ppm) in rats and from 16.9 to 22.8 mg/L (3,907-5,267 ppm) in the mouse. The reported 4-hour LC50 for mixed xylenes ranged from 27.5 to 47.4 mg/L (6,350-10,950 ppm) in rats. In o-, m- and p-xylene, rat oral LD50s of 3580, 5010 and 4020 mg/kg were reported. In mixed xylenes rat oral LD50 values of 3500, 5,779 and 8,600 mg/kg were reported. While a dermal LD50 of 12,180 mg/kg (rabbit) was reported for m-xylene and LD50 values of 3200 mg/kg and 4300 mg/kg were reported for the mixed xylenes. Mixed xylenes and xylene isomers are irritating to the skin and eyes.

In repeated dose studies, the principle effects of xylenes were adaptive changes in the liver, body weight changes, organ weight changes and altered motor coordination. Oral administration of 200 mg/kg o-xylene for up to 6 months resulted in formation of vacuolar structures in hepatocytes visible via electron microscopy. Inhalation exposure of male rats to m-xylene at 1000 ppm (4330 mg/m^3) for 3 months or 100 ppm (433 mg/m^3) for 6 months resulted in slight changes in liver ultrastructure primarily limited to proliferation of the smooth endoplasmic reticulum. Several studies with mixed xylenes show similar adaptive changes on the liver and liver metabolising enzymes. A 13-week oral gavage study in rats to m-xylene resulted in a dose related significant decrease in body weight gain (NOEL females 200 mg/kg, males 100 mg/kg) A similar study using p-xylene reported a slight decrease in body weight for both males and females at 800mg/kg, the highest dose tested (NOEL 200mg/kg). Oral administration of mixed xylenes orally to mice at 2000mg/kg/day for 13 weeks resulted in mortality [2F], clinical signs lasting up to 1hr after dosing, and reduced body wt gain. [particularly in females] but did not cause overt signs of toxicity or pathological changes. A NOAEL and LOAEL of 1000 and 2000 mg/kg/day respectively, could be derived from this study. This study, in conjunction with an earlier 14-day study was used to establish doses for a 2-year cancer bioassay. . In rats, administration of mixed xylenes orally at 1000 mg/kg/day for 13 weeks resulted in reduced body wt gain [particularly males] but did not cause overt signs of toxicity or pathological changes. A NOAEL and LOAEL of 500 and 1000 mg/kg/day respectively could be derived from this study. This study, in conjunction with an earlier 14-day study was used to establish doses for a 2-year cancer bioassay. Rats exposed to inhalation concentrations (600, 1500 or 4000 mg/m^3 ; 139, 346, 923 ppm) of mixed xylenes for 8h/day for up to 6 months had a NOEL of 346 ppm and a LOEL of 923 ppm. Increased liver weights; hypertrophy of the centrilobular zone in the liver including a change of the smooth and rough endoplasmic reticulum; and an increase in liver enzymatic activity (first six weeks of the study) were noted.

Rats exposed via inhalation to m-xylene 6 hour/day, 5 days/week for 1,2 or 3 months at 0, 50 of 100 ppm (0, 217, 433 mg/m^3) resulted in motor coordination disturbances (rotorod performance) and increased sensitivity to pain (NOEL 50 ppm based on rotorod performance). In addition, three repeated-dose ototoxicity studies in rats have been conducted with mixed xylenes. These studies reported an increase in auditory response thresholds at certain frequencies at inhalation concentrations of 800 ppm (3464 mg/m^3) and 1000 ppm (4330 mg/m^3) using prolonged dosing regiments (14hr/day for 6 weeks and 18hr/day for 61 days, respectively) for two of the studies and at 2,500 ppm (10825 mg/m^3), 6hr/day for 5 days, in the third study. One of these studies also reported a slight impairment of auditory response at 1,200 ppm (5196 mg/m^3), 14hr/day for 6 weeks.

Available data from both *in vitro* and *in vivo* studies suggest that xylenes are not genotoxic. Furthermore, rats exposed up to 500 mg/kg and mice exposed up to 1000 mg/kg body weight mixed xylenes for 103 weeks showed no treatment related increases in any tumor type for either sex.

Inhalation exposure of rats from gestation day 6-20 for 6h/day to o-, m-, p-, or mixed-xylene resulted in maternal toxicity at 1000 (4330 mg/m^3) and 2000 ppm (8660 mg/m^3). All test materials produced fetal toxicity effects at 1000 and 2000 ppm, in the presence of maternal toxicity. With o- and mixed-xylene, fetal toxicity also occurred at 500 ppm (2165 mg/m^3), in the absence of maternal toxic effects. However, the only indication of a treatment related effect was a slight decrease in fetal weights. No teratogenic effects were reported. The NOAEL for maternal and developmental effects was 500 ppm for m-, and p-xylene. For o- and mixed-xylene, the NOAEL for maternal and developmental toxicity were 500 and 100 ppm, respectively. In a developmental neurotoxicity study impaired performance in a motor ability test was reported in rats exposed to mixed xylene on days 4-20 of gestation (LOAEL 200 ppm; 866 mg/m^3) 200 ppm). In a follow-up developmental neurotoxicity study in rats exposed to mixed xylenes on days 7-20 gestation additional effects on learning and memory were observed at 500 ppm. In a one-generation reproductive study no dose related effects on mating indices, mean duration of gestation, mean litter size, or pup survival were reported at exposures of mixed xylenes up to 500 ppm. Mean pup weight was significantly lower in the group where

both parents had been exposed to 500 ppm (NOAEL reproductive effects 500 ppm).

Available case reports, occupational studies, and studies on human volunteers suggest that both short- and long-term exposures result in a variety of adverse nervous system effects that include headache, mental confusion, narcosis, equilibrium, impaired short-term memory, dizziness and tremors. In addition to the CNS effects xylene is irritating to the eye and skin and to the respiratory tract. Single exposure human studies were conducted with concentrations ranging from 70 to 300 ppm for up to 4 hours. No CNS symptoms were experienced when subjects were exposed to pure xylene and no deficits in performance in neurobehavioral test applied only increases in reaction time were observed at 200 ppm TWA that included peak exposures of 400 ppm. A single repeated-dose human exposure study, at similar levels, also showed an increase in reaction time.

Environment

Xylene isomers have melting points of –25.2˚, -47.9˚and 13.3˚C, boiling points of 144.4˚, 139.1˚ and 138.3˚C vapor pressures of 665Pa, 798Pa, and 865Pa at 20˚C, Log Kows of 3.12, 3.2 and 3.15 and water solubilities of 178, 161, 162 mg/L at 25˚C for o-, m-, and p-xylene, respectively. Based on the above Log Kows, the estimated BCFs for o-, m- and p- xylene are 50, 58 and 53, respectively. The Kow values in addition results from bioaccumulation studies suggest that the relative bioaccumulation potential for xylenes is low.

The half-life in air is estimated to be 19.7, 9.47, 19.7 hours for o-, m-, and p-xylene, respectively due to direct reactions with photochemically generated hydroxyl radicals. Experiments using xylenes adsorbed on silica gel have shown that the photomineralization rates for all three isomers are low using radiation with a wavelength longer than 290 nm. As xylenes are volatile organic chemicals (VOCs), they have the potential to form ozone (smog). The calculated POCPs (Photochemical Ozone Creation Potentials) for o-, m- and p- xylenes are 41, 78 and 63. Based on the physical chemical properties xylenes are likely to partition primarily to the air compartment. The m-, p- and mixed xylenes are readily biodegradable under aerobic conditions in sewage sludge and are expected to biodegrade in soil and water as well. The o-xylene isomer is considered to be inherently biodegradable under aerobic conditions.

The 96-hour LC50s for *Oncorhynchus mykiss* were 7.6 mg/L, 8.4 mg/L, 2.6 mg/L, and 13.5 mg/L for o-, m-, p-, and mixed-xylenes, respectively. The 96-hour LC50s for *Pimephales promelas* were 16.4 mg/L, 28 mg/L, and 26.7 mg/L for o-, m-, and mixed-xylenes, respectively. The 48-hour EC50s for *Daphnia magna* were 3.2 mg/L, 9.56 mg/L, and 8.5 mg/L for o-, m-, and p-xylene, respectively. The 96-hour EC50s for *Crangon franciscorum* were 1.3 mg/L, 3.7 mg/L, and 2 mg/L for o-, m-, and p-xylene, respectively. The 72-hour EC50s for *Selenastrum capricornutum* were 4.7 mg/L, 4.9 mg/L, and 3.2 mg/L for o-, m-, and p-xylene, respectively. Algal data for mixed-xylenes included a 72-hour EC50 of 10 mg/L for *Skeletonema costatum*. A chronic fish study on mixed-xylenes using *Oncorhynchus mykiss* reported a NOEC ≥ 1.3 mg/L.

Exposure

The principal population at risk of exposure is the occupational workforce, which can be exposed to the emissions of mixed xylenes during its production and end-use, as well as during its wide use as an industrial solvent. Exposure to the general public can arise from automobile exhausts and many consumer products (degreasing cleaners, lacquers, paints removers and pesticides but also from tobacco smoke).

Worldwide production of mixed xylenes is 1999 was estimated at 24,027,000 metric tonnes (SRI International, 2001). The US production of the xylene isomers in 1999: p-xylene was 2,850,000 metric tonnes; o-xylene was 500,000 metric tonnes, and m-xylene was 125,000-150,000 metric tonnes. In Hungary, mixed xylenes production decreased from 60,000 tonnes in 1996 to 40,000 tonnes in 2001.

The primary use of the individual xylene isomers is as chemical intermediates. Almost all o-xylene produced in the U.S. is consumed in the manufacture of phthalic anhydride. Other minor uses include the use of o-xylene as a feedstock in the production of bactericides, soybean herbicides and dyes. Most m-xylene is used as a chemical intermediate in the production of isophthalic acid. Small amounts of m-xylene are also consumed in the production of meta-toluic acid, isophthalonitrile, and other compounds. Almost all U.S. production of p-xylene is consumed in

the manufacture of dimethyl terephthalate (DMT) and terephthalic acid (TPA), which are used in production of polyester fiber and plastics.

The main use of mixed-xylenes is as a component of gasoline (approximately 92% of mixed-xylenes produced is blended into fuel gasoline). It is also used as solvent in paints, and paint-related products (varnishes, lacquers, dyes, cleaning fluids, thinners, paint removers), printing inks, coatings, cements and adhesives, as a component of Canada balsam in the oil-immersion microscopy in medical laboratories, and it is further applied as a cleaning agent in histology specimen preparation.

RECOMMENDATION

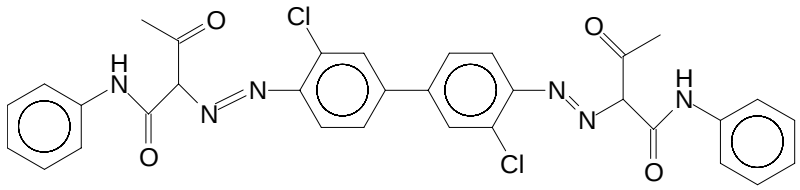
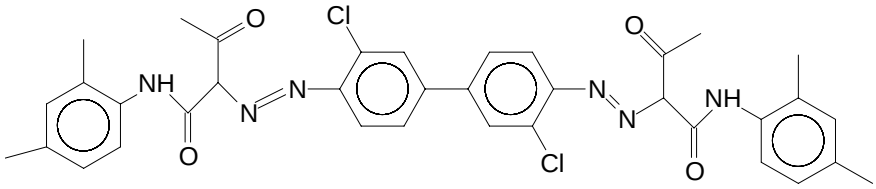
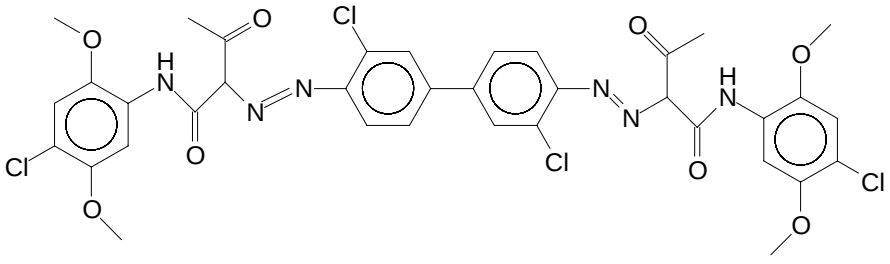
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

These chemicals possess properties indicating a hazard for human health and the environment. In addition, based on data presented by the Sponsor countries, exposure to humans and the environment is anticipated. It is known that risk management measures are being applied within OECD countries. Countries may desire to check their own risk management measures to find out whether there is a need for measures beyond those which are being applied.

An IPCS Environmental Health Criteria assessment document (EHC 190) exists for this category of chemicals.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	Pigment Yellow 12: 6358-85-6 Pigment Yellow 13: 5102-83-0 Pigment Yellow 83: 5567-15-7
Chemical Name	Pigment Yellow 12: Butanamide, 2,2'[(3,3'-dichloro[1,1'-biphenyl]-4,4'diyl)bis(azo)]bis[3-oxy-N-phenyl- Pigment Yellow 13: Butanamide, 2,2'[(3,3'-dichloro[1,1'-biphenyl]-4,4'diyl)bis(azo)]bis[N-(2,4-dimethylphenyl)-3-oxo- Pigment Yellow 83: Butanamide, 2,2'[(3,3'-dichloro[1,1'-biphenyl]-4,4'diyl)bis(azo)]bis[N-(4-chloro-2,5-dimethoxyphenyl)-3-oxo-
Structural Formula	Pigment Yellow 12:  Pigment Yellow 13:  Pigment Yellow 83: 

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The Diarylide Yellow Pigments category includes molecules with similar chemical structure; all contain the chloro-substituted biphenyl moiety, azo-moieties, keto groups and a substituted or non-substituted phenyl ring at both ends of the molecule, which is connected to the central part of the molecule via an amide bond. The only difference is in the substitution of the outer aniline rings, e.g. methyl, chloro and methoxy. They are expected to display essentially the same trend in environmental, ecotoxicological and toxicological behaviour based on the available data.

Human Health

Standard single exposure toxicokinetics studies indicate essentially no potential for uptake via the oral and dermal routes. However, following repeated oral exposure at high dose levels, there is some evidence that a very limited uptake of the compound (or its impurities) could occur, based on observations of staining of the mucosal surfaces of internal organs (although the possibility of contamination during necropsy cannot be excluded). In an oral reproductive developmental screening study, staining of the pups could indicate a potential for limited placental transfer, again at a high dose level. Given that the pigment yellows are essentially not absorbed into the body, metabolism is not relevant. However, the presence of very low levels of 3,3'-dichlorobenzidine has been demonstrated in two studies using very sensitive techniques following oral administration of some yellow pigment compounds. It seems likely that this is due to the presence of a mono-azo impurity in some of the yellow pigment parent compounds, which is absorbed and subsequently metabolised. No 3,3'-dichlorobenzidine was found in the urine of experimental animals after exposure orally or via the lungs in long term studies. Following ingestion, the vast majority of the pigments are excreted unchanged in the faeces.

The acute oral LD50 values for rats are >3000 mg/kg bw for Pigment Yellow 13 and >1,750 mg/kg bw for Pigment Yellow 83. The acute oral LD50 values derived from studies in experimental animals are >1,750 mg/kg bw for the three Diarylide Yellow Pigments. For acute dermal toxicity a single LD50 of >3,000 mg/kg bw is available for Pigment Yellow 13. No deaths or clinical signs of toxicity were observed following oral or dermal exposure. The inhalation LC50 available is >4,448 mg/m^3 for Pigment Yellow 13. Tachypnoea, dyspnoea, exophthalmos, ruffled fur and curved or ventral body position were observed, although all animals recovered and no gross abnormalities were observed at necropsy.

All three pigments may be minimally irritating when in contact with the skin. Based on the available data the pigments have a minimal to slight potential for eye irritation. There is no indication that the three pigments are sensitisers.

No adverse effects were seen after 4-7 weeks oral administration of Pigment Yellow 12 at 1000 mg/kg/day (NOAEL), the highest dose tested in a well conducted and reported test of repeated dose toxicity (OECD TG422) study. Furthermore, in the cases of Pigment Yellow 12 and 83, no toxicologically significant effects were observed in a range of chronic toxicity studies of lesser quality (in terms of reporting) in rats and mice at doses up to 6500 mg/kg/day. Based on the kinetics of the three pigments and the chemical similarities, it can be concluded that these findings can be extrapolated to all three pigments.

For the inhalation route the effects seen are related to the deposition of dust particles in the lungs, leading to Pigment Yellow 13 related effects even at the lowest exposure concentration of 54 mg/m^3 (local LOAEL). Systemically no effects were observed at the highest concentration tested, 410 mg/m^3 (systemic NOAEL).

All three pigments are not genotoxic in bacterial tests. Pigment Yellow 12 did not induce clastogenic effects in mammalian cells. Based on the chemical similarities between the three pigments, it is predicted that all three Yellow Pigments will not induce chromosomal changes in mammalian cells. There are no *in vitro* data to suggest that the pigments are genotoxic *in vivo*.

No increased tumour incidence after treatment with Pigment Yellow 12 and 83 were observed in several long-term studies in rats and mice (NOAEL (rat) > 630 mg/kg; NOAEL (mouse) > 1,960 mg/kg). Based on chemical similarity it can be

concluded that the three pigments are not carcinogenic.

It can be concluded that Pigment Yellow 12 does not have any adverse effects on reproductive parameters. There was no evidence of teratogenicity. The NOAEL for maternal and reproductive toxicity is >1,000 mg/kg bw. Supporting evidence is also available from the fact that no changes on the reproductive organs were observed in the studies of repeat dose toxicity and carcinogenicity study with Pigment Yellow 83. In view of the structural similarities and similar kinetics no effects on reproduction or development are expected from Pigment Yellow 13 and Pigment Yellow 83.

Environment

The pigments are a solid with a very low vapour pressure, a water solubility of <20 µg/L and a calculated Log Kow of 6.8-8.1. They have a calculated half-life for photo-oxidation of 1.7 – 4.5 hours (indirect reaction with OH-radical) and are expected to be hydrolytically stable. Fugacity modelling (Mackay Level III) predicts that the pigments will partition primarily to sediment (98%) if released to the aquatic compartment. Based on the log Kow the pigments have high potential for adsorption to soil (predicted Log Koc 4.0 – 5.3). The experimental data indicate that the pigments are not biodegradable.

The acute LC50/EC50 of the pigments to fish and daphnia are above the water solubility limit. In 72h algal tests with Pigment Yellow 12 and 83, the ErC50s were also above the water solubility limit. Although some effects on biomass were reported in one algal study for Pigment Yellow 12 (below 50%), significant fluctuations were observed in the algal results. Further algal testing on Pigment Yellow 12 indicated no effects at solubility and these are considered key studies based on a weight of evidence approach. The NOEC in a daphnia chronic reproduction study was set at the water solubility limit as no effects were reported at the nominal concentration of 1 mg/L. No toxicity towards micro-organisms was observed at the solubility limit. Based on the very low water and n-octanol solubility exposure of aquatic organisms to the pigments is expected to be low. There are no sediment or terrestrial effect data. Partitioning to sediment may be possible based on the high sorptive potential (Koc=4.0-5.3).

The results of calculations of bioaccumulation potential are contradictory. No solid experimental data on bioaccumulation are available. It may be hypothesised that, the large size of the molecules makes significant bioaccumulation unlikely.

Exposure

For the year 2001 the global market for the three diarylide yellow pigments under evaluation was about 50,000 tonnes. The pigments are used as colouring agents in industrial and decorative paints, inks and plastics (polymers).

Worker exposure to the pigments can occur during handling and cleaning operations. The principal route of exposure is by inhalation. Skin contact may be possible. Consumer exposure is expected to be negligible as consumer products only contain the pigments in a matrix.

There is potential environmental exposure arising from the production and processing of the substances. In addition exposure after paper recycling can not be excluded.

RECOMMENDATION

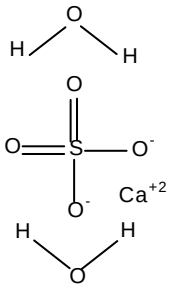
Human Health: The chemicals are currently of low priority for further work.
Environment: The chemicals are candidates for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The substances are of low priority for further work due to their low hazard potential.

Environment: From the currently available data, it is difficult to determine the bioaccumulation potential of the substances. The bioaccumulation potential is being further considered and investigated in some OECD countries and also within the framework of the EU.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	10101-41-4
Chemical Name	Calcium sulfate, dihydrate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information on toxicokinetics, metabolism and distribution.

The acute oral toxicity study [OECD TG 420, Fixed dose procedure] of calcium sulfate, dihydrate showed that this chemical did not cause any changes even at 2,000 mg/kg b.w. Therefore, the oral LD_{50} value was more than 2,000 mg/kg b.w. for female rats without specific clinical signs.

Calcium sulfate, dihydrate was not irritating to the skin of rabbits at 1, 24, 48 and 72 hours after removal of the patches [OECD TG 404]. There is no indication of skin sensitisation in guinea pigs [OECD TG 406].

In a Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test in rats [OECD TG 422], calcium sulfate, dihydrate was administered by gavage at the dose levels of 0, 100, 300 and 1,000 mg/kg bw/day for more than 35 days and 41 ~ 45 days for male and female animals, respectively. Calcium sulfate, dihydrate had no critical influence on test items such as mortality, body weights (organ weight), food consumption, necropsy, reflex action, grip strength and behaviour of the animals. However, the values of total protein, albumin, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase and creatinine were decreased at 300 mg/kg bw/day and 1,000 mg/kg bw/day treatment for male animals showing that the test substance might affect the excretion process, distribution or metabolism of test substance in relation to the kidney. Based on these results, the LOAEL and NOAEL were determined to be 300 mg/kg bw/day and 100 mg/kg bw/day for male rats. In case of female rats, no effects were observed at the top dose tested (1,000 mg/kg bw/day).

In the above mentioned reproduction/developmental toxicity screening test [OECD TG 422], male and female rats, were dosed for 35 days and 41 ~ 45 days respectively and the pre-mating exposure period was 14 days. No adverse effects were observed in terms of fertility, delivery and nursing in parent animals during the test period. There were no signs of reproduction/developmental toxicity on the body weight, gestation index, sex ratio, clinical signs or viability up to 1,000 mg/kg/day (highest dose tested).
Bacterial gene reverse mutation tests in *Salmonella typhimurium* (strains TA98, TA100, TA1535 and TA1537) and *Escherichia coli* WP2 *uvr*A with and without metabolic activation gave negative results. An i*n vivo* mammalian erythrocyte micronucleus assay using male ICR mice [OECD TG 474], tested at the dose levels of 1,250, 2,500 and 5,000 mg/kg b.w, gave negative results. Accordingly calcium sulfate, dihydrate was not mutagenic *in vivo* and *in vitro.*

According to mutagenicity data, this substance would not be expected to be carcinogenic. There is no data available on carcinogenicity.

Environment

Calcium sulfate, dihydrate is a colorless solid inorganic substance with monoclinic and hygroscopic properties. It has a water solubility of 2.05 g/L at 20 °C. Vapor pressure, n-octanol/water partition coefficient and stability in water are not applicable for the salt of an inorganic substance. Photodegradation, environmental fate modeling and biodegradation are not relevant for an inorganic compound. Bioaccumulation is not expected.

The following studies for aquatic organisms are available:
Green algae (*Selenastrum capricornutum)*: EC_{g50} (72 h) > 100 mg/L (growth rate),
EC_{b50} (72 h) > 100 mg/L (biomass)
Invertebrates (*Daphnia magna):* EC_{50} (48 h) > 100 mg/L.
Fish (*Oryzias latipes*): LC_{50} (96 h) > 100 mg/L.

No data are available on terrestrial organisms. Data from limit tests of 100 mg/L in fish, invertebrates and algae show no harmful effects..

Exposure

In Korea, the estimated production amounts of calcium sulfate, dihydrate were 1,447,000 tonnes in 2002. The total estimated amounts of import were about 59.1 tonnes from four countries in 2002 such as 46 tonnes from China, 3.6 tonnes from Nauru, 1.5 tonnes from South Africa and 8 tonnes from Morocco.

Calcium sulfate, dihydrate is produced in two companies as a waste-solid in the phosphatic fertilizer industry in Korea and this chemical is used as a primary material in gypsum industry, in which residues of calcium sulfate, dihydrate are recycled. Calcium sulfate, dihydrate is used in portland-cement retarders, tiles, polishing powders, paints, paper, dyes, metallurgy, wallboard, food additives and desiccants.

Releases of calcium sulfate, dihydrate into environment might be considered to be significant. As for human exposure, there is a potential for exposure to workers via dust inhalation and dermal routes at the manufacturing or using process. No data were available for workplace measurement of calcium sulfate, dihydrate but measured monitoring data for total dust in workplace was below the exposure limit value TWA of 15 mg/m^3.

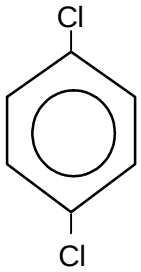
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-46-7
Chemical Name	1,4-Dichlorobenzene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

For toxicological endpoints, absorption of 1,4-dichlorobenzene (1,4-DCB) occurs rapidly via the digestive and respiratory tract. 1,4-DCB is of low acute inhalation, oral and dermal toxicity. Human ocular and nasal irritation appears from 50 ppm; human respiratory irritation appears from 160 ppm.

Regarding sensitisation, the interpretation of the results of the maximisation tests is difficult in view of the low concentration used. In humans only one questionable case was reported despite the widespread use of the 1,4-DCB. Therefore, a low sensitising potential can be anticipated.

The NOAEL was 75 ppm for inhalation repeated dose toxicity (76 weeks and 2 years) in mice and rats with slight liver and kidney effects from 158 ppm. The NOAEL was 10 mg/kg bw/day from a one-year oral dog study with liver effects observed from 50 mg//kg bw/day.

For genotoxicity, the so-called standard tests (*in-vitro* and *in-vivo*) do not suggest that 1,4-DCB has any genotoxic potential ; but evidence pointing in this direction comes from non standard tests (comet assay, DNA-adducts).

For carcinogenicity, renal adenocarcinomas were observed in male rats from 150 mg/kg bw/day, the underlying mechanism being male rat specific hyaline droplet nephropathy. Hepatocarcinoma associated in some animals with hepatoblastomas and histiocytosarcomas appeared in B6C3F1 mice from 600 mg/kg bw/day in a two year gavage study and in BDF1 mice from 300 ppm in a two year inhalation study at doses where hepatotoxicity was observed. It has to be noted that mice are of very high sensitivity towards hepatotoxic chemicals. Even if the mechanism by which these liver tumours are induced has not been clearly identified, a threshold mechanism for 1,4-DCB is proposed and NOAELs determinated : 75 ppm in BDF1 mice and 300 mg/kg bw/day in B6C3F1 mice.

No toxicity to fertility was observed (rat, inhalation exposure up to 538 ppm and oral exposures up to 270 mg/kg bw/day). For developmental toxicity, no increased risks to offspring were observed in the absence of parental effects (3 studies: rat oral up to 1000 mg/kg bw/day, rat inhalation up to 508 ppm and rabbit inhalation up to 800 ppm) except in a two generation study in rats by gavage where effects were observed from 90 mg/kg bw/day, with more severe effects at 270 mg/kg bw/day (dose with maternal toxicity). The effects seen were a reduced mean body weight in pups at birth and an increased total number of pups decreased between 1-4 (both reversible and in one out of 2 generations).

Environment

1,4-Dichlorobenzene is "readily biodegradable" and has a high potential for accumulation (Koc = 155 - 748; BCF = 55 - 1400).

For algae, EC50 values range from 1.6 mg/l (96 hours) to 34.3 mg/l (48 hours). For daphnids, acute toxicity results range from an EC50 (48 hours) of 0.7 mg/l to an EC50 (24 hours) of 3.2 mg/l. Regarding long-term effect tests, a NOEC of 0.22 mg/l (28-day) was observed. Acute toxicity to fish ranges from an LC50 (96 hour) of 1.12 mg/l for rainbow trout to an LC50 (96 hours) of 14.2 mg/l for fathead minnow. In early life stage testing, a NOEC (14-16 day, *Joranella floridae*) of 0.2 mg/l was observed. For soil dwelling organisms, the 14-day LC50 was 128-229 mg/kg dw for *Eisenia andrei*. For terrestrial plants ,the 14-day EC50 was 213-248 mg/kg dw for *Lactuca sativa*.

Long-term test results are available with aquatic species from three trophic levels and the PNEC for the aquatic compartment is estimated to be 20 µg/l.

Exposure

The worldwide consumption volume of 1,4-dichlorobenzene was ca. 113 000 t/a in 1989, with a general decreasing tendency. The consumption in the EU in 1994 is estimated to be 15000 t/a. It is mostly used as an intermediate for the production of dichloronitrobenzene and also directly as a moth repellent or air freshener.

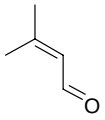
RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

In the context of the EU Existing Substances Regulation 793/93, a risk reduction strategy is being developed for this substance as a consequence of concerns about human health risks. OECD Member countries outside the EU are invited to take note of this strategy and to investigate the necessity for risk assessment in their own countries.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-86-8
Chemical Name	3-methyl-2-butenal
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No specific studies are available regarding toxicokinetics and metabolism of the substance.
3-Methyl-2-butenal is of moderate acute oral and acute inhalation toxicity and of low acute dermal toxicity.
LD_{50} rat (oral): 690 mg/kg bw; symptoms: labored breathing, stagger, tremors, apathy.
LC_{50} rat (inhalation): 3,700 mg/m³/4h (vapor); symptoms: lacrimation, nasal discharges, closed lids, labored breathing, dyspnoea, stagger, tremors, apathy.
LD_{50} rabbit (dermal): 3,400 mg/kg bw; symptoms: dyspnoea, stagger, abdominal position, apathy, local skin irritation.
Undiluted 3-methyl-2-butenal is corrosive to the skin and highly irritating to the eyes. Vapors of the material are irritating to the skin, the eyes, and the respiratory tract. In a well documented guinea pig maximization test, 3-methyl-2-butenal showed a skin sensitizing potential.

In a 28-day inhalation study (OECD TG 412) with rats, the NOAEC for systemic toxicity was at the highest tested concentration of 300 ppm (1,020 mg/m^3, approx. 252 mg/kg bw/day). Symptoms of irritancy were seen in the respiratory tract at 100 ppm in terms of focal metaplasia of respiratory epithelium of the nasal cavity into squamous epithelium, changes in cartilage of larynx, and in some cases atrophy of the olfactory epithelium at 300 ppm. Purulent rhinitis in all males and some females was seen at 300 ppm. This was regarded to be responsible for reduced body weight development in both sexes (-59.8% in males and –39.7% in females compared to controls) and impaired terminal body weight in the high dose males (-14.1%), rather than systemic toxicity. There were no other findings which would indicate systemic toxicity. The NOAEC for local irritation was determined to be 30 ppm (100 mg/m^3, approx. 25 mg/kg bw/day), the LOAEC was 100 ppm (340 mg/m^3, approx 84 mg/kg bw/day) due to the histopathological changes observed in the respiratory tract.
As part of a one generation study in rats (OECD TG 415), 3-methyl-2-butenal was administered subchronically at concentrations ranging from 50 - 800 ppm (about 6 – 77 mg/kg bw/day) via the drinking water for a period of 18 weeks. The highest test concentration (about 77 mg/kg bw/day) did not lead to any adverse findings in both sexes of the F0 parental animals. No higher dose levels were achievable using drinking water due to palability problems that were already noted at the highest tested concentration.

In vitro genotoxicity studies (Ames test) failed to produce coherent results. 3-Methyl-2-butenal revealed no mutagenic effect in the classical Ames test whereas positive effects were reported from a Liquid Suspension Assay in the strain TA 100 with and without metabolic activation. In the mouse micronucleus test (OECD TG 474) the material was not clastogenic nor did it impair chromosome distribution during mitosis. No unscheduled DNA repair was induced in rat liver cells by the test material or metabolites in an *in vivo* test system according to OECD TG 486.

In a one-generation study (OECD TG 415) in rats with administration of 3-methyl-2-butenal in the drinking water, no impairment for reproductive performance and fertility, systemic toxicity and developmental toxicity was found at the

highest tested dose of 800 ppm (about 77 mg/kg/day) thus representing the NOAEL for the F0 parental animals and their progeny.
In a prenatal toxicity study (OECD TG 414), 3-methyl-2-butenal had no effects on the gestational parameters and induced no signs of embryo- and fetotoxicity, in particular no indications for teratogenicity. The NOAEL for maternal toxicity and prenatal developmental toxicity was found at 300 mg/kg bw/day. A higher dose (450 mg/kg bw/day) could not be evaluated since it lead to severe toxicity or was lethal for the dams.

Environment

3-Methyl-2-butenal is a colorless-faint yellowish liquid with a water solubility of 110 g/l at 20°C. The vapor pressure is 7.5 hPa at 20°C. The melting point is lower than –20°C (calculated value –76.8°C) and the boiling point is 136°C. 3-Methyl-2-butenal has a density of 0.876g/cm³ at 20°C. The flash point is at 37°C and therefore, the substance is flammable.
The calculated Henry´s Law Constant based on measured data for water solubility and vapor pressure is 0.57 Pa*m³/mole, otherwise using the EPIWIN calculation program a constant of 2.85 Pa*m^3/mole could be calculated. Due to the measured log K_{ow} of 0.53 at 25 °C and the calculated log K_{oc} of 0.9 (Koc = 7.9), bio- and geoaccumulation are not to be expected. Distribution modeling using Mackay Level I indicates water (83%) and air (17%) to be the main target compartments. 3-Methyl-2-butenal is readily biodegradable according to OECD evaluation criteria (CO_2 –Headspace Test; ISO 14593, 80-90 % after 28 d) and the 10-days time window was fulfilled. Hydrolysis at environmental pH conditions is not expected according to the structure. In the atmosphere, the substance will be indirectly photodegraded by reaction with OH-radicals (calculated $t_{½}$ = 8.2 h) or ozone (calculated $t_{½}$ = 23.2 h).
The acute aquatic toxicity has been determined for fish (*Leuciscus idus* LC_{50} (96h) 17.6 mg/l), invertebrates (*Daphnia magna* EC_{50} (48h) 13.5 mg/l) and green algae (*Scenedesmus subspicatus* ErC_{50} (72h) 22.4mg/l, EbC_{50} (72 h) 16.7 mg/l). Due to a moderate volatility the LC_{50} for fish was corrected and therefore, the effective LC_{50} (96h) was 12.7 mg/l. Prolonged or chronic studies are not available. Based on the most sensitive data, LC_{50} (96h) 12.7 mg/L (corrected), a $PNEC_{aqua}$ of approximately 13 µg/l can be derived by applying an assessment factor of 1,000, according to the Technical Guidance Document for the EU risk assessment procedure.

Exposure

The worldwide production volume of 3-methyl-2-butenal was 6,000 - 13,000 metric tonnes in 2001. 3-Methyl-2-butenal is mainly used as an intermediate (99 %) in closed systems for chemical synthesis and only 1% are sold to German clients as well as exported to Switzerland.
The substance is used internally and further processed to citral and vitamin A. Worker protection is adequate and includes the use of appropriate technical equipment during substance handling, monitoring of concentrations in the air at the work place, the use of protective equipment, etc. However, the risk of exposure to 3-methyl-2-butenal may exist after spillages and during accidental exposure.
An estimated volume of < 10 t/a is used for reconstitution of essential oils and other natural products.
Consumer exposure is negligible since only small amounts of the 3-methyl-2-butenal are contained in food at maximum concentrations of 50 ppm. The substance naturally occurs in several plants, e.g. in blackberries (up to 0.34 %) and wild ginger (0.05 %). Further, the substance was detected in raw meat (0.36 %) and barbecued chicken (9 µg/kg). Also, exposure of the general population via the environment is negligible. 3-Methyl-2-butenal was listed in the Swiss Product Register (2002) as to be found under the collective term “aromas, perfumes” in 9720 products without any information about the concentrations of the substance. How many of these products indeed contain 3-methyl-2-butenal cannot be resolved. The substance is not contained in products registered in Denmark, Sweden, Finland or Norway.
Releases into the environment may occur during production and processing of 3-methyl-2-butenal as intermediate as well as from direct use of the substance and from formulation and use of products containing it.
During production and processing at the sponsor company the effluent concentration of the sewage treatment plant was below 20 µg/l. Less then 25 kg/a were emitted into the air.

RECOMMENDATION

The substance is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment:
The chemical is currently of low priority for further work. 3-Methyl-2-butenal possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute toxicity, which may become evident only at very high exposure levels, they should nevertheless be noted by chemical safety professionals and users.

Human Health:
The chemical possesses corrosive and sensitizing properties indicating a hazard for human health. Given the main use as a chemical intermediate in closed systems and the very low content of the substance in consumer products in the Sponsor country, the substance is considered to be 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.	110-19-0
Chemical Name	Isobutyl Acetate
Structural Formula	CH_3-COO-CH_2-(CH_3)CH-CH_3

SUMMARY CONCLUSIONS OF THE SIAR

Based on the rapid and complete hydrolysis of isobutyl acetate to isobutanol, *in vivo* data from isobutanol is useful when assessing the hazards associated with the systemic toxicity of isobutyl acetate exposure. Exposure to isobutyl acetate via dermal, inhalation, and water or dietary administration results in the rapid appearance of isobutanol in the systemic circulation due to metabolism of the acetate ester within barrier tissues. Since exposure to either isobutyl acetate or isobutanol results in systemic exposure to isobutanol, systemic toxicity data from studies that administer isobutanol directly are useful in identifying hazards associated with isobutyl acetate exposure. Endpoints of isobutyl acetate toxicity that are associated with direct contact-mediated effects (e.g. eye, skin, and respiratory tract irritation) cannot be extrapolated from isobutanol data due to the difference in physical-chemical properties of the two materials.

For acute aquatic toxicity, database of isobutyl acetate was supported using data from structural analogs, alleviating the need for additional testing on isobutyl acetate. Data from propyl acetate (CAS# 109-60-4), n-butyl acetate (CAS# 123-86-4), and 2-ethylhexyl acetate (CAS# 103-09-3) were used. These analogs have molecular backbones ranging from C3 to C8.

Human Health

This chemical has low acute toxicity by all routes. The oral LD_{50} ranges from 4,763 mg/kg bw in rabbits to 15,000 mg/kg bw in rats. Dermal LD_{50} values range from >5,000 mg/kg bw to >17,400 mg/kg bw in rabbits. Inhalation LC_{lo} values for vapor exposures were 38,000 mg/m^3 (8,000 ppm) with an LC_{100} of 99,750 mg/m^3 (21,000 ppm).

Isobutyl acetate is a moderate eye and skin irritant but not a dermal sensitizer. Inhalation of 200 ppm (950 mg/m^3) isobutyl acetate or higher has been reported to cause strong irritation to the throat of human subjects, while lower exposure concentrations were without effects. Repeated inhalation exposures would likely exacerbate the irritative effects.

Repeated exposures to moderate to high concentrations of isobutanol by the inhalation and oral routes of exposure are well tolerated in rats. In a 90-day inhalation study, rats were exposed to isobutanol at 0, 758, 3030, and 7575 mg/m^3 (0, 250, 1000, and 2500 ppm). A reduced response to an external stimulus was noted in the exposed animals only during the exposure period. Repeated exposures did not exacerbate these transient effects. There was no evidence of neurotoxicity based on functional observational battery (FOB), quantitative motor activity, neuropathy and scheduled-controlled operant behavior endpoints. The NOAEL was 3030 mg/m^3 or 1000 ppm based on increases in erythrocyte count, hemoglobin, and hematocrit measures in female rats. The NOAEL for neurotoxicity was 7575 mg/m^3 or 2500 ppm. A 13-week oral gavage study was conducted with isobutanol with dose levels of 0, 100, 316, and 1000 mg/kg bw/day. Hypoactivity and ataxia were noted in the 1000 mg/kg bw/day dose groups after dosing. In addition slight decreases in body weight gain and feed consumption was noted in the first two weeks of the 13-week study in the 1000 mg/kg bw/day dose group. The 100 and 316 mg/kg bw/day dose groups

were unaffected. The use of toxicity data from a metabolic series has been used in previous SIDS documents (e.g. n-butyl acetate and n-butanol, ethyl acetate, and ethanol) to provide toxicity information for related members.

An *In vitro* mutagenicity study indicates that isobutyl acetate is not a genotoxicant. In addition, isobutanol was negative in an *in vivo* mouse micronucleus study.

An inhalation two-generation reproductive toxicity study conducted with isobutanol (up to 7575 mg/m^3 or 2500 ppm) did not cause any parental systemic, reproductive, or neonatal toxicity when administered for two generations via whole-body exposure. No adverse developmental effects were noted in rats or rabbits exposed to 10,000 mg/m^3 (10 mg/L) isobutanol during gestation days 6-15 (rats) or 7 –19 (rabbits).

Environment

The available physicochemical data are adequate to describe the properties of isobutyl acetate. Isobutyl acetate has a vapor pressure of 18 hPa at 20^{0}C, a water solubility of 6 g/l at 20^{0}C and a Log K_{ow} of 1.78 (assumed at 25^{0}C). The photochemical removal of isobutyl acetate as mediated by hydroxyl radicals occurs with calculated half lives of about 1.9-2.3 days.

Isobutyl acetate is readily biodegradable under aerobic conditions. Isobutyl acetate volatilises easily from moving rivers, but volatilises only moderately from quiescent lakes and other surface water bodies (calculated volatilization half-lives of 2.9 hours from a river and 5.08 days from a lake). Isobutyl acetate is not persistent in the environment and is not likely to bioaccumulate in food webs.

Based on Level III distribution modelling it is estimated that the majority of isobutyl acetate released to the environment will partition into water (42.7%) and soil (44.9%), with a smaller amount in air (12.3%). The stability of isobutyl acetate in water is pH dependent, at neutral pHs (7) the $T_{1/2}$ = 3.3 years at 20^{0}C and at higher pHs (8) the $T_{1/2}$ is shortened to 122 days.

Aquatic toxicity data are available for isobutyl acetate. However, since the duration of the isobutyl acetate studies was either shorter or longer than current OECD guidelines and because of uncertainties in study details, data for analogous compounds are presented. The analogous compounds used were propyl acetate (CAS# 109-60-4), n-butyl acetate (CAS# 123-86-4), and 2-ethylhexyl acetate (CAS# 103-09-3). For propyl acetate, a flow-through test was conducted using fathead minnows (*Pimephales promelas*) and reported a 96-h LC50 of 60 mg/L. For n-butyl acetate, a flow-through test was conducted with fathead minnows and reported a 96-h LC50 of 18 mg/L. For 2-ethylhexyl acetate, a static-renewal test (daily renewals) with rainbow trout (*Oncorhynchus mykiss*) was conducted using the water accommodated fraction (WAF) method for compounds that are difficult to solubilize in water. A 96-h LC50 of 8.27 mg/L was reported. For 2-ethylhexyl acetate, a test with *Daphnia magna* was conducted using the WAF method, reporting a 48-h EC50 of 22.9 mg/L. Also using 2-ethylhexyl acetate, test with the green alga *Selenastrum capricornutum* was conducted using the WAF method, reporting a 72-h EC50 of >21.9 mg/L. Terrestrial data are not available, but based on low potential for bioaccumulation and the low hazard indicated by the mammalian toxicity data adverse effects on terrestrial mammals are not expected.

Exposure

Approximately 74,000 tonnes (163 million pounds) of isobutyl acetate was manufactured in the world in 2001, in continuous, closed processes. Environmental release from production facilities is low. Isobutyl acetate is used as a solvent in liquid formulation products, typically coatings, thinners, sealants, adhesives, printing inks, and cleaners. Application of these materials results in exposure via the dermal and inhalation routes, and release of isobutyl acetate into the environment through volatilisation. Due to the physical-chemical properties of isobutyl acetate, the material is not typically present as an aerosol. In regards to physical hazard, the chemical has a low flash point and a flammable range of 1.3 to 10.5% volume in air. Isobutyl acetate is also a natural component of nectarines, bananas, apples, and other fruits as well as milk.

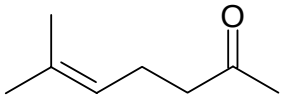
RECOMMENDATION

Isobutyl Acetate is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health (dermal, respiratory, and eye irritation) and the environment. Although these hazards do not warrant further work, as they are related to transient effects or acute toxicity 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.	110-93-0
Chemical Name	6-methylhept-5-en-2-one
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

6-Methylhept-5-en-2-one was found to be of low toxicity after acute oral administration, skin contact and inhalation. The oral LD_{50} for the rat was 3,570 mg/kg bw. The main symptoms described were apathy, atonia, dyspnea, abdominal and lateral position (1,360 mg/kg bw or higher). A dose response was observed, with symptoms getting progressively worse with increasing doses and recovery occurred in survivors within 5 days at dosages of 4,250 mg/kg bw or lower. After inhalation of vapors of the substance, a LC_{50} of > 13.96 mg/l/4 hrs (> 13,960 mg/m^3/4hrs) could be estimated for rats using Haber's rule (LC_{50} > 6.98 mg/l/8 hrs, > 6,980 mg/m^3/8 hrs). The acute dermal LD_{50} for rabbits exceeded 5,000 mg/kg bw.

In rabbits, the undiluted substance was only slightly irritating to the skin and the eyes. Sensitization studies in guinea pigs (modified Draize protocol and Open Epicutaneous Test) did not reveal any indication of a skin sensitizing potential. In a human maximization test, the substance produced no skin sensitization in 25 volunteers at a test concentration of 3 % in petrolatum.

In a 90 day study (OECD TG 408), administration of 6-methylhept-5-en-2-one by gavage up to 1,000 mg/kg bw/day for 13 weeks caused substance-related effects in all dose groups. The target organs were kidney, liver and testes. Thus, under the conditions of this study, the no observed adverse effect level (NOAEL) was 50 mg/kg bw/day in females due to an increase of 21% in platelet counts at 200 mg/kg bw/day (LOAEL) and lower than 50 mg/kg bw/day in males due to an in increase of 12% and 14 % in relative and absolute kidney weights. The kidney effects in all dose groups in the males were induced by accumulation of α_{2u}-globulin which was confirmed by immunohistochemical staining. This finding is known to be a rat specific phenomenon without a toxicological correlate in humans.

No mutagenic effect was found in the Ames Test (OECD TG 471; standard plate and preincubation conditions) and *in vivo* in the mouse micronucleus test (OECD TG 474).

The results of a well conducted subchronic study with gavage administration of 6-methylhept-5-en-2-one indicate that the test compound caused testicular toxicity affecting spermatogenesis at the high dose level of 1,000 mg/kg bw/day. At the mid and low dose (50 and 200 mg/kg bw/day), no effects on sperm or testes were observed. In females, no adverse effects on reproductive organs or estrous cycle were observed up to and including the highest tested dosage of 1,000 mg/kg bw/day.
6-Methylhept-5-en-2-one was tested in a prenatal developmental toxicity study according to OECD TG 414 with gavage application. The no observed adverse effect level (NOAEL) for maternal and prenatal developmental toxicity was found at 200 mg/kg bw/day. Thus, signs of prenatal developmental toxicity in the form of mild growth retardation occurred only at a dose level which was also clearly toxic to the dams. There were no indications for teratogenicity up to and including 1,000 mg/kg bw/day.

Environment

The colorless-yellowish liquid 6-methylhept-5-en-2-one has a water solubility of 3.02 g/l (at 25 °C) and a vapor pressure of approximately 1 hPa at 18 °C. Based on measured data for vapor pressure and water solubility a Henry's Law Constant of 6.68 Pa*m³/mole could be calculated, whereas by a model calculation a Henry's Law Constant of 21.5 Pa*m³/mole was derived. Distribution modeling using Mackay Level I indicates air (69 %) and water (30 %) to be the main targets. The substance is readily biodegradable according to OECD criteria (>70 % in 28 days; 10-days time window fulfilled; OECD 301F). Due to the chemical structure hydrolysis can be excluded. In the atmosphere 6-methylhept-5-en-2-one will be indirectly photodegraded by reaction with OH-radicals ($t_{1/2}$ = 4.2 hours) or ozone ($t_{1/2}$ = 38.4 minutes). Due to the measured $logK_{ow}$ of 2.4 (at 25 °C) and calculated $logK_{oc}$ of 1.57 and 2.04 a bio- or geoaccumulation is not to be expected.

The acute aquatic toxicity has been determined for the fish *Leuciscus idus* with a LC_{50} (96h) of 68 mg/l and for *Pimephales promelas* with a LC_{50} (96h) of 86 mg/l. Furthermore, for the waterflea *Daphnia magna* an EC_{50} (48h) of 129 mg/l and for the green alga *Scenedesmus subspicatus* an ErC_{50} (72h) of 191 mg/l (endpoint: growth rate) could be determined. Due to the moderate volatility of 6-methylhept-5-en-2-one an experiment for determining the evaporation from the test systems was performed and the effect values for fish, daphnids and algae were corrected. This resulted in an LC_{50} (96h) for *Leuciscus idus* of approximately 50 mg/l, an EC_{50} (48h) for *Daphnia magna* of approximately 83 mg/l and an ErC_{50} (72h) for *Scenedesmus subspicatus* of approximately 116 mg/l.
Results from prolonged or chronic studies are not available.
According to the EU Risk Assessment Procedure a $PNEC_{aqua}$ for the most sensitive aquatic species, the fish *Leuciscus idus*, of 50 µg/l can be calculated by applying an assessment factor of 1,000.

Exposure

The worldwide production volume of 6-methylhept-5-en-2-one in the year 2001 was between 10,000 and 30,000 t/a and has been reported to take place in closed systems.
In the Sponsor country 6-methylhept-5-en-2-one is to > 95 % used as an intermediate in closed systems for the synthesis of fine chemicals (e.g. vitamins, aroma chemicals, active ingredients used in pharmaceuticals). Only up to 5 % 6-methylhept-5-en-2-one is filled and distributed to industrial clients which are using it on the one hand as an intermediate for chemical syntheses and on the other hand as a flavouring compound and / or aroma additive in e.g. cosmetics and food. Monitoring data at the workplace are not available. However, worker protection in the Sponsor country is adequate and includes the use of appropriate technical equipment during substance handling and the use of protective equipment, etc. The risk of exposure to 6-methylhept-5-en-2-one may exist after spillages and during accidental exposure. Likewise dermal contact may result only from accidental exposure since the majority of the material (ca. 95%) is used as an intermediate in closed systems, and only small quantities (ca. 5%) are filled and distributed to industrial clients. No information is available on exposure scenarios following this use. Consumer exposure is widespread but anticipated to be low since only small amounts of 6-methylhept-5-en-2-one are contained in cosmetics at usual concentrations of up to 0.01 % and in food in maximum amounts ranging from 0.5 – 10 ppm. Some information suggests that there are products containing higher concentrations (of up to 2 %) that are assumed not to be available to the general public.
The substance naturally occurs as a biogenic volatile organic compound and shows an ubiquitous occurrence in the air due to emissions from plants or several herbs. It was also identified in several fruits as well as in drinking water- and in wastewater samples.
In European product registers products containing 6-methylhept-5-en-2-one are listed (cleaning/washing agents, cosmetics).
Exposure to workers is adequately controlled in the industry of the Sponsor country.

RECOMMENDATION

Human Health: The chemical is a candidate for further work.

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

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment:

The chemical possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute aquatic toxicity, which may become evident only at very high exposure levels, they should nevertheless be noted by chemical safety professionals and users.

Human Health:

The chemical possesses properties indicating a hazard for human health. Testicular toxicity was induced in rats after repeated exposure at a dose of 1,000 mg/kg bw/day. Developmental effects at maternal toxic doses of 1000 mg/kg bw/day were observed. The main use is as a chemical intermediate predominantly in closed systems. However, up to 5 % of the substance are used outside the production site by industrial clients. An exposure assessment for this scenario is recommended, and, if indicated, a risk assessment should be performed.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	115-11-7
Chemical Name	Isobutylene
Structural Formula	CH3 | CH2=C-CH3

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Isobutylene has a low order of acute toxicity. As isobutylene is a gas at normal temperature and pressure, ingestion or dermal absorption of this material is unlikely. The 2-hour LC50 of isobutylene in mice was 180,000 ppm (415 mg/L) and the 4-hour LC50 in rats was 270,000 ppm (620 mg/L). Inhalation of isobutylene can produce central nervous system depression, anesthesia and/or asphyxiation. However, these effects are only seen at very high concentrations, i.e., approximately 20% or higher. Isobutylene is predicted to produce narcosis in humans at concentrations exceeding the lower explosive limit (LEL) of 18,000 ppm.

There are no data to evaluate the dermal or ocular irritation potential of isobutylene. However, should skin or eye contact occur to this chemical in its liquid state, tissue freezing, severe cold burn, and/or frostbite may result.

Repeated dose toxicity clearly demonstrated that isobutylene is not toxic to rodents at concentrations up to 8,000 ppm (18.4 mg/L) for 14 weeks. There was a minimal increase in right kidney weights of 4,000 and 8,000 ppm (9.18 and 18.4 mg/L, respectively) male rats and 8,000 ppm (18.4 mg/L) male mice and the relative (to body weight) right kidney weights of all exposed groups of male rats and 8,000 ppm (18.4 mg/L) male mice were greater than those of the chamber controls. The absolute liver weights of female rats exposed to 1,000 ppm and above, and the relative (to body weight) liver weights of all exposed groups of female rats were greater (up to 20%) than those of the chamber controls. However, the increases in absolute and relative (to body weight) liver weights did not occur in a concentration-related manner. The absolute and relative (to body weight) right kidney weights of all groups of exposed female mice were greater (up to 18%) than those of the chamber controls, but in general, were not exposure concentration related. There were no histopathologic effects associated with increased kidney or liver weights as a result of isobutylene exposure. There were no exposure-related gross lesions in the rats. Some minimal hypertrophy of goblet cells lining the nasopharyngeal duct in the most caudal section of the nasal cavity was observed in all groups of exposed male and female rats but not mice. There were no clinical findings or biologically significant effects on male or female reproductive organs attributed to isobutylene exposure in rats or mice. The NOAEL was 8,000 ppm (18.4 mg/L).

Although isobutylene produced an increase in follicular cell carcinomas of the thyroid in male rats exposed for 105 weeks, this was observed only at the highest exposure concentration (i.e., 8000 ppm) and did not occur in female rats nor male or female mice. Overall, the data suggest that isobutylene has a low carcinogenic potential. In addition, the follicular cell carcinomas in the thyroid were reported to be morphologically similar to spontaneously developing follicular cell carcinomas and there was no concurrent increase in the incidence of follicular cell hyperplasia or adenoma in male rats. It should also be noted that there was no evidence of any carcinogenic activity in female rats or mice up to 8000 ppm. Taken in concert, these data suggest that isobutylene has a low carcinogenic potential. The NOAEL was 2,000 ppm (4.5 mg/L).

Test data clearly demonstrate that isobutylene is not mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies. Isobutylene was not mutagenic when tested in reverse mutation assays conducted in *Salmonella typhimurium* and *Escherischia coli* either in the presence or absence of metabolic activation. Isobutylene did not increase the number of transformed foci in C3H/10T1/2 clone 8 mouse embryo fibroblast cells. There was no evidence of mutagenic activity in mouse lymphoma L5178Y cells either in the presence or absence of metabolic activation. In addition, isobutylene did not induce an increase in micronuclei formation in mouse bone marrow cells from animals exposed up to 10,000 ppm.

In a prenatal developmental toxicity study, inhalation exposure of pregnant Wistar rats to isobutylene on days 5 to 21 (inclusive) of gestation elicited no maternal toxicity at all tested concentrations up to 8,000 ppm. There was no effect of isobutylene on the number, growth or survival of the fetuses *in utero* and no adverse effects on fetal development. These findings, along with the with findings of no biologically significant effects on male or female reproductive organs attributed to isobutylene exposure in 14-week repeat dose inhalation studies in two rodent species, leads to a conclusion of low concern for reproductive toxicity.

Environment

Isobutylene is a flammable gas with a reported vapour pressure of 2,9732 hPa (25 °C); a water solubility of 263 mg/l (25 °C), a log K_{ow} of 2.34, a melting point of –140.4°C, a boiling point of –6.9°C and a density of 0.588 g/cm^3 (25°C).

Results of distribution modelling show that isobutylene will partition primarily to the air compartment (99.99%), with a negligible amount partitioning to water (0.01%). In spite of its water solubility, wet deposition of isobutylene is not likely to play a significant role in its atmospheric fate because of rapid photodegradation. Volatilisation to the air will contribute to the rapid loss of isobutylene from aqueous and terrestrial habitats. In the air, isobutylene has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals and ozone with calculated degradation half-lives ranging from approximately 2 to 8 and 25 hours, respectively, depending on hydroxyl radical and ozone concentrations. Aqueous photolysis and hydrolysis will not contribute to the transformation of isobutylene in aquatic environments because it is either poorly or not susceptible to these reactions.

The photochemical ozone creation potential index for isobutylene has been reported to range from 62.7 to 70.3. Because of the relatively short half-life of isobutylene in the atmosphere and the low environmental concentrations typically found, its contribution to potential global warming can be considered minor. The ozone depletion potential of this substance is negligible.

Isobutylene concentrations have been reported to range in urban air samples ranging from 1 to 10 ppb.

Although the biodegradability of isobutylene has not been evaluated, studies have demonstrated that 1-butene can be degraded by bacteria isolated from soil and surface water samples. The results from these studies suggest that isobutylene may also be subject to microbial degradation because of the similarity between these two aliphatic alkenes. However, biodegradation is unlikely to contribute to the overall degradation of isobutylene in the environment because it is a gas. Isobutylene is not expected to sorb significantly to organic matter in soil, sediment, and wastewater solids based on a log K_{oc} of 1.55.

Due to the fact that isobutylene is a gas at ambient temperature and pressure and is expected to partition predominantly to the atmosphere, no aquatic toxicity testing has been conducted. The ECOSAR model was used to predict aquatic toxicity using the equation for neutral organics, a reliable estimation method for this class of substance. Calculated acute toxicity values for fish and invertebrates are 19.9 and 21.9 mg/L, respectively. For algae, the calculated 96-hr EC50 is 13.9 mg/L. Chronic toxicity values of 2.7, 1.3, and 1.7 mg/L are calculated for fish (based on survival/growth), invertebrates (based on survival/reproduction), and algae (based on growth), respectively. Isobutylene has a low potential to bioaccumulate in aquatic species based on a calculated bioconcentration factor of 12.6.

A calculated 14-day LC_{50} value of 271.2 mg/kg soil has been calculated for an earthworm.

Exposure

Worldwide isobutylene production from all sources exceeds 10,000 kilotonnes/year. Approximate production volumes are reported for Japan, 1,000 kilotonnes/year, Western Europe, 995 kilotonnes/year, and the United States, 8,300 kilotonnes/year.
Isobutylene is a component of natural gas and crude oil and is used as a chemical intermediate. Although isobutylene has been identified in natural environments, this has traditionally been associated with losses from petrogenic sources resulting from offgassing or venting. Anthropogenic sources of isobutylene can result from combustion of fossil fuels and losses from gas plants and refineries.

Exposure to isobutylene may occur at workplaces where it is manufactured. Based on physical properties, the primary workplace exposure would be by inhalation. No consumer exposure is foreseen because there are no direct sales to consumers.

RECOMMENDATION

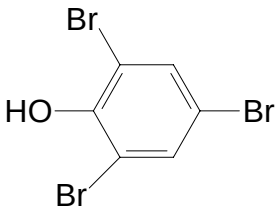
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:
The chemical may possess properties indicating a hazard for human health (carcinogenicity, although it is unknown if the findings related to carcinogenicity are of relevance to humans). Based on data presented by the sponsor country, exposure to human 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 suggesting a hazard for the environment. Although this does not warrant further work (as it is related to acute aquatic toxicity which may become evident only at very high exposure levels), it should nevertheless be noted by chemical safety professionals and other users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	118-79-6
Chemical Name	2,4,6-tribromophenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

2,4,6-Tribromophenol is rapidly absorbed from the gastro-intestinal tract and is rapidly excreted via urine and feces.

The acute oral LD_{50} in rats is 1,486 mg/kg bw. The acute inhalation LC_{50} in rats is greater than 50,000 mg/m^3. The acute dermal LD_{50} in rats is greater than 2,000 mg/kg bw.
This substance is considered to be non-irritating to the skin, but irritating to the eye. This substance is considered to be a sensitiser in guinea pigs.

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] was conducted in SD rats administered by gavage at the doses of 0 (vehicle), 100, 300 and 1,000 mg/kg/day. At 1,000 mg/kg/day, body weight gain suppression, and increase of absolute and relative liver weight were observed in both sexes and increases of total protein, albumin, A/G and ALP in blood were observed in male rats. At 300 mg/kg/day, salivation was observed in both sexes and increase in blood creatinine was observed in male rats. The NOAEL for the repeat dose toxicity is considered to be 100 mg/kg/day in rats of both sexes.

Two independent *in vitro* gene mutation studies in bacteria [OECD TG 471] were negative. One *in vitro* chromosomal aberration test [OECD TG 473] was positive with and without metabolic activation. In one *in vivo* micronucleus assay up to MTD (maximum tolerance dose) [OECD TG 474] by intraperitoneal injection, no evidence of genotoxicity was observed.

In the above described combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], SD (Crj: CD) rats received gavage doses of 0 (vehicle), 100, 300 and 1,000 mg/kg/day. No adverse effects were observed on estrous cycle, copulation index, fertility index and duration of gestation period, number of corpora lutea, and delivery findings as well as number of implants, number of total pups and live pups born, implantation index and delivery index in any of the substance-treated groups. Neonatal viability on day 4 of lactation and neonatal body weights on days 0 and 4 of lactation in the 1,000 mg/kg/day group were lower than those in the control group (about 50% for neonatal viability in the treated group). In maternal animals at the same dose, body weight was reduced by about 8 % and liver weight was increased by about 15 %. In conclusion, the oral NOAEL for reproduction/developmental toxicity is considered to be 300 mg/kg/day.

Environment

2,4,6-Tribromophenol is a white to almost white crystalline powder, which is slightly soluble in water (59 mg/L at 25 °C). Melting point, boiling point, vapour pressure, and partition coefficient are 93.9 °C, 244 °C, 0.042 Pa (25 °C), and log Kow = 3.89 (25 °C), respectively. This substance is abiotically not hydrolyzed regardless of the pH. Direct photolysis by UV indicated a half-life of 4.6 hours. This substance is biodegradable (BOD = 49 % after 28 days) [similar to OECD TG 301C] and the most conservative measured bioconcentration factor in fish is BCF = 513. A Mackay level III fugacity model shows that if this substance is released to water and soil, it is unlikely to be distributed into other compartments. When this substance is released to air, 29.2 % stays in air and 21.4 % is transported to water and 47.8 % is transported to soil.

This substance has been tested using aquatic species (algae, invertebrates and fish). An acute toxicity test with algae (*Selenastrum capricornutum*), resulted in a 72-h EC_{50} and a 72-h NOEC (biomass) of 0.76 and 0.22 mg/L, and a 24-72h EC_{50} and a 24-72h NOEC (growth rate) of 1.6 and 1.0 mg/L, respectively [OECD TG 201]. A 48-h EC_{50} for daphnids (*Daphnia magna*) was 0.26 mg/L [OECD TG 202 part 1]. A 96-h LC_{50} for fish (*Cyprinus carpio*) was 1.1 mg/L [OECD TG 203]. A chronic toxicity test was performed with daphnids (*Daphnia magna*) [OECD TG 211]. The 21-d NOEC for reproduction was reported to be 0.1 mg/L. A test with protozoae (*Tetrahymena pyriformis*) was performed and a 60h-IGC50 (50%inhibitory growth concentration) of 2.95 mg/l was reported.

Exposure

The production volume of 2,4,6-tribromophenol was estimated at approximately 2,500 t/year in Japan and 9,500 t/year worldwide in 2001. This substance is industrially produced in a closed system in Japan. This substance is used almost entirely as a chemical intermediate to make a flame retardant or directly as a flame retardant. The way to use this substance as a flame retardant is called "capping" i.e. the terminal -OH group of a polymer is

capped with 2,4,6-tribromophenol. The reaction occurs during polymerization of oxirane to form 2,4,6-tribromophenoxy-ether. Consequently, the resulting polymer becomes flame retardant/resistant. From the use pattern of the substance, it has been suggested that it is released to the environment through various waste streams. There are some available monitoring data on environmental concentrations of this substance in Japan and over the world. The causes are ascribed to the fact that this substance is known to occur naturally through biosynthesis by benthic animals along with various bromophenols. The intake of this substance by food and water may happen because of the indirect exposure.

During production and use of this substance, occupational exposure is possible by inhalation and by the dermal routes. The workplace exposures during manufacturing processes are controlled. This chemical is normally transported from the producer to the downstream user in form of pellets in Japan. Workers normally wear protective gear such as masks, rubber gloves and goggles to prevent exposure.

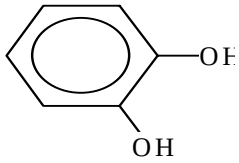
RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for the human health (sensitisation, irritation and uncertainty regarding reproductive toxicity in a screening test) and the environment. It is recommended to investigate the industrial exposure in down stream application and the possible use as a germicide. If necessary a risk assessment should be performed. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	120-80-9
Chemical Name	1,2-Dihydroxybenzene (pyrocatechol, catechol),
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Catechol is absorbed by oral and dermal route as well as by the respiratory tract. A part of catechol is metabolized to o-benzoquinone by enzymatic oxidation. After oral administration catechol is conjugated with glucuronic acid and sulfuric acid and eliminated mainly and rapidly via urine.
The acute oral toxicity by gavage in rats is: LD50 = 300 mg/kg bw. The body weight gain increased and the animals that died during the observation period revealed hyperaemia of the stomach and intestine. In an acute inhalation study with rats the LC0 value was ≥ 2.8 mg/L, signs of intoxication observed were irritation and persisting tremors. Loss of distal portions of the tail and digits at doses of 2.8 mg/L and 2.0 mg/L were dose-related. The dermal acute toxicity is moderate: LD_{50} in rats is 600 mg/kg bw.

Catechol produced slight to moderate erythema and slight oedema after 24 hours on the intact skin of rabbits, and was highly irritating to the eyes of rabbits. An epidemiology study on human workers exposed to catechol and phenol vapors, indicated irritation for the respiratory tract (cough, sputa, throats). Skin sensitisation tests with guinea pigs were positive.

None of the available publication on repeated dose toxicity was reliable. However, the carcinogenicity studies allow an estimation of the toxicity level after prolonged exposure. No clinical abnormalities or deaths related to catechol were observed during exposure via the diet, (in contrast to acute gavage). Body weight gain was clearly delayed (about 15%) in male rats exposed to 0.8% (318 mg/kg bw/day) catechol from week 1 to the termination (week 34 or 104) but not in those given 0.4% (141 mg/kg bw/day) or less. Slight thickening of the pyloric region was apparent in the 0.8% and 0.4% groups at week 34. Marked to moderate thickening was also found in rats fed 0.2% (65 mg/kg bw/day) and above, at the end of the study. Other gross lesions observed in the present study were considered to be of spontaneous nature and typical of this strain of rat. The NOAEL can be estimated to be 0.1% (33 mg/kg bw/day) at 34 weeks and LOAEL = 0.1% (33 mg/kg bw/day) at 104 weeks. Another study with male and female rats by oral feeding during 104 weeks at 0.8% indicated no differences between both sexes.

Regarding genetic toxicity with catechol *in vitro*, 8 reverse mutation assays with *Salmonella typhimurium* were negative with and without metabolic activation. In one mutoxitest with *Escherichia coli*, a positive result was obtained without metabolic activation and the result was negative with metabolic activation. Addition of metabolic activation completely inhibited the mutagenesis of catechol. Four gene mutation assays in cultured mammalian cells without metabolic activation were positive. . In chromosome aberration assays *in vitro*, catechol induced positive results without metabolic activation, and with S9 the toxicity of catechol was decreased. *In vitro* tests on damaging effects of catechol were positive only without metabolic activation in different cell lines. Positive results were obtained in a Sister chromatid exchange assay, without metabolic activation, at concentrations that were not cytotoxic (10 and 30

µM). Additional testing on cell transformation *in vitro* indicated that catechol at the concentration levels of 1 and 3 µM may induce morphological transformation in Syrian Hamster Embryo. An *in vivo* genetic toxicity spot test in mice was negative. *In vivo* micronucleus assays with mice were positive, indicating that administration of catechol at doses of 40 mg/kg by gavage and by intraperitoneal route at 10, 20, and 30 mg/kg bw induced chromosomal aberrations.
Results from an i*n vivo* replicative DNA synthesis test were positive. Two UDS tests gave opposite results and a test on DNA breaks was negative. In conclusion, *in vitro* tests were positive without metabolic activation and negative with metabolic activation, indicating ambiguous results concerning the mutagenic potential of catechol. *In vivo*, a positive micronucleus assay with mice, and a replicative DNA synthesis test indicated a potentially mutagenic effect of catechol.

Regarding carcinogenicity, several studies by oral route reported catechol to induce positive responses in rat stomachs. Tumours are mainly caused by local irritation, inflammation, and ulceration leading to regenerative hyperplasia. Only studies by the oral route are available, but concerns for carcinogenicity at other sites of first contact cannot be dismissed.
At low levels of catechol no promoting effects were described, probably because any hydroxyl radicals, formed by oxidation-reduction cycles through metabolism, are detoxified and there is no cytotoxicity and therefore, no increase in cell duplication. Carcinogenic responses of catechol occur, at a high dose (0.8%), at cytotoxic effects, leading in turn to inflammatory responses, increased DNA synthesis and cell duplication rates. Overall, these phenomena might select cells with altered gene structure, typical of neoplasia, generally in the point of application of the substance (forestomach in rats). In conclusion catechol can be considered as an animal carcinogen at high doses while it is not at low doses. Although there is some evidence that catechol is mutagenic, the exact mechanism of carcinogenicity is uncertain; however results of carcinogenicity studies tend to indicate that catechol acts by a non-genotoxic mechanism as there seems to be a threshold level.

No studies were performed to assess the effect of catechol on fertility. In the carcinogenicity studies where reproductive organs were examined, no lesions, no alteration or abnormalities were described after long term exposure (34 and 104 week) at concentrations of 0.1, 0.2, 0.4, 0.8% (respectively 33, 65, 141, 318 mg/kg bw/day).
In one developmental study with rats, one generation, with a single day administration by gavage at the 11^{th} day of gestation , maternal toxicity was described at each dose tested (333, 667, 1000 mg/kg bw) by reducing body weight gains. Mortality in the dams at 1000 mg/kg was 67%. Litter size decreased at 667 mg/kg bw in postnatal day 6 and at 1000 mg/kg in postnatal day 1. Litter biomass decreased in postnatal day 1 at 667 mg/kg bw. A syndrome of malformation involving the limb, tail and urogenital system was observed. The litter incidence regarding hindlimb paralysis and/or short kinky tails was 21.4%, 66.7% and 80.0% for 333, 667 and 1000 mg/kg respectively.
As this study is not a standardized study (single day administration) and it is the only one available for catechol, analogy with a parent product, hydroquinone (para-diphenol), presenting similar antioxidant properties, similar metabolism, and a similar toxicological profile, was used. In a developmental toxicity study with hydroquinone, doses up to 300 mg/kg were given to pregnant rats during organogenesis. Hydroquinone was not selectively toxic to the developing conceptus. The NOEL for both maternal and developmental toxicity was 100 mg/kg bw, based, in the 300 mg/kg group, on a decrease in body weight gain and feed consumption in dams and on an increase in the incidence of total common vertebral variations in foetuses.

Neurotoxicity was studied with application of catechol on the external surface of an isolated dorsal root ganglion cell of American bull frog. Catechol inhibited specifically fast K+ current, but not the slow Ca+, Na+ currents. The ED50 for the prolongation of action potential was estimated from Lineweaver-Burk and Eadie-Hofsee plots of the data to be about 71.6 mg/L
In an immunotoxicity test, catechol was reported to inhibit the mitogenesis of B-cells in a dose dependent manner, and cytotoxicity was observed on T-cells.
Studies on hematotoxicity of Catechol reported effects on hematopoietic and human blood cell.
In *in vitro* hepatotoxicity studies, no influence of catechol was observed on cytochrome P450 of rats and on human liver microsomes at a dose of 110 mg/L.

Environment

Catechol has a low vapor pressure (0.03 hPa at 25 °C) and a high water solubility (median value of 449 g/l at 20°C).

Since it has a pKa of 9.23, catechol reactivity and transfer between environmental compartments could be affected by pH. The measured log Kow is 0.84-1.01 at 20°C.

According to the Mackay level I model, the preferred targeted compartment of catechol will be water (99.2%). Based on its vapor pressure and its Henry's law constant ($7.35\ 10^{-4}$ $Pa.m^3.mol^{-1}$), catechol is expected to have a low volatility from dry soil surfaces and aqueous media. Removal of catechol from surface water by means of photodegradation should not be expected for the non-ionized form, whereas it could occur for the ionized form (absorption maximum at 313 nm in basic solution). Atmospheric oxidation half-life has been estimated by QSAR to be 0.6 days. Hydrolysis is not expected to occur: phenols are generally resistant to hydrolysis. Catechol has shown a high potential to polymerize with humic acids present in soil; the polymers formed were highly stable. In a clay loam soil, catechol has been found to be very mobile.

Biodegradation studies have shown that catechol was readily biodegradable in aerobic conditions. In anaerobic conditions, biodegradation is also possible. With an estimated bioconcentration factor of 3, catechol is not expected to bioconcentrate in aquatic organisms.

In acute aquatic toxicity studies, the lowest EC/LC_{50} values were 8.9 mg/L (96 h) for freshwater fish, 1.7 mg/L (24 h) for *Daphnia magna*, 22 mg/L (96 h) for algae and 19.6 mg/L (48 h) for micro-organisms. No chronic toxicity tests were performed with aquatic organisms. This leads to a derived PNECaqua of 1.7 µg/L, using an assessment factor of 1000.

Exposure

The production volume in the Sponsor country is 10 000- 50 000 metric tonnes/year.

The principal use of catechol is as an intermediate for chemical synthesis for 97%, 3% is used as an etching agent in the electronic engineering industry. Use of catechol in leather industry is only suspected but as the consortium does not sell the substance to leather industry, this information is not verifiable.
Occupational exposure can occur at production (during sampling, conditioning, during operations on the machine making flakes), at processing (chemical or electronic industries); monitoring data are not available, but as appropriate occupational hygiene practices are used, including personal protective equipment, occupational exposure is kept as minimal as possible. Knowledge of production and processing schemes suggests that the final marketed products (aroma products, agrochemicals and pharmaceuticals) do not contain catechol. Therefore, consumer exposure is not expected.
From catechol chemical industry, environmental exposure would be from production and processing. At the production site, the effluents, containing about 500 ppm of catechol, are driven to a biological waste water treatment plant (Consortium companies, internal data). No measurements have been performed in the STP effluent. Based on its biodegradability, a model estimate indicates that 87% is removed during waste water treatment.
In electronic industry, for surface treatment, given the potential toxicity of other treatment products, the effluents are expected to be all collected and destroyed in the Sponsor country (Lead company, internal data).
Human exposure via the environment is expected to be low since catechol is readily biodegradable and non bioaccumulative.

RECOMMENDATION

The chemical is currently of low priority for further work

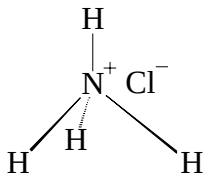
RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health :
The chemical possesses properties (irritant, skin sensitizing agent, anti-oxidant, mutagenic, carcinogenic at high dose levels and possibly developmental toxicant) indicating a hazard for human health. 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 possesses properties indicating a hazard for aquatic organisms. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at a high exposure level, it should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	12125-02-9
Chemical Name	ammonium chloride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The toxicity of ammonium chloride depends on ammonia which enters the living organism and thence the cell. This substance is readily absorbed by the gastrointestinal tract, and utilized in the liver to form amino acids and proteins.

The acute oral LD_{50} was 1,630 mg bw/kg in male rats and 1,220 mg/kg bw in female rats. The acute oral LD_{50} was 1,300 mg/kg bw in male mice. No data for inhalation and dermal acute toxicity are available.
This substance is considered to be moderately irritant to the skin and eye. In a study on sensitization, ten percent of the animals of a treatment group demonstrated a positive reaction after the challenge exposure (below the limit value of 30 percent). The study showed that the substance had no sensitising potential.

A repeated dose toxicity study was conducted using Sprague-Dawley rats (10 males/group) fed a diet containing this substance at 684 mg/kg bw/day (12,300 ppm) for 70 days. This substance had no effect on clinical signs, body weights, food consumption or necropsy findings. The urine pH was approximately 6.0 compared to a pH of 7.56 or greater in the control group, and the concentration of urinary calcium was increased. However no crystals were found in the urine. The other urinary chemistries (the concentration of magnesium, creatinine, phosphate, protein, and osmolality) were unchanged. Also no histopathological changes ascribable to this substance were found. The NOAEL for oral repeated dose toxicity is considered to be 684 mg/kg bw/day (12,300 ppm) in male rats. No data on repeated dose toxicity by inhalation and dermal exposure are available.

A reverse mutation study in bacteria [OECD TG 471] gave negative result. An *in vitro* chromosomal aberration test with Chinese hamster lung cells (CHL/IU) without metabolic activation was positive. This result is ascribable to the acidity of this substance. An *in vivo* micronucleus assay up to the maximum tolerance dose was negative. Based on the weight of evidence, this substance is considered to be not genotoxic.

Sprague-Dawley rats were administered 1 mL/kg bw of a solution at 1/6 M (8.9 mg/kg bw/day) by gavage on days 7 to 10 of gestation. Neither maternal toxicity nor developmental toxicity including teratogenicity was found.

There are three studies in which this substance was tested for carcinogenicity and for promotion effect on the initiator-induced carcinogenesis in the urinary system. These studies showed negative results on carcinogenicity of this substance in rats and mice.

Environment

Ammonium chloride is highly soluble in water and is dissociated to its respective ions (283 g/L at 25 °C).

Depending on pH and temperature of water, these ions exist in the following equilibrium, $NH_4^+ + Cl^- + H_2O \Leftrightarrow H_3O^+ + Cl^- + NH_3 \Leftrightarrow HCl + NH_4^+ + OH^-$. Melting point, boiling point, and vapour pressure are 338 °C (decomposition), 520 °C (sublimation), and 0.0065 Pa at 35 °C, respectively. That indicates that this substance released into the environment is distributed into the water compartment in the form of ammonium ion and chloride ion. This substance is not expected to be adsorbed in soil. It is subjected to ion exchange to form inorganic or organic salts with other counter ions in soil and water. It is known that ammonia (NH_3 or NH_4^+) is easily mineralized to nitrite (NO_2^-) by numerous species of bacteria. This substance is not expected to undergo photolysis. The fugacity model cannot be applied to estimate the distribution of this substance in environment because this substance is beyond the application limit of these models. Based on its physical-chemical properties, it can be assumed that water is the preferred compartment of the substance. Considering its propertiesit is not likely to accumulate in living organisms.

This substance has been tested in aquatic species (algae, invertebrates and fish). An acute growth inhibition test for algae was performed using algae (*Chlorella vulgaris*). The EC_{50} (biomass; 0-5 d) was 1,300 mg/L. An acute toxicity test with daphnids (*Daphnia magna*) and bivalves (*Mulinia lateralis*) reported results of 101 mg/L (survival; 48-h LC_{50}) and 42.0 mg/L (growth weight; 10-d EC_{50}), respectively. The 96-h LC_{50}s using various kinds of fish were in a range of 96.2 [the lowest; fathead minnow (*Pimephales promelas*)] to 218 mg/L. The lowest acute toxicity value of this substance was 42.0 mg/L (10-d EC_{50} for bivalves). A chronic test for algae was performed using *Navicula sp*. The NOEC (growth rate; 0-10 d) was 26.8 mg/L. A chronic reproduction toxicity test was performed using daphnids (*Daphnia magna*). The 21-d NOEC was 14.6 mg/L. And NOECs from 28-d and 44-d chronic tests for fish were in a range of 8.0 to 23.9 mg/L. The lowest chronic toxicity value of this substance was reported for a marine fish, inland silverside (*Menidia beryllina*) to be 8.0 mg/L for 28-d NOEC.
In soil organisms, a LC_{50} for earthworms (*Eisenia fetida)* was reported to be 163 mg/kg. As a conclusion of effect in the environmental organism, effects are rather mild and transient.

Exposure

The production volume of ammonium chloride in Japan was 85,600 tons in 2001. In Europe, the same range of production volume as in Japan is estimated and in the U.S., a production volume of 10,000 – 50,000 tonnes per year is presumed. This substance is mainly used (approximately 70%) as a fertilizer for water paddies in Japan. This substance is also used as an electrolyte for dry cell batteries, flux agent for coating sheet iron with zinc, agents for tinning, food additives, therapeutic drugs etc. In the U.S., this substance is mainly used as a feed additive to prevent the formation of calculi for cattle. This substance has been ingested for a long time by humans. This substance can be added directly to human food in the U.S. and is Generally Recognized As Safe (GRAS) [US FDA]. Bottled water containing this substance as chloride up to 250.0 mg/L is allowed as potable [US Federal Food, Drug and Cosmetic Act]. This substance is approved as drug in several countries for electrolyte replenishment or expectorants and as food additive (fermentation and blowing agent) without use restrictions in Japan. This substance is also used as food additive (flavors) in Germany. This substance has been available as a therapeutic agent in Canada since its introduction in 1925. It has been used as a mild diuretic, an expectorant, a weight-reducing agent and a urine-acidifying agent.
This substance released into the environment is distributed into the water compartment in the form of ammonium ion and chloride ion, and exposure to aquatic biota is possible. Occupational exposure is possible by inhalation (as dust) and dermal routes. In the case, the workers wear protective equipments. Consumer exposure is also possible by inhalation (as dust) and dermal routes. It should be noted that the use of ammonium chloride as a fertiliser may cause a concern when assessing the potential eutrophication hazard including drinking water quality in certain regions.

RECOMMENDATION

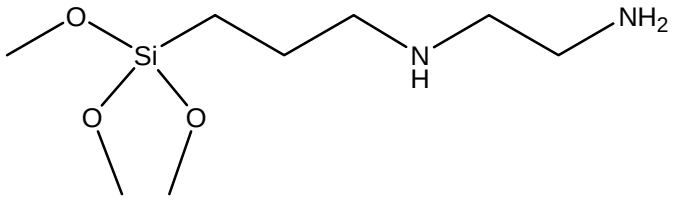
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health (acute toxicity and irritation) and the environment. Although the hazard do not warrant further work (as they are related to transient or non-lasting effects or to acute toxicity which may become evident only at very high exposure level), they should nevertheless be noted by chemical safety professionals and users.

Although the substance has a low inherent hazard potential for the environment, it degrades in the environment to nitrite. It is recommended that the use of ammonium chloride as a fertiliser is taken into account when assessing the exposure of nitrite and nitrate to humans through drinking water.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1760-24-3
Chemical Name	N-[3-(trimethoxysilyl)propyl]ethylenediamine (AEAPTMS)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute oral toxicity of N-[3-(trimethoxysilyl)propyl]ethylenediamine (AEAPTMS) is described by an LD50 in the rat of 2.4 g/kg. The dermal LD_{50} was 16 ml/kg in rabbits. In rabbits, AEAPTMS is moderately irritating to the skin and severely irritating to the eyes. AEAPTMS showed a skin sensitizing potential in a guinea pig maximization test.

AEAPTMS was tested in rats in a combined repeated dose toxicity test with a reproductive/developmental screening test, following the OECD test guideline 422 (28-39 days). Clinical findings attributed to the test substance included clear perioral soiling in several high dose animals and either increased nasal sounds, labored respiration, or soft vocalizations in approximately half of the high dose females and one high dose male. These signs were not seen in the control animals and infrequently seen in either of the two lower dose groups. Observations recorded at dosing indicated a dose-related resistance to dosing. Evaluating all 30 animals/dose over the entire dosing period, the incidence of resistance was 3, 5, 27 and 62% for the controls, 25, 125 and 500 mg/kg bw/day dose groups, respectively. Similar incidence patterns were noted for salivation just prior to dosing, wetness around the mouth at dosing, and wetness around the mouth 5-30 minutes following dosing. These clinical findings are anticipated based on the amine-functionality of the material and indicative of irritation, rather than systemic effects. There were no test substance-related effects on body weight, organ weights or organ-to-body weight ratios, food consumption, FOB or motor activity parameters, or hematology or serum chemistry parameters, and no macroscopic or microscopic findings were attributed to the test-substance. Based on the results of this study, the NOAEL for the systemic toxicity of this material in the rat via oral dosing for at least 28 consecutive days was considered to be 500 mg/kg bw/day.

AEAPTMS has been tested in an Ames test, an *in vitro* Chinese hamster ovary cell HGPRT assay and sister chromatid exchange assay, and an *in vivo* mouse micronucleus assay. These *in vivo* and *in vitro* screening assays have not revealed any evidence of genotoxic potential of AEAPTMS.

Rats exposed to AEAPTMS by gavage to doses of 0, 25, 125, and 500 mg/kg bw/day, as part of an OECD guideline 422 study, no test substance-related effects were observed in any of the reproductive parameters evaluated. Based on the results of this reproductive/developmental screening study, the NOAEL for maternal (systemic toxicity) and developmental toxicity of AEAPTMS in the rat via the oral dosing was 500 mg/kg bw/day (the highest dose tested).

Environment

The vapor pressure is 0.002 hPa at 20 °C, the melting point is -38 °C and the boiling point is 264 °C at 1013 hPa.

The estimated partition coefficient LogKow is 1.67 and the estimated water solubility is $1x10^6$ mg/l; these values may not be applicable because the material is hydrolytically unstable. The half-life in the atmosphere due to the reaction with photochemically induced OH radicals is estimated to be approximately one hour. However, photodegradation as a mode of removal is unlikely because AEAPTMS is hydrolytically unstable. 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.

AEAPTMS is hydrolytically unstable ($t_{1/2}$ < 1 hour) over a range of environmentally relevant pH and temperature conditions. At pH 7, the half-life = 0.025 hours. Rapid hydrolysis of this material produces methanol and trisilanols. The Si-C bond will not further hydrolyze. That bond is hydrolytically stable and the aminopropyl group will not cleave. Only the methoxy groups will be hydrolyzed. The transient silanol groups will condense with other silanols to yield:

$NH_2CH_2CH_2NHCH_2CH_2CH_2$–Si $(OR)_3$ type resins where R = H or $Si(CH_2CH_2CH_2NHCH_2CH_2NH_2)(OR)_2$

Hydrolytically stable bond

As a result, aminoethylaminopropyl-functional resins are generated. The EQC Level III model was used to evaluate the fate, transport and distribution of AEAPTMS between environmental matrices. 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 AEAPTMS: air = 31.3%; soil = 63.6%; water = 5.2 %; sediment = 0.00 %. However, AEAPTMS is unlikely to be found in the environment, as this material is hydrolytically unstable. AEAPTMS is not readily biodegradable, the observed biodegradation (39% after 28 days) is of the hydrolysis products (methanol and trisilanols). The rapid hydrolysis of AEAPTMS means that it is unlikely to be present in the environment. Bioaccumulation is not anticipated since this material is hydrolytically unstable.

In spill conditions, the concentration of the parent silane is very high. The silanol concentration could also be high; however, the silanol rapidly self-condenses to form water insoluble, resinous oligomers and polymers. The molecular weight of the resulting oligomers and polymers is predicted to be over 1000. Anecdotal evidence suggests the molecular weight of the polymers resulting from spills is 5000 – 10000. As the parent silane and the resulting silanol are diluted, it is predicted that the polymers resulting from condensation will be of lower molecular weight. At sufficiently low silanol concentrations, low MW oligomers are favored. It is calculated that at 1000 ppm of a related trialkoxysilane, the equilibrium concentration will be 86% silanol monomer and 14% silanol dimer. At still lower concentrations, the silanol will exist as the uncondensed monomer. These polymers will not be bioavailable. However, such materials are likely to cause toxicity in aquatic species due to physical effects (encapsulation, blockage of gills). The 96-hour LC50 of AEAPTMS for three species of freshwater fish (*Lepomis macrochirus*, *Oncorhynchus mykiss* and *Pimephales promelas*) is greater than 100 mg/L. The 48 hour EC50 is 90 mg/L for the water flea (*Daphnia magna*). The EC50s for freshwater green algae *Selenastrum capricornutum* (green algae) are 5.5 mg/l for the 72-hour EbC50 and 8.8 mg/l for the 72-hour ErC50. Since AEAPTMS is sensitive to hydrolysis, which may occur during preparation of the dosing solutions and/or during the testing, the observed toxicity is likely due to the hydrolysis products methanol and trisilanols.

Exposure

The commercial uses of this material include various applications such as coupling agents and adhesion promoters in fiberglass, adhesives and sealants, foundry resins, and in pre-treatment for coatings. 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 pipes rather than in open systems to minimize loss of this material (hydrolysis) although some customers do transfer the material in open systems. AEAPTES is transported from the production site as the parent silane to processors/formulators. Generally, AEAPTMS is used by the processor/formulator at levels <1%. In some applications, AEAPTMS is used as a crosslinker; these use levels are higher and can approach 3 to 5 %. Once AEAPTMS is added to a consumer or industrial product, the parent silane reacts with the components of the formulation and is generally present as the parent silane at 0.1-0.2% until after

curing (use). After curing the parent silane is consumed into the polymer matrix and no longer exists, which greatly reduces the potential for consumer or worker exposure. AEAPTMS polymerizes during use. Consumer products will be labeled as containing a sensitizer according to individual member country regulations. Any toxicological effects originating from the alkoxysilane or amine groups of the silane are greatly reduced as a result of this coupling process. The annual production volume of AEAPTMS in the Sponsor country was 871 tonnes in 2002.

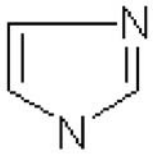
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health (skin sensitization and skin and eye irritation) and to the environment (acute toxicity to algae). Based on data presented by the Sponsor country, adequate risk management measures are being applied, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently a low priority for further work.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	288-32-4
Chemical Name	Imidazole
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Imidazole is readily absorbed and excreted in humans and in test animals after oral and rectal administration. Peak plasma levels are reached within 15 to 30 minutes in rats and within approx. 3 hours in humans. Elimination half-life in humans is approx. 2 to 3 hours. Therefore a potential for bioaccumulation is unlikely. Induction of microsomal P450 enzyme in the liver cells of rats and rabbits is restricted to certain isoenzymes such as 7-ethoxycoumarin-O-deethylase and isoenzyme 3a. However, no such induction was seen in the Syrian golden hamster.

Imidazole is of moderate oral toxicity in a scientifically valid study. LD_{50} in rats was determined to be 960-970 mg/kg body weight. 80% Imidazole is corrosive to skin under occlusive conditions. Imidazole is irritating to rabbit eye when tested according to OECD TG 405. Persistent large size cornea opacity indicates the potential of severe eye injury after eye contact. No sensitization study is available.

Liver and kidney are target organs in subacute and subchronic (OECD TG 408) rat studies at dose levels of 180 mg/kg body weight per day and above. Slight centrilobular liver cell hypertrophy and relative liver weight increase was noted. Diffuse α2u-microglobulin accumulation was noted in the proximal tubules of the renal cortex only in male rats but was considered to a species-specific effect. The NOAEL was approximately 60 mg/kg body weight per day. Red blood cells were additionally affected in 28-d experiments. Female rats receiving 125 mg/kg body weight per day or more and male rats receiving 500 mg/kg body weight per day were affected. The NOAEL was approximately 62.5 mg/kg body weight per day. This finding was, however, not confirmed in the 90-day guideline study when rats received up to 180 mg/kg body weight per day.

Imidazole was not mutagenic in bacterial test systems generally meeting OECD TG 471 with the Salmonella typhimurium strains TA 98, TA 100, TA 1535, or TA 1537, with or without the presence of metabolic activation by S-9 mix containing rat liver microsomes, with or without preincubation. Imidazol did not induce Unscheduled DNA Synthesis in rat primary hepatocytes in a study equivalent to the OCED TG 482. It was not clastogenic in the mouse micronucleus test according to the OECD TG 474 when imidazole hydrochloride was tested in vivo. The salt dissociates into protonated imidazole and chloride in the stomach following oral gavage.

No reproductive toxicity studies are available. However, no changes of the male and female reproductive organs including sperm quality were noted in a rat subchronic 3-months study according to OECD TG 408 imidazole was given by gavage at 20, 60, and 180 mg/kg bodyweight per day.. The NOAEL for these endpoints was 180 mg/kg body weight per day. In a study conducted in accordance to OECD TG 414 imidazole was developmental toxic and teratogenic at a dose of 180 mg/kg body weight per day showing some maternal toxic effects which is not likely to be the sole cause of the teratogenic effect. The incidence of external and skeletal malformations were significantly increased up to 10%. Furthermore there were soft tissue variations observed. The NOAEL was 60 mg/kg body weight per day for maternal toxicity, developmental toxicity, and teratogenicity.

No studies concerning the long-term toxicity and/or carcinogenic potential of Imidazole are available. It is, however, mentioned that imidazole was negative in the mouse fibroblast cell transformation test.

Environment

Imidazole is a colourless – yellow solid with an amine-like odour. It has a water solubility of 663 g/l at 20 °C (pH 10.5 for 68 g/l at 20 °C). Imidazole is a heterocyclic compound containing two nitrogens with pK_a = 7.0 and pK_a =14.9. The melting point ranges from 88.3 to 89.9 °C, the boiling point is at 267.8 °C at 1013.3 hPa and the vapour pressure is 0.00327 hPa at 25°C.
The distribution of the substance between the compartments of air, biota, sediment, soil and water was calculated according to Mackay Level I fugacity model. The non-charged molecule distributes mainly to the water (99.98 %).
A soil adsorption coefficient (K_{oc}) of 9.72 was estimated for imidazole. This K_{oc} value suggests that this compound would be mobile in soil and adsorption to suspended solids would not be important. From the pK_a-value of 14.9 it can be assumed that under environmental conditions the substance is available as a cation. Therefore, binding of the substance to the matrix of soils with high capacities for cation exchange (e.g. clay) cannot be excluded. However, no data was available for ionic-ionic interactions in soil. The calculation of a Henry's law constant with the model HENRYWIN 3.1 yields a value of 0.38 Pa*m³/mol at 25 °C. Using the above described values for water solubility and vapor pressure, a Henry's law constant of 0.000034 Pa*m³/mol can be calculated. This low value and the water solubility of imidazole suggest that volatilization from water would not be an important fate process. Hydrolytic degradation is not to be expected under environmental conditions.
The half-life for photodegradation in air was calculated to be 10.7 hours. Half-lives for photolysis in water between 4.4 hours and 307 days have been reported dependant on OH concentrations and light intensity. The substance has no considerable potential for bioaccumulation (log K_{ow} = -0.02, measured). The compound is readily biodegradable (OECD 301 A, 98% after 18 days 10d-window fulfilled). The EC_{50} (30 min) for activated sludge was determined to be >1000 mg/L.
The following aquatic effect concentrations are available:
Leuciscus idus LC_{50} (48 h) = 284 mg/l (nominal concentration).
Daphnia magna: EC_{50} (48 h) = 341 mg/l (nominal concentration).
Scenedesmus subspicatus: E_rC_{50} (72h) = 133 mg/l, with a NOEC of 25 mg/l (corresponding values for biomass are 127 and 10 mg/l respectively; nominal concentration)
Pseudomonas putida EC_{50} (17 h) = 1175 mg/L (nominal concentration)
Tetrahymena pyriformis : IGC_{50} (48 h) = 680 mg/L (nominal concentration)
Although no analytical monitoring of the test substance concentration was performed, and the substance is subject to photolysis in water, it is assumed that the effect values will not be below 100 mg/l.
Using the aquatic toxic effect on the most sensitive species, *Scenedesmus subspicatus*, of 133 mg/l for endpoint growth rate (127 mg/l endpoint biomass) a PNECaqua of 133 µg/l is derived by applying an assessment factor of 1000 according to the EU Technical Guidance Document. This factor is justified, because only short-term toxicity values were available.

Exposure

In 2002, the estimates for imidazole for the world market amounted to approx. 1000– 5000 tonnes/year. The substance was not imported into the European Union in 2002.
The organic compound is used in the chemical industry as an intermediate in the production of pharmaceuticals, pesticides, dye intermediates, auxiliaries for textile dyeing and finishing, photographic chemicals and corrosion inhibitors.
The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Therefore, the bulk of imidazole produced is used in the preparation of biologically active compounds.
According to Swiss, Danish, Finnish, Swedish and French Product Registers imidazole is contained in a large number of products. Due to Swiss information consumer products contain imidazole in concentrations up to 10 %. Danish, Finnish, and Swedish Product Register did not confirm that information regarding consumer products.
There is a potential of releases into the environment during the production and processing of imidazole as an

intermediate, and – according to the cited applications in the European Product Registers – from the formulation, processing and use of products containing the substance. During production and internal processing, less than 5 kg/a were emitted into the air by the German producer. Monitoring data of the substance in the sewage and effluent of waste water treatment plants are not available. The exposure of workers at the German production and internal processing plants is controlled. Imidazol is produced under closed system conditions. Exposure measurements at workplace were in a range between 0.21 mg/m³ and 0.32 mg/m³. From the reported use in consumer products, it can be concluded that most of the imidazole is released into wastewater, but part of it may also be released into the atmosphere.

RECOMMENDATION

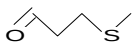
Human Health: The chemical is a candidate for further work.
Environment: The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:
The chemical possesses properties (corrosivity to skin, irreversible damage to eyes, teratogenic effects) indicating a hazard for human health. Humans are exposed by consumer products (chemical concentrations up to 10%) and at the workplace. Therefore, the chemical is a candidate for further work. An exposure assessment and if indicated a risk assessment is recommended.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3268-49-3
Chemical Name	3-(Methylthio) propionaldehyde
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

3-(Methylthio) propionaldehyde can readily be recognized by its characteristic odor. The odor threshold of 0.00036 mg/m^3 is very low compared to its toxicity.
No data on toxicokinetics are available.
The mode of action is in particular characterized by the local irritation potential of 3-(methylthio) propionaldehyde to skin and mucous membranes. With regard to respiratory irritation it is unclear from the existing studies whether the observed local effects in inhalation studies are attributable to 3-(methylthio) propionaldehyde or acrolein that can be enriched in the vapor phase under the test conditions. However, at up to 50 ml/m^3 no respiratory irritation was detected in a study with repeated exposure with acrolein-free 3-(methylthio) propionaldehyde. No consistent mode of action with regard to a possible systemic toxicity can be deduced from the toxicity studies conducted.
The 4-h LC50 for rats derived from studies following OECD TG 403 and GLP ranged from 4500 to 4800 mg/m^3 (1036 to 1105 ppm) for male rats and was > 4800 mg/m^3 (1105 ppm) for female rats. The dermal LD50 for rats derived from a study conducted similar to OECD TG 402 was 2631 mg/kg bw. In rabbits dermal toxicity determined in non-GLP studies either similar to OECD TG 402 or according to US EPA OPP 8-12 ranged from 748 to 1700 mg/kg bw. The oral LD50 obtained in a GLP study similar to OECD TG 401 was 490 mg/kg bw for male and 1050 mg/kg bw for female rats. The major effects are related to local irritation at the site of contact.
3-(Methylthio) propionaldehyde was a skin irritant in rabbits in a number of studies that did not fully comply with OECD TG 404 and induced irreversible damage to rabbit eyes in studies conducted similar to OECD TG 405.
3-(Methylthio) propionaldehyde revealed a skin sensitizing potential in guinea pig maximization tests following or similar to OECD TG 406.

Limited repeated dose studies by inhalative, dermal, and oral exposure are available.
Repeated exposure of Sprague-Dawley rats to 3-(methylthio) propionaldehyde vapor for 9 days in a GLP study following OECD TG 412 did not reveal any treatment-related toxicity up to the highest tested concentration of 216 mg/m^3 (50 ppm).
Dermal exposure of Sprague-Dawley rats for 9 days (6 h occluded exposure per day) resulted in a slight decrease in body weight gain at a dose of 527 mg/kg bw/d. The systemic NOAEL in this study was 211 mg/kg bw/d.
After 28 days oral administration of 3-(methylthio) propionaldehyde by gavage to Wistar rats in a study similar to OECD TG 407 3-(methylthio) propionaldehyde revealed a slight hemolytic effect with reduced red blood cell counts and hemoglobin levels, increases in blood bilirubin levels and indications of increased hematopoesis in the spleen at 521 mg/kg bw/d. The NOAEL was 104 mg/kg bw/d.
3-(Methylthio) propionaldehyde did not induce gene mutations in bacterial cells in a GLP test following OECD TG 471 and the mouse lymphoma TK+/- assay similar to OECD TG 476. However the mouse lymphoma TK+/- assay revealed an increase in mutations for sigma colonies indicative of a clastogenic effect in vitro in particular without S9 mix. With S9 mix significant increases in mutation rates were only observed at highly cytotoxic concentrations.
An inhalation mouse micronucleus study that suffered from a number of deficiencies and inconsistencies revealed an

equivocally positive result. In a valid i.p. mouse micronucleus study according to OECD TG 474 and GLP, 3-(methylthio) propionaldehyde showed a negative result, indicating that the possible clastogenesis observed in an *in vitro* study does not occur *in vivo*.

Data on fertility are not available. Limited information is available on effects on the gonads from studies with repeated exposure. Testes were examined in two studies, while ovaries were only examined in the 9-day inhalation study. In the 28-day oral study testes weights were determined and histological examination of the testes performed. In the 9-day inhalation study testes and ovaries were weighed and examined histologically. No effects on the sex organs of rats have been observed in these studies. Because of the almost exclusive use of the product as closed system intermediate with a very low exposure potential no further study for reproductive toxicity was conducted. Due to the use as isolated intermediate with controlled transport reduced SIDS testing for the endpoint fertility is considered appropriate for this chemical.
3-(Methylthio) propionaldehyde did not reveal any developmental toxicity in a study with Sprague-Dawley rats according to OECD guideline 414 and GLP by the inhalation route at exposure concentrations that were clearly maternally toxic. Signs of maternal toxicity included reduced body weight gain and food consumption in all dose groups. High dose group dams had additional red brown stains around the snout and the nose and showed lacrimation, labored breathing and closed eyes. Some high dose dams also had a mucoid nasal discharge, salivation and chromodacryorrhea. The NOAEL was 553 mg/m^3 (128 ppm), the highest concentration tested. Slight maternal toxicity was already observed at the lowest applied concentration of 43.2 mg/m^3 (10 ppm).

Environment

3-(Methylthio) propionaldehyde is a colorless to light yellow organic liquid with a water solubility of about 75 g/l at 20 °C, a melting point of -58°C, a boiling point of 170 °C at 1013 hPa, a vapor pressure of 0.53 hPa at 20 °C, a density of about 1.04 g/cm^3, and a measured log Kow of 0.34. The low octanol-water partition coefficient indicates a low potential for bio- or geoaccumulation. 3-(Methylthio) propionaldehyde is readily biodegradable (92 % after 28 days in a DOC-die away test) and undergoes hydrolytic degradation at pH 7 and 9 (half-lives of 75 and 6.5 days respectively). A photochemical degradation via oxidation by OH-radicals with estimated half-lives of about 7.3 hours in air and about 16 days in water takes place. The generic fugacity model level I indicates that 3-(methylthio) propionaldehyde is preferably distributed to the water phase (97.5 %) with a low amount distributing potentially into air (2.5 %).

Acute data for 3 trophic levels are available indicating similar sensitivity of the tested species. The 24 h LC50 for fish (*Brachydanio rerio*) was 14 mg/l, the 48 h EC50 for *Daphnia magna* 4.5 mg/l and the 72 h EC50 for algae (*Scenedesmus subspicatus*) was 5.7 mg/l with a NOEC of 1 mg/l (EbC50 = 2.1 mg/l, NOEC = 0.5 mg/l). This is also supported by QSAR estimations for the 96h LC50 for fish of 9 resp. 29 mg/l.
Based on the lowest EC_{50} for daphnia of 4.5 mg/l a PNEC of 4.5 µg/l can be derived using an assessment factor of 1000 according to the EU Technical Guidance Document.

Exposure

Worldwide production was estimated by the producers to be approximately 485,000 t in 2000.
The substance is almost exclusively used as an on-site and off-site intermediate with controlled transport by rail car or ship. A minor use of 3-(methylthio) propionaldehyde as a food flavoring agent has been identified.
The substance is not present in marketed preparations registered in the product registers of Switzerland, Sweden, Denmark, Finland and Norway
3-(Methylthio) propionaldehyde was quantified in a number of plant and aqueous animal species as well as in processed foods (4 - 40 µg/kg in plants, 1.1 – 167 µg/kg in crab meats, and 0.4 – 399 µg/kg in different foods). The use as a flavoring agent with amounts of 230 kg/a (Europe) and 130 kg/a (USA) as well as natural occurrence in plants, aquatic animal species and processed foods (estimated amount 637 kg/a) results in an estimated combined exposure of 1.5 µg/kg bw/d. Another minor use in probably low amounts as flavoring agent in tobacco products has been allocated.
Due to the almost exclusive use as industrial intermediate and the incineration or stripping of wastewater and

exhausts there is very little possibility for 3-(methylthio) propionaldehyde to enter the environment from production and use.
3-(Methylthio) propionaldehyde is produced and further reacted in closed systems. Only limited potential exposure may occur at the workplace. When used in chemical synthesis, the only process relevant for use, the substance is completely converted by reaction with hydrogen cyanide to produce intermediate products of the methionine process. Workplace exposure to humans is anticipated to be low, because exposure in occupational settings is well-controlled and because indirect exposure is low. Exposure measurements during production and use were all below 100 µg/m^3 (8 h TWA), or below detection limit.

RECOMMENDATION

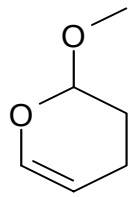
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:
The chemical possesses properties indicating a hazard for human health (skin sensitization, irritant effects on skin and respiratory system, irreversible damage to the eye). In the sponsor country the substance is only used as an isolated intermediate with controlled transport, exposure in occupational settings is well-controlled and indirect exposure is anticipated to be low. The use of the substance as food additive is regulated by food agencies of national governments. This use has been evaluated by JECFA and it was concluded, that based on a category approach using toxicological data of the analogue methylsulfide and intake figures from 2000 the use as a flavoring agent is of no safety concern for human health. Countries may wish to investigate any exposure scenarios that were not presented by the sponsor.

Environment:
The chemical possesses properties indicating a hazard for the environment. 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

CAS No.	4454-05-1
Chemical Name	3,4-Dihydro-2-methoxy-2H-pyran
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute oral LD_{50} for 3,4-dihydro-2-methoxy-2H-pyran (MDP) in the rat ranged between 1640 and 3740 mg/kg bw. Clinical symptoms included staggering and unsteady gait, lachrymation, apathy, laboured breathing and narcosis. The 4-hr-inhalation LC_{50} in rat was > 1310 ppm (> 6000 mg/m³) with transient signs of ocular and respiratory irritation. The dermal LD_{50} in rabbits was 4920 mg/kg bw. Toxicity of the technical product may be influenced by impurities such as acrolein (cf SIAR on acrolein).
Undiluted MDP was irritating to the skin and eyes of rabbits. In acute toxicity studies, high concentrations of vapors were also irritating to the eyes and the respiratory tract. No adequate sensitization data are available.

The main effects following repeated inhalation exposure to MDP in rodents were reduced body weights, sedation, and irritant effects on the respiratory tract. Toxicity may be largely influenced by the presence of toxic impurities, predominantly the highly toxic and irritant acrolein. The results from a limited 14-day repeated inhalation study did not permit the establishment of a NOAEC, since reductions in body weights and signs of respiratory irritation were still present at the lowest tested concentration in the rat (LOAEC: 100 ppm = 480 mg/m³). In mice, bone marrow cytotoxicity of questionable biological significance was still seen at 5 ppm (LOAEC, 5d: 5 ppm = 24 mg/m³). No systemic effects were found up to and including the highest tested dose level of 1000 mg/kg bw/day in a dermal study on rats, limited by its duration of only 14 days.

In vitro, MDP was mutagenic in bacterial and mammalian cell systems (Ames test, HPRT test). In two *in vivo* studies, both of which performed in accordance with contemporary requirements, MDP was not clastogenic in mice dosed by the oral route or repeatedly via inhalation.
There are no experimental data for MDP available for reproduction and developmental toxicity. Since exposure is anticipated to be very low due to its sole use as chemical intermediate with controlled transport to a limited number of locations and because acute and repeated dose toxicity studies are available for the most relevant routes of accidental exposure (inhalation, dermal), no animal tests were performed for these endpoints. No studies concerning the long-term toxicity and/or carcinogenicity of MDP have been conducted.

Environment

The flammable MDP is a colourless-yellowish liquid with an ether-like odour, with a solubility in water of 16 g/l at 25 °C, a density of 1.00 g/cm³ at 20 °C, a vapour pressure of 12.4 hPa at 20 °C and of 16.7 hPa at 25 °C. A Henry´s law constant of 31.2 Pa*m³/mol at 25 °C was calculated. Flash point, melting point and boiling point of the substance

are 22.8 °C, < –60 °C and 127.1 °C respectively. It is stable at neutral pH, but hydrolyzes at low pH to glutaraldehyde and methanol.
From the physico-chemical properties the compartments air (80.4 %), and to a minor degree water (19.5 %), are identified as target compartments for the substance. However, in air, MDP is expected to be quickly photodegraded by reaction with OH radicals with a half life of 4.5 h. For reaction with O_3 a half-life of 4.8 h can be calculated. The substance is not readily biodegradable according to OECD evaluation criteria (OECD 301 F-Test, 0 % after 28 d). However analytical data from an industrial waste water treatment plant demonstrated that about 60 % of the chemical were eliminated.
The log K_{OW} was measured to be 1.3 at 25 °C, hence bioaccumulation is unlikely to occur. This was confirmed in a bioaccumulation study with fish (BCF = 1.5 – 1.7). The calculated log Koc 0.19 indicates a low potential for adsorption to soil.
The following aquatic effects concentrations are available:
Oryzias latipes: LC_{50} (96 h) = 232 mg/l (effect concentration; corrected for evaporation, ca. 730 mg/l nominal).
Scenedesmus subspicatus:
EC_{50} (72 h) > 165 mg/l (effect concentration; corrected for evaporation, > 500 mg/l nominal).
Daphnia magna:
EC_{50} (48 h) > 100 mg/l (nominal concentration, closed system, measured concentrations > 90 % of nominal values).
Pseudomonas putida: EC_{50} (17h) = 5991 mg/l (nominal concentration).
Using the aquatic toxic effect on the most sensitive species, *Daphnia magna*, of >100 mg/l a $PNEC_{aqua}$ of 100 µg/l is derived by applying an assessment factor of 1000 according to the EU Technical Guidance Document. No data are available on terrestrial organisms and from prolonged or chronic studies.

Exposure

There are only two known producers in Europe and the U.S. In 2000, the estimates for MDP for the world production amounted to approximately 10,000-25,000 tons. The chemical is exclusively used as an intermediate in the chemical industry for the production of glutaraldehyde. The compound is shipped directly from the production sites to ca. 10 subsidiaries world wide. There the substance is hydrolyzed under strongly acidic conditions (pH 2 – 2.5) to the final product glutaraldehyde and the by-product methanol. The concentration of MDP in the end-use product is below the limit of detection (<50 ppm).
Occupational exposure is well controlled under normal working conditions and may only occur in case of accidental spills via skin contact and the respiratory route. MDP is produced in closed systems at sites open to the environment, and, thus the risk of accumulation in case of accidental spills is minimized. Workers are only close to the production plant during sampling for analytical purpose and control inspections. MDP handling involves quality control sampling and analysis, filling and unfilling of tanks and drums. Personal protective equipment (gloves, face shield, goggles) is used during this work. Technical and organizational means to control exposure comprise the use of closed systems during production, transportation and hydrolysis, and vapor abstraction with encapsulation during filling of tanks or drums. Prior to repair and maintenance work vessels, pipes and other equipment is rinsed to remove MDP.
Acrolein is a minor impurity in the MDP product. Current acrolein concentration in MDP is less than 100 ppm (0.01 %) with a detection limit of 30 ppm. Thus acrolein concentration is considerably lower than it was in the 1980s (0.037%). Reduced acrolein content, natural ventilation at the work place, and the acrolein odor threshold of only ca. 0.1 ppm avoid the potential of unobserved or unintended exposure to acrolein.
MDP is not known to occur in consumer products and is not listed in the product registers of Denmark, Finland, Norway, Sweden and Switzerland (2002).
The exposure of workers at the manufacturing sites and the transport to a limited number of processing sites is effectively controlled. Consumers are generally not exposed to this chemical.

RECOMMENDATION

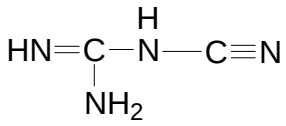
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:
The SIDS data requirement for reproductive toxicity is not fulfilled and the repeated dose toxicity studies are limited, but full studies were not demanded due to very limited and controlled occupational exposure at sites of the two producers. MDP possesses properties indicating a hazard for human health (irritant effects on skin, eye and respiratory system, potential genotoxicity). Exposure to humans is anticipated to be low, because exposure in occupational settings is well controlled by the two producers and because there is no consumer exposure. Therefore this chemical is currently of low priority for further work.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	461-58-5
Chemical Name	Cyanoguanidine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No metabolism data specific to cyanoguanidine is available.

The oral LD_{50} is greater than 30,000 mg/kg bw in female rats. Data on inhalative and dermal acute toxicity are not available.
This substance is considered to be irritating to the skin in guinea pigs. Data on eye irritation are not available. No sensitising potential has been demonstrated in guinea pigs in three maximization studies. The potential was not clearly demonstrated in human. Most workers did not become sensitive to this substance, however, there might be some workers who became sensitive for specific reasons (cross sensitisation or adjuvant effect of co-factors).

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] was conducted using SD rats at doses of 0, (vehicle; 3% gum arabic solution), 40, 200, and 1,000 mg/kg/day. The dosing period for males was 44 days, and females were dosed from 14 days before mating to day 3 of lactation. This substance had no effect on clinical signs, body weights, food consumption or necropsy findings. The organ weights were similar among all groups. No histopathological changes ascribable to this substance in these organs were found in either sex. The NOAEL for the repeat dose toxicity is considered to be 1,000 mg/kg/day for both sexes.

The reverse mutation studies in bacteria [OECD TG 471 and 472] gave negative results. The *in vitro* chromosomal aberration test with Chinese hamster lung cells (CHL/IU) [OECD TG 473] with and without metabolic activation was also negative. Therefore, this substance is not genotoxic.

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] (0, 40, 200, 1,000 mg/kg/day) was conducted using SD rats. This substance had no effects on reproductive 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 behavior. On examination of neonates there were no significant differences between the control and treated groups in the number of offspring or live offspring, sex ratio, live birth index, viability index or body weight. No abnormal findings ascribable to this substance were found for external examination or clinical signs or on necropsy of the offspring. The NOAEL for reproductive and developmental toxicity is considered to be 1,000 mg/kg/day.

A carcinogenicity study was conducted in male and female Fischer 344 rats fed diets containing this substance at 0, 2.5 and 5% (male: 837.2 and 1958.6, female: 1001.3 and 2169.2 mg/kg bw/day) for up to 2 years. The study did not suggest an association of the substance with an increased tumor incidence.

Environment

Cyanoguanidine is a white crystalline powder, which is soluble in water (40 g/L at 25 °C). Melting point, boiling point, and vapour pressure are 209.5 °C, solidified at 252 °C , and equal or less than 0.0045 Pa (100 °C), respectively. This substance does not hydrolyse under environmental conditions. Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life of 3.1 hours. This substance is not readily biodegradable under aerobic condition within 28 days (BOD = 0 %). However, a prolonged study showed that this substance is completely biodegraded within 34 weeks under aerobic conditions, while two-thirds of the total is biodegraded within 60 weeks under anaerobic conditions. This substance has a low bioaccumulative potential (BCF (*Cyprinus carpio*, 48days): equal or less than 3.1). Fugacity modeling (Mackay level III) predicts that if the substance is released to water, it will not migrate into other compartments. When this substance is released to air or soil, it is mainly distributed to water and soil.

This substance has been tested in aquatic species (algae, invertebrates and fish). An acute growth inhibition test was performed using green algae (OECD TG 201, *Selenastrum capricornutum*). The EC_{50} (biomass; 0-72 h) was 935 mg/L and the EC_{50} (growth rate; 24-72 h) was > 1,000 mg/L. An acute toxicity test for invertebrates was performed using water fleas (OECD TG 202, *Daphnia magna*). The 48-h EC_{50} was > 1,000 mg/L. An acute toxicity test [OECD TG 203] and a prolonged toxicity test [OECD TG 204] for fish were performed using Medaka (*Oryzias latipes*). The 96-h LC_{50} and the 14-d LC_{50} were both >100 mg/L. A chronic reproduction toxicity test for invertebrates was performed using water fleas (OECD TG 211, *Daphnia magna*). The 21-d EC_{50} and the 21-d NOEC were 69.6 mg/L and 25.0 mg/L, respectively. In microorganisms, this substance is known to have an inhibition activity of the nitrification of ammonium in various systems.

Exposure

The production volume of cyanoguanidine was estimated to be approximately 40,000 t/year worldwide in 2002, and not manufactured at present in Japan. This substance is a basic chemical, and used in industry for electrical/electronic engineering, metal extraction, refining and processing of metals, paper, pulp and board, textile processing, pharmaceuticals and intermediates. This substance is also used as absorbent, adhesive, binding, coloring, electroplating, surface-active agents, and agricultural chemicals (fertilizer).

During production and use of this substance, occupational exposure is possible by inhalation and dermal route. The workplace exposures during manufacturing processes are controlled by personal protective equipment. Consumer exposure is also possible by inhalation and dermal route.

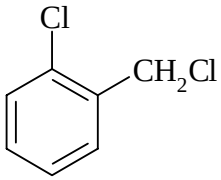
RECOMMENDATION

The chemical is currently of low priority for further work.

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 potential.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	611-19-8
Chemical Name	Benzene, 1-chloro-2-(chloromethyl)-
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No data are available regarding toxicokinetics, metabolism and distribution of 1-chloro-2-(chloromethyl)benzene (*o*-chlorobenzyl chloride; OCBC).
The acute inhalation LC_{50} value in male/female rats was 2.8 mg/l [OECD TG 403]. The acute dermal LD_{50} values were 1,700 (male) and 2,200 mg/kg bw (female) in rabbits and higher than 2,000 mg/kg bw in rats of both sexes. The oral LD_{50} values in rats were in the range of 350 and 951 mg/kg bw. OCBC primarily caused irritation-related histological damage to a tissue where the substance was administered; lung by inhalation, skin by dermal application and stomach by oral administration.
OCBC is irritating but not corrosive to the skin of rabbits [OECD TG 404]. The substance is also irritating to the eyes of rabbits [OECD TG 405]. Respiratory irritation was noted for OCBC with the RD_{50} value of 32.9 mg/m^3 for male mice. There are no reliable data available for sensitisation of OCBC.

In an inhalation repeated dose toxicity study [OECD TG 412], rats were exposed to OCBC vapour for 6 hours a day for 4 weeks (5 days/week) at concentrations of 0, 0.01, 0.03 and 0.10 mg/l. At 0.10 mg/l, signs indicative of irritation to the respiratory tract such as enlarged tracheobronchial lymph nodes, increased lung weights, damage to the nasal mucosa, tracheas and bronchi, and lymphoid hyperplasia in the tracheobronchial lymph nodes were observed. There was no treatment-related change in rats exposed at 0.01 and 0.03 mg/l. The NOAEL for inhalation repeated dose toxicity was determined to be 0.03 mg/l in rats of both sexes.
In an oral repeated dose toxicity study performed as a combined repeat dose and reproductive/developmental toxicity screening test [OECD TG 422], OCBC was administered by gavage to rats at doses of 0, 2, 10 and 50 mg/kg bw/day. The administration periods were 45 days for males and 41-48 days for females including all the periods between pre-mating and post-delivery. Thickening of the forestomach wall, and squamous epithelium hyperplasia, erosion and ulceration in the forestomach were observed in males at 10 and 50 mg/kg bw/day and in females at 50 mg/kg bw/day. Histological changes in the kidney, such as increases in the numbers of hyaline droplets in the proximal tubular epithelium, eosinophilic bodies, granular casts and basophilic tubules, were also observed in males at 50 mg/kg bw/day. The NOAEL for oral repeated dose toxicity was considered to be 2 mg/kg bw/day in male rats and 10 mg/kg bw/day in female rats.

One bacterial mutation study revealed that OCBC was negative with or without exogenous metabolic activation. Another bacterial mutation study showed weakly positive response without metabolic activation but negative with metabolic activation [OECD TG 471]. An *in vitro* chromosome aberration test using CHL/IU cells was positive in the presence or absence of an exogenous metabolic activation system only at cytotoxic concentrations [OECD TG 473]. The micronucleus assay using male and female rats was negative tested up to the maximum tolerated dose [OECD TG

474]. Based on the weight of evidence, OCBC is not anticipated to be genotoxic *in vivo*.

There is no data available for carcinogenicity of OCBC.

As for reproductive/developmental toxicity, no effect of OCBC was observed on any reproductive and developmental parameters in the above-mentioned combined repeat dose toxicity study at doses up to 50 mg/kg bw/day [OECD TG 422]. Thus the NOAEL for reproductive/developmental toxicity was considered to be 50 mg/kg bw/day in rats.

Environment

OCBC has a water solubility of 100 mg/l at 25°C, a vapour pressure of 0.2 hPa at 25°C and a Log K_{OW} of 3.32. The K_{OC} of 856 indicates a moderate potential of the substance for adsorption to soil and sediment. The half life of OCBC by reaction with OH radicals in air was calculated to be 103 hr. A bioconcentration factor of 71.85 was calculated for OCBC, indicating that the bioaccumulation potential of the substance is low. In the biodegradation test [OECD TG 301C], OCBC is not readily biodegradable (BOD 0% after 28 days). OCBC is hydrolyzed in water via an abiotic process to generate *o*-chlorobenzyl alcohol, which is then slowly biotransformed by oxidation to *o*-chlorobenzoic acid via *o*-chlorobenzaldehyde. An inherent biodegradability test [OECD TG 302B] showed that OCBC is inherently biodegradable with adapted industrial sludge.
The distribution of OCBC released into a particular environmental compartment was estimated with a fugacity-based model, Mackay level III. The model predicted that OCBC released into water is distributed to water (73.5 %), air (12.2%), sediment (7.7%) and soil (6.6%) while the substance released into air is distributed mainly to air (64.1%) and soil (34.6%). Almost all of the substance (99.8%) released into soil, on the other hand, was predicted to remain in its original compartment.

Acute toxicity studies with algae, invertebrates and fish have been reported. The results obtained from these studies are the 72-hr EC_{50} of 0.78 mg/l (biomass) and 1.2 mg/l (growth rate) for *Selenastrum capricornutum* [OECD TG 201], the 48-hr EC_{50} of 0.38 mg/l for *Daphnia magna* [OECD TG 202], and the 96-hr LC_{50} of 0.27 mg/l for *Oryzias latipes* [OECD TG 203].
A chronic toxicity test was performed with *Daphnia magna* [OECD TG 211]. The 21-day NOEC for its reproduction was 0.020 mg/l. The 72-hr NOEC for the growth of *Selenastrum capricornutum* based on the biomass and growth rate were 0.045 and 0.18 mg/l, respectively [OECD TG 201]. No chronic toxicity results with fish are available.
Based on the stability of OCBC in water (half-life, 33.1 hours at pH7), considerable hydrolysis of OCBC to *o*-chlorobenzyl alcohol is anticipated. Thus the aquatic effect of *o*-chlorobenzyl alcohol was taken into consideration. Although no toxicity data is available for this substance, the analysis by ECOSAR (ECOWIN v0.99g) showed 96-hr LC_{50} of 15.7-189.7 mg/l for fish and 48-hr LC_{50} of 0.3-0.6 mg/l for Daphnia, suggesting that *o*-chlorobenzyl alcohol is not more toxic to aquatic organisms than OCBC. Consistent with this prediction, the 96 hr LC_{50} values (nominal) of OCBC for fish obtained in a static system (0.5-0.71 mg/l for *Danio rerio* and 0.71-0.96 mg/l for *Pimephales promelas*) were higher than that obtained in a flow-through system (0.27 mg/l for *Oryzias latipes*).

Exposure

In 2002 the chemical was produced in Germany, Japan and Belgium. The total production volume was about 1,000 tonnes per year for the last five years. In each country, only one company, which has one production site, currently operates the production of the substance.
OCBC is produced by chlorination of *o*-chlorotoluene in a closed system. There is no process that generates waste water in the production of OCBC. The waste residue is incinerated. The off-gas of the reaction is incinerated or treated on active carbon. Therefore there is no release of OCBC to the environment from its manufacturing plants. The use pattern of OCBC is also limited to the use as an intermediate for the production of agrochemicals. In the Sponsor country, only one agrochemical is manufactured from OCBC in a closed system. Because OCBC is reacted away in the process, there is no release of OCBC from the production site of the agrochemical. No contamination of OCBC is detected in the agrochemical (detection limit 0.002%). OCBC is not detected in soil as degradation products of agrochemicals. Based on these facts, it is considered that the impact of OCBC to the environment (aquatic and terrestrial) is negligible.

In Japan, the number of workers engaged in manufacturing and processing of the substance at the production site is limited to less than twenty, and the operation period at the plant is also limited (approx. 2-6 weeks/year in 1999-2003). The monitoring data revealed that the OCBC concentrations in the air of workplace atmospheres at the production site were minimal. Furthermore, workers are obliged to use personal protection equipments such as mask, safety glasses and gloves during the operation. At the user site in the sponsor country, the number of workers and the operation period is also limited, and OCBC is treated in a similar way than at the production sites. Therefore, occupational exposure to OCBC is considered to be minimal.
Consumer exposure is also considered negligible because no contamination of OCBC is detected in the product manufactured from OCBC in the sponsor country.

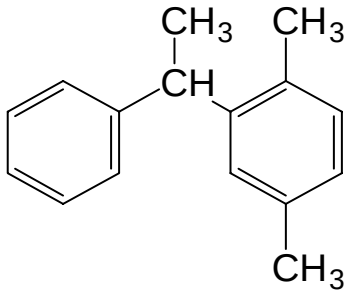
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health (repeated dose toxicity) 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6165-51-1
Chemical Name	1,4-dimethyl-2-(1-phenylethyl)benzene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There are no available data on toxicokinetics, metabolism, or distribution.

In the acute toxicity study [OECD TG 401] with 1,4-dimethyl-2-(1-phenylethyl)benzene in Crj:CD(SD)IGS rats (5 animals/sex/dose), deaths were found in one male and two females at 2000 mg/kg bw. Soiled perianal region, decreased locomotor activity, bradypnea, and lateral position were observed in both sexes at 2000 mg/kg bw. The body weight gain was decreased at 1000 mg/kg bw and higher. The oral LD_{50} values were considered to be more than 2000 mg/kg bw in rats of both sexes.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], Crj:CD(SD)IGS rats (12 animals/sex/dose) were given 1,4-dimethyl-2-(1-phenylethyl)benzene by gavage at 0 (vehicle: olive oil), 12.5, 50, or 200 mg/kg bw/day. Males were dosed for 47 days from day 14 before mating and females were dosed for 42-45 days from day 14 before mating to day 3 of lactation throughout the mating and pregnancy period. The body weight gain was decreased at 200 mg/kg bw/day in both sexes (5-8%). In urinalysis, increases in the volume and crystals and decreases in the osmotic pressure and specific gravity were detected at 200 mg/kg bw/day in males. Extension of the blood clotting time was observed at 50 mg/kg bw/day and higher in males. An increase in the total cholesterol levels was found at 50 mg/kg bw/day and higher in males. Increases in the γ-GTP and phospholipids levels of males and increase in the glucose levels of females were detected at 200 mg/kg bw/day. The liver weight was increased at 50 mg/kg bw/day and higher in males and at 200 mg/kg bw/day in females. The adrenal weight was decreased at 12.5 mg/kg bw/day and higher in males. In histopathological examinations, hypertrophy of the hepatocytes was observed at 50 mg/kg bw/day and higher in males and at 200 mg/kg bw/day in females. In the adrenals of male rats, atrophy of the zona fasciculate and an increase in the incidence of hypertrophy of the zona glomerulosa were found at 12.5 mg/kg bw/day and higher and at 200 mg/kg bw/day, respectively. Based on the pathological findings in the adrenals in males and in the liver in females, no NOAEL could be derived in male rats for repeated dose toxicity and the LOAEL for repeated dose toxicity was considered to be 12.5 mg/kg bw/day in male rats. In female rats, the LOAEL for repeated dose toxicity was 200 mg/kg bw/day and the NOAEL for repeated dose toxicity was considered to be 50 mg/kg bw/day.

In a reverse gene mutation assay [OECD TG 471], 1,4-dimethyl-2-(1-phenylethyl)benzene was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA1537, and TA98 or in *Escherichia coli* WP2 *urv*A either with or without an exogenous metabolic activation. In the chromosomal aberration test [OECD TG 473], 1,4-dimethyl-2-(1-phenylethyl) benzene did not induce structural chromosomal aberrations or polyploidy either with or without an

exogenous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells.

The above-mentioned combined study [OECD TG 422], showed that the reproduction/developmental parameters, i.e., mating, pregnancy, delivery, lactation, and viability and body weight of pups, were not affected by administration of 1,4-dimethyl-2-(1-phenylethyl)benzene at up to 200 mg/kg bw/day. The NOAEL for reproduction/developmental toxicity was considered to be 200 mg/kg bw/day in rats. At 200 mg/kg/day, some parameters, number of implantations, implantation index, and numbers of newborns and live newborns (24%), were decreased, but not statistically significant. These values are within the range of historical control data for the performing laboratory.

No information on carcinogenicity is available.

Environment

1,4-Dimethyl-2-(1-phenylethyl)benzene is a colourless liquid with a melting point of $\leq$ -50 °C (OECD TG 102), boiling point of 305.9 °C (MPBPWIN v. 1.40), vapour pressure of 2.1 x 10^{-4} hPa (OECD TG 104) and water solubility of 0.96 mg/L at 25 °C (OECD TG 105). The measured log Kow is 5.39 (OECD TG107).
1,4-Dimethyl-2-(1-phenylethyl)benzene is photodegraded in the atmosphere by reaction with OH radicals with a half-life of 0.5 days. The hydrolysis rate of the substance is slow and no degradation was observed in a preliminary test (pH conditions of 4, 7 and 9, at 50 °C for 5 days) (OECD TG 111). 1,4-Dimethyl-2-(1-phenylethyl)benzene is not readily biodegradable (OECD TG301C). A generic fugacity model (Mackey level III) indicates that the substance mainly partitions to soil if released into soil or air and mainly to sediment if released into water. Experimentally derived BCF values of 760 and 620 (OECD TG 305) showed that the substance has a potential for bioaccumulation.

The ecotoxicity of 1,4-dimethyl-2-(1-phenylethyl)benzene have been studied by using aquatic species among three trophic levels. For fish an acute toxicity result 96 h LC50 of 0.31 mg/L (OECD TG 203, *Orizias latipes*, semistic test with analytical monitoring) is available. For daphnids an acute toxicity result on immobility, a 48 h EC50 of 0.25 mg/L (OECD TG 202 part 1, *Daphnia magna*) was reported. For aquatic plants an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum*) resulted in a 72 h ErC50 (growth rate) and a 72 h EbC50 (biomass) of >1.54 mg/L and 0.93 mg/L, respectively.
On chronic effects of this substance to aquatic organisms, two toxicity tests were carried out. For daphnids, a 21 d reproduction test (OECD TG211, *Daphnia magna*) showed a NOEC of 0.009 mg/L. For an aquatic plant, NOECs on algal growth inhibition were available. Those were (growth rate) NOEC (24-48 hr) of 0.37 mg/L, (growth rate) NOEC (0-72 hr) of 0.73 mg/L and (biomass method) NOEC (0-72 hr) of 0.047 mg/L based on the mean measured concentration (OECD TG 201, *Selenastrum capricornutum*). Results from chronic tests with fish are not available.

Exposure

In the year 2002 in Japan, only one company, produced 1,4-dimethyl-2-(1-phenylethyl)benzene as a mixture consisting of four homologue chemicals (CAS Nos. 6169-95-8, 6165-53-2, 64800-83-5 and 6416-39-3) with a total production volume of ca. 8000 tonnes (purity in a commercial product ca. 10%). It is assumed that few companies in Korea and China produce this substance as one component of a commercial product with a total production volume of a mixture ca. 1000 and 1500 tonnes in each country. No information on production volumes in other OECD countries is available.
1,4-Dimethyl-2-(1-phenylethyl)benzene is produced in a closed system by alkylation of styrene and xylene isomers in the presence of a solid acid catalysis. In Japan, 1,4-dimethyl-2-(1-phenylethyl)benzene is used as a substitute substance of PCBs and its main usage are as a solvent for pressure sensitive dyes (ca. 60%) and condenser oil (ca. 40%) for industrial use. Small amounts of 1,4-dimethyl-2-(1-phenylethyl)benzene are also used as a plasticizer for epoxy and uretane polymers, and a solvent as a substitute for trichloroethane.

Occupational exposure through inhalation of mist and dermal route is possible. Inhalation of vapor is expected to be minimal because the vapor pressure of this chemical is low.

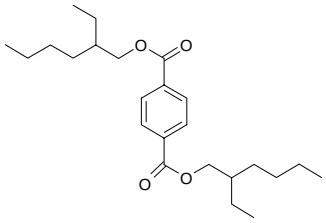
RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health, including repeated dose toxicity and uncertainty regarding reproductive toxicity in a screening test, and the environment (aquatic toxicity). It is recommended that an exposure assessment be performed to address possible exposure levels to the environment, workers and consumers based due to its use as a solvent, an alternative to PCBs and due to the recycling process of papers containing this chemical. Furthermore, a hazard assessment to sediment organisms and plants is also recommended and if necessary an environmental risk assessment should be performed.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6422-86-2
Chemical Name	Di(2-ethylhexyl)terephthalate (DEHT)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Di(2-ethylhexyl)terephthalate (DEHT) has been shown in both *in vitro* and *in vivo* studies to have the potential to undergo complete hydrolysis to yield terephthalic acid and 2-ethylhexanol (2-EH), which are rapidly eliminated. Results of these metabolism studies also indicate DEHT was not well absorbed within the gastrointestinal tract, with 36% of it recovered in the feces still intact. In addition, a study to assess dermal absorption rate indicated that DEHT has a very low potential to penetrate the skin (0.103 µg/cm^2/hr), which further limits systemic exposure potential.

The acute oral LD_{50} values are in excess of 3,200 mg/kg in mice and 5,000 mg/kg in rats. The acute dermal LD_{50} value is in excess of 19,670 mg/kg bw in guinea pigs, and skin and eye irritation studies in animals and/or humans indicate that DEHT has only a slight potential to induce irritation. In studies with some limitations, no skin sensitization was observed in humans or animals.

In one repeated dose study, rats were fed diets containing up to 2.5% (approx. 2,000 mg/kg bw/day) DEHT for 21 days, while in the other they received up to 1% DEHT in the diet for 90 days (approx. 561 mg/kg bw/day for males and 617 mg/kg bw/day for females). The NOELs in both studies were 0.5 % (approximately 500 mg/kg bw/day in the 21 day study and 277 – 309 mg/kg bw/day in the 90 day study). The only effect noted at 1.0 % in the 90 day study was increased relative liver weight. In the 21-day study, administration of 1.0 % was associated with increased relative liver weight in females but was without effect in males. Peroxisome proliferation in the liver was not noted in animals treated with either of these dosing regimens.

DEHT has been shown to be negative in both mutagenicity and chromosomal aberration assays with and without metabolic activation. No carcinogenicity data are available.

The reproductive toxicity of DEHT has been assessed through a two-generation study in rats following OECD Test Guideline 416. The NOAEL for reproductive toxicity was 1.0% in the diet (500-700 mg/kg bw/day for males and 800-1000 mg/kg bw/day for females; highest dose tested), and the NOAEL for parental and offspring toxicity based on reduced body weight gains was 0.3% (150-200 mg/kg bw/day for males and 250-300 mg/kg bw/day for females). Mean maternal body weights and body weight gains were reduced for F0 and F1 females in the 1.0% group throughout pregnancy and decreased mean terminal body weights were noted in F1 males and females given 0.6% or 1.0% test material. The results of this study, in conjunction with the 90-day study described above which also showed no effect of DEHT on histology of reproductive organs indicate that DEHT has a low potential to induce reproductive toxicity.

Developmental toxicity was evaluated in a dietary study following OECD Test Guideline 414. The NOEL for maternal toxicity was 0.6% (458 mg/kg/day) and the NOEL for developmental toxicity was 1.0% (747 mg/kg/day; highest dose tested). The ability of DEHT to induce anti-androgenic like effects in male offspring was assessed by giving pregnant rats 750 mg/kg DEHT by gavage on gestation day 14 until postnatal day (PND) 3. No changes indicative of a feminization effect were induced in male pups. Results of a uterotrophic assay in which immature females were given up to 2000 mg/kg/day DEHT by gavage on PND 19-21 also indicate that DEHT does not possesses estrogenic activity.

Environment

DEHT is a high boiling liquid (boiling point 383°C at 1015 hPa) with a very low vapour pressure (estimated to be $2.85x10^{-5}$ hPa at 25°C by EPIWIN). It has a melting point of -48°C, a water solubility of 0.0004 mg/l and an EPIWIN-estimated octanol/water partition coefficient LogKow of 8.39. The atmospheric photodegradation half-life is 0.487 days (5.84 daylight hours). Based on its molecular structure, DEHT is not anticipated to undergo rapid hydrolysis in the presence of water. Level III fugacity modeling assuming equal distribution indicates 0.743% to air, and 7.26% to water with greater percentages in the soil and sediment compartments (28% and 64%, respectively). These results are supported by a Koc value of $1.62x10^{5}$. While the vapour pressure of DEHT is very low, the Henry's Law Constant is relatively high ($1.02x10^{-5}$ atm-m^3/mol) due to the substance's offsetting low aqueous solubility. A biodegradation study failed to show that the material was "readily biodegradable" under the method and conditions of the test, but did show 40.2% conversion to CO_2 in 28 days indicating that the material is ultimately biodegradable. Results of an activated sludge respiration inhibition test indicate that DEHT is not toxic to wastewater microbes. Studies assessing acute and chronic toxicity to fish (Fathead minnow and Rainbow trout) and invertebrates (Daphnia magna, Planorbid snail, Eastern oyster), and acute affects on algal (*Selenastrum capricornutum*) growth showed no effects at water concentrations that were often significantly greater than its limit of solubility in distilled, deionized water that is free of particulate matter (0.0004 mg/L). Terrestrial plant growth in three species was not affected by DEHT exposure A bioconcentration study in oysters indicated that the material has a medium to low potential to bioconcentrate (BCF = 393). However, due to its propensity to be eliminated by higher trophic organisms, it is not expected to bioaccumulate.

Exposure

A single U.S. manufacturer produces DEHT using a continuous reactor, distillation column and storage tanks. Annual production is about 25-50 thousand metric tonnes. Occupational exposure is limited by the closed process, and also because the substance is a high boiling liquid of limited volatility. The primary use of DEHT is as a plasticizer whereby it is bound in a polymer matrix, limiting consumer exposure. Some consumer exposure may occur based on a minor use in coated fabrics, but the application is on the exterior of the fabric, away from direct dermal contact, and the DEHT is bound up in the polymer. Concentrations of DEHT in the environment in air or water have not been reported, but there is limited potential for release into the environment. Environmental releases during manufacture and processing are limited by the use of enclosed processes and by in-plant treatment of any waste streams through biodegradative waste treatment or incineration. DEHT is released slowly into the environment from various uses of PVC, such as in PVC waterstops, gaskets, weather stripping, shoe soles, pond linings and wire coatings. Any DEHT that may enter the environment will have a strong tendency to be adsorbed onto solid matter such as soil and sediment.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

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

Environment:
This chemical is a candidate for further work for sediment toxicity testing and/or exposure assessments due to its potential to partition to sediment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-87-5
Chemical Name	1,2-dichloropropane (propylene dichloride)
Structural Formula	CH_2Cl-$CHCl$-CH_3

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Toxicokinetic data from the rat demonstrate that 1,2-dichloropropane (PDC) is rapidly absorbed and widely distributed within the body after both oral and inhalation exposure, with subsequent excretion in urine (major route of elimination) or exhaled air (carbon dioxide). Only trace amounts remained in tissues 48 hr after treatment, demonstrating its rapid elimination. Metabolic analyses showed that three N-acetylcysteine conjugates predominated in urine.

Its low boiling point and high vapor pressure suggest that evaporative losses will minimize dermal contact with liquid PDC and point to inhalation as the most relevant route of exposure.

Although results from early animal studies indicate that PDC is of relatively low inherent toxicity after ingestion (rat oral LD_{50} approx. 2000 mg/kg bw), skin contact (rabbit dermal LD_{50} approx. 10,000 mg/kg bw), or inhalation (rat 4-hr LC_{50} approx. 2000 ppm; 9300 mg/m^3), human case-reports suggest that the liver and red blood cells may be adversely affected following over-exposure. Thus PDC is considered harmful by ingestion or inhalation, is only slightly irritating to the skin but is irritating to the eye, causing redness, swelling, and slight opacity that were fully reversible after one week. Other case-reports provide equivocal evidence that it may cause allergic skin conditions after uncontrolled exposure in individuals with pre-existing skin irritation and dermatitis; however, these observations are not supported by results from a murine Local Lymph Node Assay, which were negative.

The liver is a target organ in rodents exposed repeatedly to PDC, with a chronic oral NOAEL of 62-125 mg/kg bw/d in rats (LOAEL 125-250 mg/kg bw/d) and a chronic LOAEL of 125 mg/kg bw/d in mice (no NOAEL established); centrilobular congestion, fatty change, hepatocytomegaly, and necrosis were among the changes described, along with decreased body weights. No functional or histopathological changes were reported in brain or nervous tissue from rats given PDC at doses up to 200 mg/kg bw/d by gavage as part of a 13-week neurotoxicity study. Following a 13-week inhalation exposure, no adverse systemic effects were noted in rats and mice exposed to 150 ppm PDC (NOAEL), whereas red blood cell parameters (regenerative anemia) were altered in rabbits with a LOAEL of 150 ppm in males and a NOAEL of 150 ppm in females. Body weight was slightly but statistically significantly decreased in rats (NOAEL 15 ppm) but not mice (NOAEL: 150 ppm) or rabbits (1000 ppm) in these subchronic inhalation studies. Site-of-contact effects, consistent with repeated local irritation, have been described in stomach (mouse, NOAEL/LOAEL 125 mg/kg bw/d after oral gavage, dependent on sex) and nasal tissue (rat, NOAEL 15 ppm after inhalation).

Results from *in vitro* genotoxicity tests (bacterial, fungal, mammalian systems; with and without metabolic activation) are mixed, with both positive and negative studies, indicating that PDC has *in vitro* mutagenic potential. However, results from two modern guideline, *in vivo* tests demonstrate that PDC was not active in a mouse micronucleus test (up to 600 mg/kg bw, 2 consecutive daily doses) or a rat dominant lethal assay (up to 162 mg/kg bw/d; 13-wk exposure). These findings indicate that PDC is not an *in vivo* somatic or germ cell genotoxicant.

The carcinogenic potential of PDC has been evaluated under the US National Toxicology Program, which found ‘no

evidence for carcinogenicity' in male rats (125 mg/kg bw) and 'equivocal evidence' in females (250 mg/kg bw; increased incidence of mammary tumors in the presence of a major reduction in survival), while 'some evidence of carcinogenicity' was noted for mice (both sexes), reflecting an increased incidence of hepatocellular neoplasms (primarily adenomas; 250 mg/kg bw). It is noted that the incidence of liver adenomas was within the historical control range for this strain of mouse suggesting the finding was of marginal toxicological significance. When reviewing these data, IARC concluded that 1,2-dichloropropane is *not classifiable as to its carcinogenicity to humans (Group 3)*. Overall, these considerations indicate that PDC is not a direct-acting carcinogen, that there is equivocal evidence of an increase in mammary tumors in female rats, and that other factors (such as spontaneous biological variation) may have contributed to the increased incidence of mouse liver tumors.

No adverse impact on reproduction was noted in male and female rats exposed to PDC in drinking water over two generations. Although neonatal body weight was decreased, and neonatal mortality higher in litters from high-dose dams consuming up to 250 mg/kg bw/d during pregnancy or up to 500 mg/kg bw/d during lactation, this was considered secondary to dehydration and a 20% reduction in gestational body weight gain, rather than a direct effect on reproduction. Overall there is no evidence that PDC selectively targets the male or female reproductive system. Results from developmental toxicity studies in rats and rabbits were consistent with delayed fetal development (reduced ossification of the bones of the skull) in the presence of clear maternal toxicity (clinical signs, lower body weight gain) with a common maternal/fetal NOAEL of 30 mg/kg bw/d for rats and 50 mg/kg bw/d for rabbits (LOAELs of 125 and 150 mg/kg bw/d, respectively). There was no evidence of a teratogenic effect at any dose in either species.

Environment

1,2-dichloropropane is a liquid with a vapour pressure of 66.20 hPa (25°C), water solubility of 2800 mg/l (25°C), and Log Kow of 2.0.

Taking into account that PDC emissions will be mainly to air, results of distribution modelling show that PCD will stay predominantly in air (98.6%), with negligible amounts partitioning into the water compartment (1.2%). In the air, PDC has the potential to degrade through indirect photolytic processes mediated primarily by hydroxyl radicals with a calculated degradation life-time in the troposphere of approximately 25 days, however wet deposition is not likely to contribute significantly to its atmospheric fate. Based on the data for dichloroethane, oxidation of PDC will not result in the introduction of chlorine into the stratosphere, and its ozone depleting potential is negligible.

Based upon a log Pow of 2 and a measured BCF of 0.5-7, little or no bioaccumulation of PDC in environmental species is expected.

Although PDC is not readily or inherently biodegradable, published data show a co-factor dependent degradation by organisms present in acclimated municipal waste treatment systems. It is not expected to adsorb significantly to organic matter in soil, sediment, or wastewater solids, based on a Koc of 50-299.

The acute toxicity of PDC toward aquatic species has been investigated in fish (fathead minnow, 96 hr EC_{50} 140 mg/l), invertebrates (*Daphnia*, 48 hr EC_{50} 56 mg/l) and saltwater algae (72 hr IC_{50} 15-16 mg/l). Chronic data are also available for three trophic levels (fish, invertebrate, plant) with consistent chronic NOEC values in a range 4-11 mg/l. The saltwater invertebrate *Mysidopsis bahia* appears to be the most sensitive species, with a 28-d NOEC (mortality, reproduction, growth) of 4.1 mg/l.

Exposure

PDC is used primarily as a site-limited or limited-transported co-product/raw material for the manufacture of many chlorinated compounds. Estimated annual global production of PDC in 2001 was about 350 kilotonnes (about 770 million pounds). Based on information from the Swiss Product Registers, there are only 2 recognized consumer applications (likely used in the auto industry), while the Danish and French Product Registers listed no consumer applications. There is no specific information on potential consumer exposure from these 2 applications.

Agricultural use is prohibited in North America and Europe. A total of 46 industrial products were listed in the Swiss Product Register as containing PDC, including as main applications, use in 'paints, lacquers, & varnishes' and 'solvents, degreasers, diluters, & strippers'. Most OECD member countries have established occupational exposure levels for PDC of 75 ppm.

Its high volatility indicates there is some potential for exposure of the general population. Historical data indicate trace amounts in ambient air (maximum reported value identified as 3.4 µg/m^3 or 0.7 ppb), while historical aquatic monitoring data demonstrate typical maximum concentrations <50 µg/l, with a single reported maximum of 1.2 mg/l from a site following application of PDC as a pesticide. More recent analyses of groundwater by the US Geological Survey (for the period 1986-1999, *i.e.*, as agricultural uses ceased) point to concentrations in the range <0.2-19.4 µg/l, with the majority (1911 out of 1926 total samples) containing no detectable PDC (limit of detection 0.2 µg/l).

Potential exposure to PDC in the occupational setting is limited since it is handled and used predominately in closed systems. As a result of the deregistration of PDC for use in agricultural pest control products, the potential for human exposure following deliberate release of PDC to the environment is of diminishing concern.

RECOMMENDATION

The chemical is currently of low priority for further work.

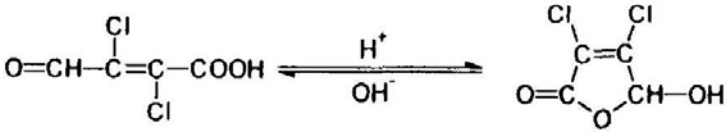
RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Adequate data exist to evaluate all of the SIDS endpoints, and sufficient data are available to characterize its hazards.

Human Health:
PDC is harmful after ingestion or inhalation, slightly irritating to the skin, and is irritating to the eye. These hazards do not warrant further work given their transient (irritation) and acute (high exposure) nature. These hazards should nevertheless be noted by chemical safety professionals and users. The chemical is currently of low priority for further work because of its recognized hazard profile and anticipated low exposure.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	87-56-9
Chemical Name	Mucochloric acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There are no reliable experimental data on the toxicokinetic behavior of mucochloric acid (MCA) *in vivo* available. From the results of acute toxicity studies, it is very likely that MCA itself or its metabolites are systemically available after oral exposure. *In vitro*, MCA reacted with N-acetylcysteine, cysteine and glutathione (GSH).

The acute toxicity (LD_{50}) of MCA was between 300 and 400 mg/kg bw in rats after oral exposure and >200 mg/kg bw (highest tested dose) in rabbits after dermal exposure. The LC_{50} after 4-hour inhalation exposure of rats was >5.1 mg/l (highest tested concentration). Clinical signs included atonia and ataxia after oral exposure, preening, dyspnoea and salivation during inhalation, and skin irritation after dermal exposure.
MCA is corrosive to the rabbit skin and eye. A guinea pig sensitization test was negative, but limited experience from occupational exposure in humans indicates a skin sensitizing potential of MCA.

There is limited data on repeated dose toxicity available, indicating that irritant/corrosive effects at the site of first contact are the main effects to be expected after repeated exposure. In pregnant rats, no systemic target organ has been identified after oral exposure from day 6 to 19 p.c. (LOAEL: 30 mg/kg bw/day, based on reduced food consumption and body weight gain together with minor clinical symptoms (ptyalism) and whitish foci in the stomach interpreted as local effects due to the corrosive properties of MCA; NOAEL: 5 mg/kg bw/day). No target organ was identified in mice after dietary exposure to 7 mg/kg bw/day for 18 months (only one dose tested). Because of the limited exposure potential and the availability of reliable, though limited, data on repeat dose toxicity, no further animal testing is warranted.

In vitro, MCA is a direct acting mutagen and clastogen in mammalian and bacterial cells, and forms exocyclic DNA adducts. *In vivo*, mucochloric acid caused a slight, but statistically significant increase in the incidence of total nuclear anomalies (including micronuclei, pyknotic nuclei and karyorrhectic nuclei) in the duodenum of mice after a single oral exposure to 60.8 and 79.4 mg/kg bw. MCA induced micronuclei in one animal out of ten per dose group in the duodenum of mice after single oral doses (38.9, 60.8, and 79.4 mg/kg bw). Based on the available *in vitro* and *in vivo* data, it can be concluded that MCA has a genotoxic potential.

Because of its corrosive properties, and the very limited exposure potential, animal tests with MCA for its effects on fertility were not performed. In an oral developmental study performed in accordance with OECD TG 414 in rats, the NOAEL for maternal toxicity was 5 mg/kg bw/day. The NOAEL for developmental toxicity was 60 mg/kg bw/day, which was the highest dose level applied. There were no signs of developmental toxicity or teratogenicity.
MCA did not induce aberrant crypt foci or intestinal tumors when given in drinking water at dose levels of 0.45 and 0.9 mg/ml over 6 weeks to rats or at dose levels of 0.18 and 0.35 mg/ml over 4 weeks with subsequent 12-weeks recovery to mice, respectively. The available data for MCA are not sufficient to judge its carcinogenicity. Given the

available data for genotoxicity there are, however, concerns with regard to this endpoint.

Environment

The solubility of MCA in water is approximately 27 g/l (pH 2.2) at 20 °C and the vapor pressure is 0.00139 hPa at 25 °C. A Henry's law constant of $8.7*10^{-4}$ $Pa*m^3*mol^{-1}$ can be calculated and the partition coefficient log K_{ow} was measured as 0.697 at 25 °C. The acid-base constant (pKa) is 4.20 at 25 °C.
The distribution modeling (Mackay fugacity model level I), indicates water to be the almost exclusive target compartment. The substance has no considerable potential for bioaccumulation (log K_{ow} = 0.697). It cannot be considered inherently biodegradable according to OECD guidelines, but is partially biodegradable after an appropriate adaptation. From the structure of MCA hydrolysis is not expected. Photodegradation is to be expected under environmental conditions with an estimated half-life of 21.4 h. An estimated K_{oc} value of 1 indicates that mucochloric acid does not tend to adsorb to soil. However, as the structure of the molecule is dependant on pH, the K_{oc} may vary significantly with pH.
Aquatic effects data are available for three trophic levels (fish: LC_{50} (96 h) = 123 mg/l; crustacea: EC_{50} (48 h) = 13 mg/l; algae: E_rC_{50} (72 h) = 65 mg/l, E_bC_{50} (72 h) = 62 mg/l). A $PNEC_{aqua}$ of 13 µg/l was calculated from the available data using an assessment factor of 1000 according to the EU Technical Guidance Document.

Exposure

In the EU there are only two known producers of MCA. The annual production volume in the EU is in the range of 1000 - 5000 tons. There is no information on imported volumes. In Eastern Europe, there is one producer in Slovakia, who produces MCA only for captive use. In China there are two known producers.
MCA was used in the 1970s and 1980s, as a gelatin hardener in the photographic industry and as an intermediate in the pharmaceutical production. Since 1990 MCA has only been used as the starting material for the production of two herbicidal substances: Chloridazon and Norflurazon. Production of MCA and processing to Chloridazon takes place in the EU in closed systems at the same site. For the production of Norflurazon, also in closed systems, MCA is transported under controlled conditions in so-called big bags to a single site in the USA and filled into the reactor via docking the big bags to it. During production, transport and processing of MCA personal protective equipment is used to minimize any workers exposure to the substance. At the production and processing sites in the sponsor country, workplaces are regularly monitored.
MCA is not emitted into the atmosphere; due to its low vapor pressure only traces of MCA are expected in the off-gases, which are held back in the scrubber liquids. There is no emission into the aquatic environment during production and processing of MCA at the sponsor company; any remaining aqueous solution is oxidized or incinerated. Solid wastes, which contain less than 100 ppm of MCA, are disposed of by incineration.
There is no evidence of MCA in the finished products, i.e. herbicide formulations (analytical detection limit: 5 ppm).
Because MCA is only used as an intermediate in closed systems and transported under strictly controlled conditions, there is very limited exposure potential from these sources in the sponsor country, both for humans and the environment.
In certain countries, and independent of its production and processing by the chemical industry, MCA was found in surface waters (µg/l range) resulting from effluents from chlorine bleaching processes and in drinking water (ng/l range) as a chlorination disinfectant byproduct from the reaction of chlorine with humic acids.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

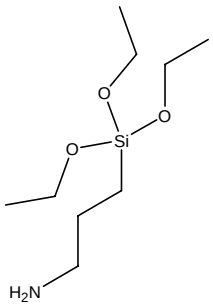
The chemical possesses properties indicating a hazard for human health (corrosivity, genotoxicity, potential carcinogenicity), but controls for occupational exposure are in place in OECD countries.

In view of concerns that the chemical may be a genotoxic carcinogen, there is a recommendation for sharing the toxicological and exposure data with regulatory agencies responsible for drinking water, because traces of MCA can occur in drinking water as a disinfection by-product. Based on this, countries may want to consider toxicokinetic/metabolism studies, and, if then indicated, further studies relating to the carcinogenicity endpoint.

Environment:

The chemical possesses properties indicating a hazard for the environment. 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

CAS No.	919-30-2
Chemical Name	3-Aminopropyltriethoxysilane [APTES]
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

3-Aminopropyltriethoxysilane (APTES) has been tested for acute toxicity by the oral, dermal, and inhalation routes of exposure. Acute oral LD_{50}s in rats range from 1570 to 3650 mg/kg bw. The dermal LD_{50} is 4.29 g/kg bw and the 4-hour inhalation LC_{50} of the hydrolysate is greater than 7.35 mg/L. Six hours of exposure to substantially saturated vapor of APTES did not kill any of the 5 male or female rats (LT50 > 6 hours). The kidney is a target organ for toxicity for oral and dermal exposures.
APTES is severely irritating to the skin and eyes. In a Buehler study in guinea pigs, 7/30 animals showed a skin sensitization response. The hydrolysis products of this material do not elicit a sensitization response in a guinea pig maximization test.

Repeated inhalation exposure of rats to 147 mg/m^3 of APTES hydrolysate respirable aerosol for four weeks produced squamous metaplasia and foci of minimal granulomatous laryngitis. No systemic toxicity was observed in rabbits after 9 repeated dermal doses of 17 or 84 mg/kg bw/day or three repeated dermal doses of 126 mg/kg bw/day of APTES; the site of contact NOAEL is less than 17 mg/kg bw/day. The no-observed-adverse-effect level (NOAEL) of APTES in a 90-day oral (gavage) study with rats was 200 mg/kg bw/day.

APTES has been tested in several bacterial reverse mutation/Ames assays, *in vitro* V79 hamster lung cell and Chinese hamster fibroblast chromosome aberration assays, two Chinese hamster ovary cell HGPRT gene mutation assays, and an *in vivo* mouse micronucleus assay. *In vivo* and *in vitro* screening assays have not revealed any evidence of genotoxic potential.

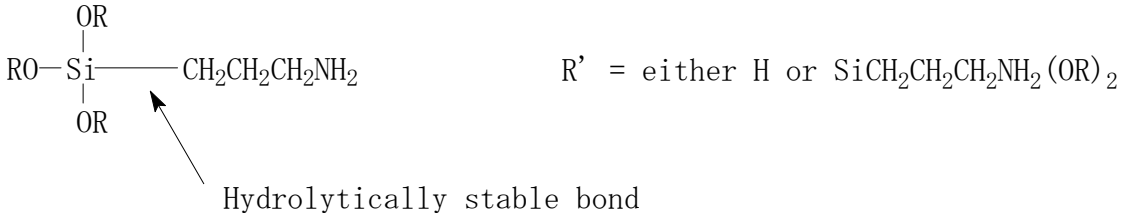
At the highest dose-level (600 mg/kg/day) in a 90 day oral gavage study in rats, no effects were seen on parameters of oestrus cycle and spermatogenesis or reproductive organs. The NOAEL for developmental effects has been identified for APTES following exposure via oral (gavage) in rats, with a value of 100 mg/kg bw/day, the NOAEL for maternal toxicity based on deaths and ulceration of the GI tract is <0.5 mL/kg.

Environment

The estimated partition coefficient Log Kow is 0.31 and the estimated water solubility is $7.6x10^5$ mg/l; these values may not be applicable because the material is hydrolytically unstable. The vapor pressure is 0.02 hPa at 20 ^oC, the

melting point is -70 °C, and the boiling point is 223 °C at 1013 hPa. Photodegradation modeling indicates the half-life in the atmosphere due to the reaction with photochemically induced OH radicals to be approximately 2.4 hours. However, photodegradation as a mode of removal is unlikely and not expected to be a significant degradation process because APTES is hydrolytically unstable.

APTES is hydrolytically unstable ($t_{1/2}$ < 1 hour) over a range of environmentally relevant pH and temperature conditions, with the exception of pH 7 at 10 or 24.7 °C. At pH 7, the half-life is 56 or 8.4 hours, for 10 or 24.7 °C, respectively. Rapid hydrolysis of this material produces ethanol and trisilanols. The Si-C bond will not further hydrolyze. That bond is hydrolytically stable and the aminopropyl group will not be cleaved. Only the ethoxy groups will be hydrolyzed. The transient silanol groups will condense with other silanols to yield:



As a result, aminopropyl-functional resins are generated. The EQC Level III model was used to evaluate the fate, transport and distribution of APTES between environmental matrices. 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 APTES: air = 0.7%; soil = 91.6%; water = 7.7 %; sediment = 0.00 %. However, APTES is unlikely to be found in the environment, as this material is hydrolytically unstable. APTES is not readily biodegradable. The observed biodegradation is of the hydrolysis products (ethanol and trisilanols). Bioaccumulation is not anticipated since this material is hydrolytically unstable.

In spill conditions, the concentration of the parent silane is very high. The silanols concentration could also be high; however, the silanol rapidly self-condenses to form water insoluble, resinous oligomers and polymers. The molecular weight of the resulting oligomers and polymers is predicted to be over 1000. Anecdotal evidence suggests the molecular weight of the polymers resulting from spills is 5000 – 10000. As the parent silane and the resulting silanol are diluted, it is predicted that the polymers resulting from condensation will be of lower molecular weight. At sufficiently low silanol concentrations, low molecular weight oligomers are favored. It is calculated that at 1000 ppm of a related trialkoxysilane, the equilibrium concentration will be 86% silanol monomer and 14% silanol dimer. At still lower concentrations, the silanol will exist as the uncondensed monomer. These polymers will not be bioavailable. However, such materials are likely to cause toxicity in aquatic species due to physical effects (encapsulation, blockage of gills). The APTES 96-hr LC_{50} is $\geq$ 934 mg/L for freshwater fish (*Brachydanio rerio*). The 48-hr EC50 for APTES is = 331 mg/L for the water flea (*Daphnia magna*). The 72-hr EbC50 for freshwater green algae (*Scenedesmus subspicatus)* is 603 mg/L. On the basis of cell growth, a 10% suppression of cell growth for the freshwater green algae (*Scenedesmus subspicatus*)was achieved at 72 hour EbC10 = 38 mg/L; on the basis of growth rate, a 10% suppression of cell growth in the same species was achieved at (0-72 hour) ErC10 = 321 mg/L. Since APTES is sensitive to hydrolysis, which may occur during preparation of the dosing solutions and/or during the testing, the observed toxicity is likely due to the hydrolysis products ethanol and trisilanols.

Exposure

The commercial uses of this material are numerous and include various applications as coupling agents and adhesion promoters in fiberglass, adhesives and sealants, foundry resins, and in pre-treatment for coatings. A small percentage of this material may be found in sealants and coatings. 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 pipes rather than in open systems to minimize loss of this material (hydrolysis) although some customers do transfer the material in open systems. APTES is transported from the production site as the parent silane to processors/formulators. Generally, APTES is used by the processor/formulator as an adhesion promoter with use levels <1%. In some applications, APTES is used as a crosslinker; these use levels are higher and can approach 3 to 5 %. Once APTES is added to a consumer or industrial product, the parent silane reacts with the

components of the formulation and is generally present as the parent silane at 0.1-0.2% until after curing (use). After curing the parent silane is consumed into the polymer matrix and no longer exists and greatly reduces potential for consumer or worker exposure. APTES polymerizes during use. Consumer products will be labeled as containing a sensitizer according to individual member country regulations. Any toxicological effects originating from the alkoxysilane or amine groups of the silane are greatly reduced as a result of this coupling process. The production volume of APTES in the sponsor country was 1992 tonnes in 2002.

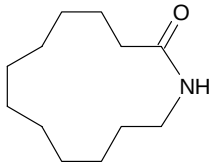
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health (skin and eye irritation, and skin sensitization). Based on data presented by the Sponsor country, adequate risk management measures are being applied, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently a low priority for further work.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	947-04-6
Chemical Name	Dodecane-12-lactam
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information available on toxicokinetics and metabolism of dodecane-12-lactam.
The acute oral LD_{50} was 2,330 mg/kg bw (rat) with central nervous system stimulation (trembling, convulsive twitches, ataxia) as the main clinical sign appearing at about 1,580 mg/kg bw. The dermal LD_{50} was greater than 2,000 mg/kg bw (rat). Decreased food consumption and stagnation of body weight development were noted. Valid acute inhalation studies are not available.
Dodecane-12-lactam was not irritating to the rabbit skin or eye (OECD TG 404, 405). It was not sensitizing in a guinea pig maximization test (OECD TG 406; 1981).

In a 90-day gavage study with rats, administration of dodecane-12-lactam at doses up to and including 25 mg/kg bw/day did not result in adverse effects (= NOAEL). At 125 mg/kg bw/day, blood examination revealed a slight increase in total serum protein and albumin levels in females and a moderate increase in potassium levels in males. Sodium excretion was also increased in males. In a few males treated with 25 or 125 mg/kg bw/day slight morphological changes in centrilobular hepatocytes (ground glass appearance) were noted, but this effect was reversible 4 weeks post-exposure, and in the absence of any other sign of liver toxicity was considered adaptive rather than adverse. No histopathological changes were found in the reproductive organs of these animals.
In a subchronic study with dogs, administration of dodecane-12-lactam with the feed at a dose of 44 mg/kg bw/day (males) and 49 mg/kg bw/day (females), respectively, was not associated with adverse effects (= NOAEL), whilst a daily dose of 350 mg/kg bw (males) and 352 mg/kg bw (females), respectively, resulted in a significant increase in liver weight (up to +34% relative to the controls). The top dose of 969 mg/kg bw/day (males) and 989 mg/kg bw/day (females), respectively, severely affected the general health conditions of the animals and was lethal for one female.

In all *in vitro* genotoxicity studies (Ames test according to OECD TG 471 (1981), HPRT test according to OECD TG 476 (1984); testing above limit of solubility neither required nor performed) and a chromosomal aberration test in human lymphocytes in compliance with OECD TG 473), dodecane-12-lactam showed negative results. Therefore it is expected that the chemical is not genotoxic *in vivo*.

In a gavage study performed in accordance with OECD TG 414 (2001), dodecane-12-lactam had no adverse effects on the development of rats up to and including the highest tested dose level of 1,000 mg/kg bw/day. Doses of 250 and 1,000 mg/kg bw/day were maternally toxic as evidenced by reduced food consumption (-7%/-11%) and reduced body weight gain (-37%/-50%) and, at 1,000 mg/kg bw/day, poor general condition (NOAEL maternal toxicity: 50 mg/kg bw/day; NOAEL developmental toxicity: 1,000 mg/kg bw/day).
No studies have been performed on the toxicity of dodecane-12-lactam to reproduction. Data from oral 90-day studies did not reveal any adverse effects on the reproductive organs in rats, whilst in dogs an impairment of sperm

maturation, decreased testes and ovary weights, and atrophy of the prostate was found at a severely toxic dose level (about 1,000 mg/kg bw/day).

Environment

Dodecane-12-lactam has a melting point of 151.8 °C, a solubility in water of 0.3 g/l at 20 °C, and a vapour pressure of 0.0012 Pa at 20 °C. The measured log K_{ow} is 2.92.
According to a Mackay Level I model calculation, the main target compartment for dodecane-12-lactam will be the hydrosphere (88.3 %), followed by sediment (5.9 %) and soil (5.8 %). The calculated Henry's law constant of 0.00079 Pa m^3/mol indicates very low volatility from surface waters. With a calculated K_{oc} of 2258 l/kg, the sorption potential to soil or sediment organic matter is expected to be high.
In the atmosphere, dodecane-12-lactam is rapidly removed by reaction with hydroxyl radicals with a calculated half-life of 12 hrs. In water, it is not expected to hydrolyse at a significant rate under environmental conditions. Photolytical degradation in surface waters is expected to be of minor importance due to its chemical structure. Dodecane-12-lactam is readily biodegradable (OECD 301B: 83 % after 28 days). Thus in surface waters, the predominant removal mechanism is expected to be biodegradation. Experimentally determined BCF values below 2.6 l/kg (*Cyprinus carpio*) indicate a low bioaccumulation potential.
The lowest valid acute test results of aquatic testing determined for fish, invertebrates, and algae were as follows:
Leuciscus idus: 48-h-LC_{50} = 50 mg/l
Daphnia magna: 24-h-EC_{50} = 41 mg/l
Scenedesmus subspicatus: 72-h-EC_{50} = 176 mg/l
From the lowest value among these, an aquatic PNEC of 0.041 mg/l is calculated using an assessment factor of 1000 according to the EU Technical Guidance Document.

Exposure

The production volume of dodecane-12-lactam is approximately 50,000 tonnes per year world wide. Production sites are in Germany, France and Japan. Dodecane-12-lactam is a chemical intermediate which is manufactured in closed systems, and which is used exclusively as a monomer for the polymerisation of polyamide. Releases into the environment may occur during production of dodecane-12-lactam as well as from its use as a monomer for polymer production. Furthermore, environmental releases are possible from residual contents of monomeric dodecane-12-lactam in the polymeric product during further processing of the polymer as well as during use and disposal of end products. Available information indicates that release from production is low. The residual monomer content in the polymer is approximately 0.2 % w/w, thus an amount of < 100 t/a may be released into the environment from formulation and from use and disposal of end products.

Dodecane-12-lactam is not used directly in consumer products. However, in Europe and the U.S. the chemical is authorized as a basic monomer for polymers to be used in food packaging materials, and residual monomers may come into contact with foodstuffs. In the EU, the specific migration limit for dodecane-12-lactam is 5 mg/kg foodstuff. Using this for a worst case estimate (uptake of 1 kg of foodstuff containing 5 mg dodecane-12-lactam every day), a 60 kg person could be exposed to a daily dose of 0.083 mg dodecane-12-lactam/kg bw/day. In the USA, no comparable migration limit has been set.
Workers could potentially be exposed during production and processing, with the main routes of exposure being the dermal and respiratory routes. There are no workplace measurements available. In the sponsor country, exposure to the chemical is controlled in occupational settings and considered to be very low due to its production and processing in closed systems.

RECOMMENDATION

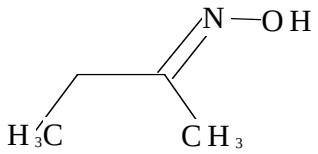
The chemical is currently of low priority for further work.

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 possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute aquatic toxicity which may become evident only at very high exposure levels they should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	96-29-7
Chemical Name	2-Butanoneoxime (MEKO)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Identity

There is only one major isomer for 2-butanoneoxime (MEKO), which is trans/anti. During the oximation process, the size of the ethyl group and its rotation favors formation of primarily (>99%) trans/anti isomer which is stable.

Human Health

Data indicate that MEKO is rapidly absorbed from the gastrointestinal tract and skin, after which it is rapidly metabolized and excreted.

Three acute oral studies in rats conducted according to GLP resulted in the following LD50s : 1) 930 mg/kg in males, and 1620 mg/kg in females, 2) 2326 mg/kg (males and females), and 3) greater than 900 mg/kg (males and females). The dermal LD50 for rabbits was between 1000 and 1800 mg/kg bw. Specifically, in one study, no lethality was observed at 1000 mg/kg bw and in a second study, all rabbits died at 1800 mg/kg. The rat LC50 (4-hr) was > 4,800 mg/m^3 (no rats died) in a well-conducted acute inhalation study. Following a single oral dose of MEKO to rats in an acute neurotoxicity study, transient effects characterized as motor incoordination were seen at treatment levels of 300 and 900 mg/kg but not at 100 mg/kg.
MEKO has been shown to be slightly irritating to the skin but is severely irritating to the eye. MEKO is an animal skin sensitizer. However, no sensitization to MEKO in workers has been reported.

Repeated inhalation and oral dose toxicity studies have shown MEKO to have effects on the red blood cells (effects on blood parameters indicative of hemolytic anemia and compensatory hematopoiesis, as well as extramedullary hemosiderosis in the spleen) and on olfactory epithelium. In several of these studies, the effects have been demonstrated to be reversible.
In a 13-week inhalation study in CD-1 mice, a NOAEL of 3 ppm (10.8 mg/m^3) was established based on olfactory effects in a small area of tissue in the nose at doses of 10 ppm (36 mg/m^3) and higher. These effects were minimal at lower doses and moderately severe at higher doses. After cessation of exposure, the effects showed reversal to varying degrees, depending on dose. (It should be noted that the nasal morphology and respiratory physiology of the rodent is different from humans such that higher local exposure of the olfactory epithelium is expected to occur in rodents as compared to humans at equivalent airborne concentrations of MEKO.) A shorter (4-week) inhalation study, also in CD-1 mice, showed a slight increase in methemoglobin levels as well as increased spleen and adrenal weights, resulting in a NOAEL of 100 ppm (360 mg/m^3) and a LOAEL of 400 ppm (1440 mg/m^3). With repeated inhalation exposure in rats for 4 weeks, a NOAEL (hematology) of 25 ppm (90 mg/m^3) and a LOAEL of 100 ppm (360 mg/m^3) have been identified for the effects of MEKO on blood parameters, including increased levels of

methemoglobin. A second inhalation study in rats also found effects on the blood, but the results were confounded by a viral infection in the treated and control groups.

Gavage and drinking water studies with durations of 4 and 13 weeks have been conducted with rats and one 13-week drinking water study has been conducted in mice. A common effect observed in these studies is hematological effects such as anemia. Degeneration of the nasal epithelium was seen in both drinking water studies. In one 13-week gavage study with rats, a LOAEL of 25 mg/kg bw/day was determined based on hemolytic anemia seen even at the lowest treatment level. At higher doses in this study, anemia was fairly serious. Other effects observed in this study include dose-related effects on spleen and liver weights and compensatory hematopoeisis. In another 13-week gavage study in rats (designed to evaluate subchronic neurotoxicity), hematologic effects (including increased methemoglobin levels) were seen at doses of 40, 125, and 400 mg/kg bw/day. In a 13-week drinking water study with Fischer rats, the NOAEL was reported as 312 ppm (about 25 mg/kg bw/day). A LOAEL of 625 ppm (50 mg/kg bw/day) was set based on erythrotoxicity observed at this and higher doses. Degeneration of the nasal epithelium was observed at 2500 ppm (200 mg/kg bw/day) and higher. A 4-week gavage study in Fischer rats found effects on the hematopoietic system at 20 mg/kg bw/day and above, with a NOAEL of 4 mg/kg bw/day. A second 4-week gavage study in rats found no significant hepatic peroxisome proliferation. However, a LOAEL of 250 mg/kg bw/day was established for this study based on increased hepatic glutathione. A 13-week drinking water study in mice resulted in methemoglobinemia, responsive Heinze body anemia, increased spleen weights, and haematopoietic effects. Degeneration of the nasal olfactory epithelium was observed in addition to hyperplasia of the transitional epithelial lining of the urinary bladder. The NOAEL from this study was at 625 ppm (110 mg/kg bw/day) based on hyperplasia of the epithelial lining of the urinary bladder in males at 1250 ppm (200 mg/kg bw/day).

In the 13-week neurotoxicity study in rats described above, dose levels of 40 and 125 mg/kg bw/day did not elicit any consistent or apparent treatment-related change in neurobehavioral function or nervous system structure. However, transient neurobehavioral changes (cage removal, handling, posture, gait, arousal, salivation, approach response, rearing responses, and aerial righting) occurred at doses of 400 mg/kg bw/day. They were noted immediately after dosing, and had resolved by the next day. No progressive long term, irreversible neurotoxic changes were associated with MEKO administration (as was seen with the positive control agent).

In the 2-year inhalation oncogenicity study in rats (with interim analysis, sacrifices at 3, 12, 18 months), similar effects on blood parameters were seen at 375 ppm (1300 mg/m^3) at 3 months and 12 months but not at 18 months in males or at 26 months (both sexes). Effects to the spleen (increased organ weight, extramedullary hematopoiesis, and hemosiderosis) were seen at 375 ppm (1300 mg/m^3). Spleen weights were increased in both sexes at 3 and 12 months, 18 months (females only), but not at 26 months. The histopathological effects persisted at the same time points as the changes in spleen weights. Splenic histopathology could not be accurately determined at termination due to spontaneous leukemia. In the 374 ppm (1346 mg/m^3) group, testes were 82 percent heavier than the control group at study termination. There was a treatment-exaggerated increase in incidence of corneal dystrophy and opacities; these changes were much more severe at 374 ppm (1346 mg/m^3). At termination, there were increased red/tan discolorations and nodules/masses in the liver in the 374 ppm group. Other non-cancer effects in the liver included increased incidence of basophilic foci and hepatocellular vacuoles, adenomas, and spongiosis hepatis. Degenerative nasal effects were also observed at 12 and 18 months.

In the 2-year inhalation oncogenicity study in mice, the effects on the blood were less clear. There was an increase in methemoglobin at 12 months only in males. Other blood parameters were affected to varying degrees. Degenerative effects observed in the olfactory epithelium resulted in a LOAEL of 15 ppm (54 mg/m^3).

The type and pattern of hematological effects from the 2-year inhalation study at a relative high dose (1,360 mg/m^3) suggests that the degree of these blood effects is less severe when exposures to similar quantities of MEKO occur over an extended time period as is with inhalation exposure compared with oral gavage exposures. The repeated-dose studies also indicate that the rat is more sensitive to the hematotoxic effects of MEKO compared with mice.

The genotoxicity potential of MEKO has been well investigated both in-vitro (gene-mutation, chromosome aberration, and DNA studies) and in-vivo (gene mutation, chromosome aberration studies, and DNA study). Six reverse bacterial mutation assays conducted by several methods in standard bacterial strains did not find a mutagenic response in the presence or absence of rat liver activating enzymes. A single reverse mutation bacterial assay conducted by the preincubation method reported a mutagenic response in only tester strain TA1535 and only in the presence of high (not standard) levels of hamster liver activating enzymes. A mouse lymphoma study found evidence of mutagenic activity in the absence of rat liver activating enzymes but not following rat liver enzyme activation. *In vitro* studies for chromosome aberrations, SCE, unscheduled DNA Synthesis (UDS) were negative. *In vivo* Drosophila (for sex-linked recessive mutations), and micronucleus studies showed no evidence of genotoxicity. An *in*

vivo rat study to investigate the potential for MEKO to produce DNA adducts found no evidence of adduct formation with MEKO. The weight of evidence suggests that MEKO is likely to be non-genotoxic.

In carcinogenicity inhalation studies with MEKO with doses up to 374 ppm in rats and 375 ppm in mice showed MEKO to be a carcinogen to the liver only. In rats, these tumors developed late in life and did not appear to affect survival. .

In a 2-generation study with doses up to 200 mg/kg bw/day MEKO, no effects on reproduction were seen. No compound related effects on reproductive organs (sperm samples and vaginal samples inclusive) could be found in the subchronic studies in rats and mice Together these results suggest that there is no specific effect on the reproductive system. In developmental studies, the highest dose was 600 mg/kg bw/d in rats and 40 mg/kg bw/day in rabbits. MEKO showed no developmental effects even at maternally toxic doses (NOAEL (rat) < 60 mg/kg bw/day; NOAEL (rabbit) = 14 mg/kg bw/day).

Environment

MEKO is a liquid, with a water solubility of 110 g/l and a vapor pressure of 3.5 hPa at 20 °C. The octanol/water partition coefficient was Log Kow = 0.65 at 25 °C and the Henry's Law Constant is 1.04 x 10^{-5} atm-m^3/mol using the bond estimation method.
Photodegradation in the atmosphere occurs by reaction with OH radicals, with a half life of 7.2 days. The fugacity distribution modeling according to Mackay Level III indicates soil (40.8 %), air (9.2%), and water (50.0 %) to be the favored compartments in a scenario where equal amounts are released to soil, water, and air. In a scenario where 100 % of the releases are to air, the majority of MEKO (62.7%) remains in the air, 17 % goes to water, and 19.9 % goes to soil. Results of a hydrolysis test showed that after 4 days at pH 7, 14 % hydrolysis was observed. MEKO hydrolyzes to form methyl ethyl ketone and a hydroxylamine salt. MEKO was found to be inherently biodegradable in one test, whereas it was not biodegradable by a second test on inherent biodegradability. The measured BCFs in fish generally range from 0.5 to less than 2.5, indicating low or no bioaccumulation potential.

The reported toxicity data for MEKO in fish and daphnia show values greater than 100 mg/L. In the 72-hour algal toxicity study, the EC50s are reported as 11.6 mg/L (growth rate) and 6.09 mg/L (biomass). NOECs from this study are 2.56 mg/L (growth rate) and 1.02 mg/L (biomass).

Exposure

Worldwide production is estimated to be 10000 - 20000 tonnes per year. The major application is as anti-skinning agent for alkyd coating resins for use in solvent based paints. The concentration of MEKO in these products is typically 0.3 % (range 0.1% – 0.8 %). The next main applications are as a blocking agent for isocyanates (used as a raw material for powder coatings) and as a reactant in the manufacturing of oxime-silanes (used as cross linkers for one-component neutral cure silicone sealants). In case of oxime-crosslinkers and sealants thereof, the level of MEKO is generally less than 1.0%.

RECOMMENDATION

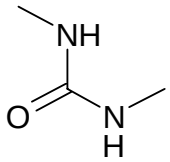
The chemical is a candidate for further work

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

MEKO possesses properties indicating a hazard for the environment and exposure assessment (production/formulation

sites and end use products) is recommended as post-SIDS work. MEKO is clearly a chemical with hazardous properties (slightly irriatant to skin, severely irritant to eyes, and sensitizing to animals) and measures should be taken to control exposures to acceptable levels. The potential for hazards to human health and exposure to consumers warrant an in-depth exposure assessment as post-SIDS work to estimate consumer exposure. In addition, the U.S. will evaluate the 2-year inhalation carcinogenicity study and mechanistic data for MEKO.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	**96-31-1**
Chemical Name	**1,3-Dimethylurea**
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,3-Dimethylurea was not tested in experimental studies for its toxicokinetics.
The approximate oral LD50 of 1,3-dimethylurea in rats was determined to be 4,000 mg/kg bw. Clinical signs of toxicity were nonspecific and included apathy and narcotic-like state at dose levels near to or exceeding the LD50. No valid test is available on the acute inhalation toxicity. 1,3-Dimethylurea has not been tested for its acute dermal toxicity.
1,3-Dimethylurea (tested as 80 % aqueous solution) was only slightly irritating to the skin of rabbits after 24 hours of occlusive exposure. The undiluted test material induced lacrimation, corneal opacities and redness in the eyes of rabbits with some effects (redness, corneal opacity). The effects were still present in one of the two studies at study termination on day 8 in one animal.

After repeated oral administration for 28 days by gavage to rats in a study following OECD TG 407 (1981), 1,3-dimethylurea caused alterations in the kidneys (tubular necroses, desquamation of tubular epithelial cells and protein casts in the tubuli) in males at 150 and 450 mg/kg bw/day, and nonspecific tubular hyperplasia in females at 450 mg/kg bw/day. The NOAEL was 50 mg/kg bw/day.

1,3-Dimethylurea was not mutagenic in bacterial and mammalian cell culture systems and did not induce chromosomal aberrations in Mouse Lymphoma cells, both in the presence and in the absence of metabolic activation systems. There is no available information from *in vivo* genotoxicity studies in mammals. It is noted that mutagenic nitrosoureas may be produced from 1,3-dimethylurea with nitrite; therefore, a mutagenic potential cannot be totally excluded.

1,3-Dimethylurea had no adverse effects on reproductive performance and fertility of rats in a combined reproduction/developmental toxicity, screening test according to OECD TG 421 (NOAEL, reproductive performance/fertility: 200 mg/kg bw/day (highest tested dose level)). No teratogenic effects, but embryo-/fetotoxicity (reduced placental and fetal body weights) and an increase in the incidence of fetuses with a soft tissue variation (hydroureter) and with delayed ossifications in sternebrae were found at maternally toxic dose levels in a developmental toxicity study in rats in accordance with OECD TG 414 (NOAEL for developmental toxicity and maternal toxicity: 30 mg/kg bw/day).

It is noted that carcinogenic nitrosoureas may be formed with nitrite.

Environment

1,3-Dimethylurea is an organic solid with a melting point of 102 – 107 °C and a density of 1.142 g/cm^3. It has a

water solubility of 765 g/l at 21.5 °C, (pH = 9 – 9.5 at 100 g/l), a vapor pressure of 0.00042 hPa (at 20 °C) and a measured log K_{OW} of –0.783 (at 25 °C).

The substance is readily biodegradable as shown in a DOC Die-Away-Test according to OECD TG 301A with non-adapted inoculum. At a test substance concentration of 50 mg/l, a biodegradation of > 93 % within 10-days was found. In unsterilized soil 1,3-dimethylurea is fairly rapidly mineralized.
The log Kow and a calculated BCF of 3 do not indicate a significant potential for bioaccumulation.
Using a fugacity model (Mackay level I), the substance is predicted to appear mainly in the aqueous compartment (> 99.9 %), with 0.0013 % in soil and 0.0013 % in sediment, and negligible amounts in air. The hydrosphere is therefore the target compartment for this substance. 1,3-Dimethylurea is potentially susceptible to hydrolysis because of the amide structure. The calculated half-life for hydrolysis, however, is over one year. The half-life for photo-oxidation in water (reaction with OH radicals) is estimated at 111 days. The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of 1,3-dimethylurea in air is 5.2 days. Adsorption to solid phase is not expected based on a calculated log Koc of 0.946.

Short-term tests with fish, invertebrates and algae are available for 1,3-dimethylurea. The lowest effects values from the short-term tests are: *Leuciscus idus*: 96h-LC_{50} ca. 10,000 mg/l, *Daphnia magna*: 48h-EC_{50} > 500 mg/l, *Scenedesmus subspicatus* 72h-E_rC_{50} > 500 mg/l (72h-E_bC_{50} = 560 mg/l). Applying an assessment factor of 1000 according to the EU Technical Guidance Document, a $PNEC_{aqua}$ of 0.5 mg/l is derived from the 48h EC_{50} for *Daphnia magna*.

Exposure

For 2001, estimated production quantities are less than 10,000 metric tonnes in Europe (Germany), less than 5,000 metric tonnes in the US and less than 15,000 metric tonnes in Asia (the worldwide production volume being less than 25,000 metric tonnes).
The substance is mainly used as an industrial intermediate in the synthesis of caffeine, pharmachemicals, textile aids, herbicides and others. According to Swiss, Danish and Swedish Product Registers 1,3-dimethylurea is contained in a large number of products. Some of them may be available to consumers and contain the substance in concentrations up to 10 %.
Releases into the environment may occur from production of 1,3-dimethylurea and from its use as intermediate as well as from use of products containing the substance.
Occupational exposure may occur during production and processing of 1,3-dimethylurea. No workplace exposure information is available with regard to the manufacturing and processing sites.

RECOMMENDATION

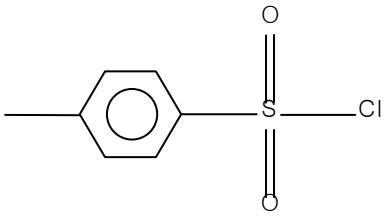
The chemical is currently of low priority for further work.

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 No.	98-59-9
Chemical Name	4-Methylbenzenesulfonyl chloride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information on toxicokinetics, metabolism and distribution.

The acute oral toxicity study [OECD TG 423] of 4-methylbenzenesulfonyl chloride in rats showed that this chemical did not cause any significant changes in terms of LD_{50} at 2,000 mg/kg b.w for 1st and 2nd steps, and 5,000 mg/kg bw for limit test. Therefore, the oral LD_{50} value in female rats was greater than the highest tested dose (5,000 mg/kg bw). However, in a dose-finding study for an *in vivo* micronucleus test, at 200 mg/kg bw, all three female mice died.

Investigation was performed to observe effects of 4-methylbenzenesulfonyl chloride such as erythema and oedema on the abraded and intact backs of New Zealand White rabbits [OECD TG 404]. According to the results, the test substance induced irritation on the skins of rabbits. regarding eye irritation, a test was performed according to the FHSA protocol, in which the eyes were exposed for 24 hours then scored at 24, 48 and 72 hours after the exposure. Accordingly, 4-methylbenzenesulfonyl chloride induced corrosion and irritation on the eyes of New Zealand Albino Rabbits.

In the Combined Repeated Dose and Reproduction/Developmental Toxicity Screening Test in rats [OECD TG 422], 4-methylbenzenesulfonyl chloride was administrated by gavage at the dose levels of 0, 150, 350 and 750 mg/kg bw/day for 35 days and 36 ~ 51 days for male and female rats, respectively. Some clinical signs were observed at the dose level of 150 mg/kg bw/day in males such as intermittent (blood-like) salivation and staining around mouth; and in females such as intermittent (blood-like) salivation, staining around mouth, difficult delivery, poor nursing, irregular respiration. Based on these results, the LOAEL and NOAEL were determined to be 150 mg/kg/day and below the lowest tested dose (150 mg/kg/day) for both sexes, respectively.

In vitro bacterial gene reverse mutation tests [OECD TG 471 and 472] gave negative results in *Salmonella typhimurium* (strains TA98, TA1535 and TA1537) and *Escherichia coli* WP2 *uvr*A with and without metabolic activation. *Salmonella tryphimurium* (TA100 strain) showed positive mutagenic effects at concentrations of 1,250, 2,500 and 5,000 μg/plate without metabolic activation and the same strain (TA100) showed negative results with metabolic activation. Furthermore, an *in vivo* mutagenicity test, mammalian erythrocyte micronucleus assay (OECD TG 474) was negative. No firm conclusion can be reached from the available mutagenicity results.

In a reproduction/developmental toxicity screening test [OECD TG 422] with male and female rats, there were no significant treatment-related changes in terms of pregnancy, fertility, examination of pups etc. Therefore, LOAEL and NOAEL for reproduction and development are considered to be greater than 750 mg/kg bw/day.

Environment

4-Methylbenzenesulfonyl chloride is a colorless to light yellow crystalline solid which is hygroscopic and highly reactive. It has a melting point of 71 °C, a boiling point of 145 - 146 °C at 15 mmHg, a density of 1.33 g/cm^3, a vapour pressure of 0.16 Pa at 25 °C and a Henry's law constant of 9.67 x 10^{-6} atm•m^3/mole at 25 °C. Due to the rapid hydrolysis of 4-methylbenzenesulfonyl chloride, water solubility and partition coefficient n-octanol/water cannot be measured. Hence a partition coefficient n-octanol/water (log P_{ow}) of 3.49 at 25 °C and a water solubility of 51.18 mg/L at 25 °C were estimated.
4-Methylbenzenesulfonyl chloride is hydrolysed to 4-methylsulfonic acid and half-lives ($t_{1/2}$) at 25 °C in water are 2.2 min at pH 4, 2.2 min at pH 7 and 2.6 min at pH 9. The substance is not readily biodegradable. The calculated half-life for photochemical-oxidative degradation in the atmosphere by OH radicals is 8.7 days. According to a level III fugacity modeling (EQC model) if 4-methylbenzenesulfonyl chloride is emitted to air, it will mainly partition to soil (97.6 %) and if it is released to water, it will mainly remain in water (79.2 %). If it is released to soil, it will mainly remain in soil (100 %). Based on rapid hydrolysis of the substance, bioconcentration of 4-methylbenzenesulfonyl chloride is not expected. 4-Methylbenzenesulfonic acid is a strong acid (pK = -1.34) and is completely dissociated at the environmental pH. According to a level III fugacity modeling (EQC model) if 4-methylbenzenesulfonic acid is emitted to air, it will mainly partition to soil (78.4 %) and if it is released to water, it will mainly remain in water (99.8 %). If it is released to soil, it will mainly remain in soil (80.6 %). The calculated BCF value of 4-methylbenzenesulfonic acid was 3.16. Both the substance and its hydrolysis product have a low potential for bioaccumulation.

The following toxicity data for aquatic organisms are available for 4-methylbenzenesulfonyl chloride:
Green algae (*Selenastrum capricornutum)*: EC_{g50} (72 h) > 100 mg/L (growth rate)
Invertebrates (*Daphnia magna):* EC_{50} (48 h) = 70 mg/L.
Fish (*Oryzias latipes*): LC_{50} (96 h) = 55 mg/L.

In preliminary tests with adjustment of pH with fish and daphnia, at 100 mg/L of 4-methylbenzenesulfonyl chloride, no effects were seen in fish and daphnia after 48 hours of exposure.

The following toxicity data for aquatic organisms are available for 4-methylbenzenesulfonic acid:
Green algae (*Chlorella vulgaris*): EC_{50}(24h) = 245 mg/L (unspecified)
Invertebrates (*Daphnia magna*) : EC_0(24h) > 2500 mg/L.
Fish (*Leuciscus idus melanotus*): LC_{50} (96h) > 500 mg/L
Microorganisms (anaerobic bact. from a domestic water treatment plant): SG(24h) > 5000 mg/L

No data are available on terrestrial organisms.

Exposure

In the Sponsor country, the production amount for 4-methylbenzenesulfonyl chloride was estimated to be about 542.7 tonnes in 2001. Around 689.8 tonnes were imported into Korea from China in 2001.
In the Sponsor country 4-methylbenzenesulfonyl chloride is produced as a by-product from the reaction of HSO_3Cl and toluene in the food additives industry and this chemical is used as a raw material for the production of foaming agents for the plastic and rubber industry, of riboflavin and antithrombotic drug in the pharmaceutical industry and of a condensing agent in the dye industry.
Environmental releases are unlikely to occur during industrial production and processing of 4-methylbenzenesulfonyl chloride as these processes take place in closed systems. If environmental releases occur during these operations, they will be in the form of the hydrolysis product 4-methylbenzenesulfonic acid.
There is a potential of exposure for workers via dust inhalation and dermal routes at the packaging process. Based on physico-chemical properties and the hygroscopic nature of this chemical, if workers are exposed, they are likely to be exposed to the acid. Although 4-methylbenzenesulfonyl chloride is used as a raw material in several industries, there is no direct use or consumer products containing the substance. Therefore, consumer exposure to the substance is not expected.

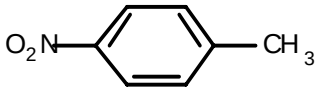
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health (e.g. irritation, uncertainty for genotoxicity). 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	99-99-0
Chemical Name	4-Nitrotoluene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

4-Nitrotoluene is rapidly absorbed via skin, gastrointestinal or respiratory tract, and distributed throughout the body. The primary metabolic pathway is side-chain or ring oxidation and conjugation with glucuronic acid and inorganic sulfates with subsequent renal excretion. In rats, the involvement of enterohepatic circulation was also observed.
4-Nitrotoluene is a methemoglobin forming chemical. Tachypnea, wheezing, somnolence and cyanosis were the predominent clinical signs following oral doses near to or exceeding the LD50 values. Methemoglobinemia was reported in rats after dermal exposure to high dose levels (LD50, oral, rat: 2144 - 4700 mg/kg bw; LD50, dermal, rats: > 750 mg/kg bw, LD50, dermal, rabbits: > 20,000 mg/kg bw; LC50, inhalation, rat: > 851 mg/m³/4h; no information on particle size available).
4-Nitrotoluene is not irritating to the skin and eyes of rabbits (OECD TG 404, 405). It was not sensitizing to the skin of guinea pigs in the Single Injection Adjuvant Test (SIAT) and in the Buehler test (OECD TG 406).

In 13 week and 2 year feeding studies with rats, 4-nitrotoluene caused hematopoiesis and hemosiderin pigment accumulation in the spleen of both sexes at all dose levels tested. Methemoglobinemia was noted at study end in the 13 week study at 10,000 ppm (male: approximately 723 mg/kg bw/day, female: approximately 680 mg/kg bw/day). At high and systemically toxic exposure levels, testicular degeneration was found in the males, and lengthened estrous cycles in the females. In male rats, α2u-globulin nephropathy was observed in all dosed groups. This effect is species specific and therefore of no relevance for humans (LOAEL: 625 ppm, corresponding to approximately 42 mg/kg bw/day, based on splenic toxicity). No relevant chemical related lesions were seen in mice in 13 week feeding studies. The NOAEL based on body weight reduction was 2500 ppm (approximately 439 mg/kg bw/day). In 2-year feeding studies, male and female mice showed an increase in alveolar bronchiolar epithelialization, and syncytial alterations in hepatocytes were found in males (LOAEL 1250 ppm = approximately 155 - 170 mg/kg bw/day). Immunological dysfunction has been reported in mice. The toxicological significance of the effects is not certain.

In vitro, 4-nitrotoluene showed no mutagenic effect in good quality Ames tests with *Salmonella typhimurium* and *Escherichia coli*, with and without metabolic activation. In cultured mammalian cells, 4-nitrotoluene has demonstrated the potential to cause mutagenicity in the presence of metabolic activation. The chemical did not induce unscheduled DNA synthesis in hepatocytes. *In vivo*, 4-nitrotoluene had no genotoxic activity. The substance did not induce micronuclei in rat and mice bone marrow cells in studies performed according to the current standard (OECD TG 474), and it did not induce unscheduled DNA synthesis in rat *ex vivo* hepatocytes.

Under the conditions of the two year feed studies, there was equivocal evidence of carcinogenic activity of 4-nitrotoluene in male rats based on the increased incidences of subcutaneous skin neoplasms. There was some evidence of carcinogenic activity in female rats based on increased incidences of clitoral gland neoplasms. There was equivocal

evidence of carcinogenic activity in male mice based on increased incidences of alveolar/bronchiolar neoplasms. There was no evidence of carcinogenic activity in female mice exposed to 1250, 2500, or 5000 ppm (approximately 155, 315, or 660 mg/kg bw/day).

4-Nitrotoluene had no adverse effects on most reproductive endpoints (insemination index, fertility index, time to insemination, gestation length, number of corpora lutea and number of implantation sites, live birth index) in a rat oral Reproductive/Developmental Toxicity Screening Test (OECD TG 421), even under conditions where overt systemic toxicity was observed. A reduction in the gestation index, increased prenatal loss and reduced litter size and pup weights were reported at parentally toxic doses. Testicular degeneration was found in subchronic studies at systemically toxic dose levels characterized by reduced body weights and toxicity to the spleen subsequent to the erythrocyte damaging effect of 4-nitrotoluene ($NOAEL_{reproductive\ toxicity}$: 25 mg/kg bw/day; $NOAEL_{developmental\ toxicity}$: 25 mg/kg bw/day, $NOAEL(male)_{general\ toxicity}$: 25 mg/kg bw/day; $LOAEL(female)_{general\ toxicity}$: 25 mg/kg bw/day).

Based on the available data, there was no evidence of a relevant hormonal activity of 4-nitrotoluene from various *in vitro* and *in vivo* screening tests.
Cases of poisoning from nitrotoluene are uncommon. They are reported only from early production units and relate to mixed exposures. The signs of intoxication included cyanosis, difficulties in breathing and tachycardia. In the recent open literature reports of human poisoning could not be identified.

Environment

4-Nitrotoluene has a melting point of 51.3 °C, a boiling point of 238 °C and a density of 1.29 g/ml at 20 °C. It has a vapour pressure of 13 Pa at 20°C. The log Kow is 2.37 . The solubility in water is 345 mg/l at 20 °C. The flash point is ca. 103 °C, the auto flammability (ignition temperatur) 450 °C.
With regard to its chemical structure 4-nitrotoluene is not expected to hydrolyse under environmental conditions. During 8 days of a stability experiment at pH 8 and 25 °C about 6 % of 4-nitrotoluene (purity of 99.5 %) were lost in water.
According to Mackay level I fugacity model the main target compartments for 4-nitrotoluene are air (63.6 %) and water (35 %). A measured Henry's law constant of 0.57 $Pa \cdot m^3 \cdot mol^{-1}$ indicates a moderate potential for volatilization of 4-nitrotoluene from aqueous solution. In the atmosphere 4-nitrotoluene is degraded due to indirect photolysis ($t_{1/2air}$: 20.8 days) and direct photolysis. In surface waters the half life is estimated to be 6 hours due to photodegradation.
Since in the MITI-test, only 0.8 % of 4-nitrotoluene were mineralised within 14 days, 4-nitrotoluene is not readily biodegradable. Nevertheless studies on inherent biodegradation show 4-nitrotoluene to be biodegradable under aerobic conditions with adapted bacteria (degradation 100 % after 21 d including 10 d adaptation).
Bioconcentration factors determined for fish were in the range of 3.7 – 27 and thus indicate no significant bioaccumulation potential of 4-nitrotoluene. Binding to soil organic matter has been calculated with Koc = 309. 4-Nitrotoluene can be regarded as a substance with medium geoaccumulation properties. The adsorption constants of 4-nitrotoluene were 5 - 45 l/kg on three clay minerals indicating a low adsorption by clays.

Concerning the acute toxicity of 4-nitrotoluene towards aquatic species reliable experimental results of tests with fish, daphnids, and algae are available.
The acute fish toxicity was 10.5 mg/l for Carassius auratus (48 h-LC_{50}), ca. 40 mg/l for Cyprinus carpio (96 h-LC_{50}), 50 mg/l for *Pimephales promelas* (96 h-LC_{50}), and 74 mg/l (48 h-LC_{50}) for *Oryzias latipes.* For *Daphnia magna* 48 h-EC_{50}-values of 4.2, 7.5, and 11.8 mg/l were found. In the algae growth inhibition tests with *Chlorella pyrenoidosa* the 96 h-EC_{50} was 22.2 mg/l, and with *Scenedesmus obliquus* the 48 h-ErC_{50} was 25 mg/l.
The long-term toxicity to fish (*Oryzias latipes*, *Poecilia reticulata*) for the endpoints mortality and swimming behaviour, was evaluated by two 28 days tests. The NOEC values were 0.8 mg/l and 10 mg/l. A chronic toxicity test for the endpoint hatching rate of *Oryzias latipes* yielded a 40 d-NOEC of 32 mg/l. For the endpoints mortality, growth, and swimming behaviour of *Oryzias latipes,* a 40 d-NOEC of 1 mg/l were determined. Two chronic tests with *Daphnia magna* are available. The 21 d-NOECs were 0.7 mg/l and 1 mg/l, respectively, both for the endpoint reproduction rate. In a non-guideline study with the non-standard test species, the mollusc *Lymnaea stagnalis*, a 40 d-NOEC of 0.32 mg/l was determined for the endpoint reproduction. In the growth inhibition test with algae (*Scenedesmus pannonicus*) no effect on biomass was observed at 10 mg/l 4-nitrotoluene after 4 days.

Based on the chronic aquatic toxicity data on three trophic levels (fish, invertebrate, algae), a Predicted No Effect Concentration (PNEC) can be calculated with an assessment factor of 10. Using a 40 d-NOEC of 0.32 mg/l of *Lymnaea stagnalis*, a PNEC of 32 µg/l was determined.

Exposure

About 77,000 tonnes of 4-nitrotoluene were produced worldwide in 2000; Western Europe 30,000 t/a, China 26,000 t/a, US 9,000 t/a, Eastern Europe 5,000 t/a, India 4,000 t/a, and South Korea 3,200 t/a. The total manufacturing capacity of the lead company amounts to 28,000 t/a in 2000.
4-Nitrotoluene is a basic chemical for the synthesis of intermediates which are further processed to optical brighteners, coloring agents, pharmaceuticals, and agrochemicals, and others within the chemical industry. A direct use is not known.
From the production and processing site of the lead company virtually no 4-nitrotoluene was emitted into the environment in 2001. Taking into account the detection limit (2 µg/l), the 10 percentile of the river flow (1050 m^3/s), and the dilution factor (700), for the receiving water a Predicted Environmental Concentration (PEC) of < 2.8 ng/l is calculated.
In Gemany in 1999, the 90-percentile of the 4-nitrotoluene concentrations in the River Rhine was < 0.5 µg/l and in the River Danube < 0.02 µg/l. For the River Elbe the maximum was 0.05 µg/l.
During manufacturing and processing of 4-nitrotoluene workers may be exposed through the inhalational, dermal and oral routes. At the lead company the exposure of workers is well below the German Occupational Exposure Limit of 5 ppm (28 mg/m^3). The levels of metabolic products of 4-nitrotoluene in workers are not higher than in the unexposed population.
4-Nitrotoluene is formed during tobacco smoking. At former munition manufacturing sites or at historic landfills 4-nitrotoluene might occur in groundwater and leachate. A significant indirect exposure of the general public via the environment is however not expected.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:
The chemical possesses properties indicating a hazard for human health. Based on data presented by the sponsor country, exposure is controlled in occupational settings, and is negligible for consumers. Any exposure scenario not presented by the Sponsor country will have to be investigated, however.

Environment:
The chemical possesses properties indicating a hazard for the environment. 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, e.g. exposure from munitions dumps or former munitions sites.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-31-2 97-72-3
Chemical Name	Isobutyric Acid (CAS No. 79-31-2) Isobutyric Anhydride (CAS No. 97-72-3)
Structural Formula	Isobutyric Acid $HO-C(=O)-CH(CH_3)-CH_3$ Isobutyric Anhydride $CH_3-CH(CH_3)-C(=O)-O-C(=O)-(CH_3)-CH-CH_3$

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The category members isobutyric acid (CAS No. 79-31-2), and isobutyric anhydride (CAS No. 97-72-3) are closely related since the anhydride rapidly hydrolyzes in the presence of water to form the acid. Since testing of the anhydride is in reality testing of the acid form, these materials share toxicity characteristics and form the basis of the category. As a result, the metabolic series approach can be used to address the non-acute health endpoints.

Increased blood levels of isobutyric acid have been demonstrated following administration of isobutanol, a metabolic precursor of isobutyric acid. Hazard identification studies using isobutanol exposures have been used to identify the hazards associated with systemic exposure to isobutyric acid. Therefore, isobutanol (78-83-1) is used as an analog to either address or supplement the respective systemic toxicity endpoints for isobutyric acid.

Based on hydrolysis data, the acute aquatic toxicity endpoints of both isobutyric acid and isobutyric anhydride have been addressed using data from structural analogs, alleviating the need for additional testing on isobutyric acid. As a result, available data from propionic acid (CAS No. 79-09-4) and pentanoic acid (CAS No. 109-52-4) have been used to address the acute aquatic toxicity of isobutyric acid. In addition, data from propionic acid (CAS No. 79-09-4), n-butyric acid (CAS No. 107-92-6) and pentanoic acid (CAS No. 109-52-4) have been used to address the biodegradability of isobutyric acid.

Human Health

The acute oral and dermal LD_{50} values for isobutyric acid are >500 mg/kg/bw (rat) and >200 mg/kg/bw (rabbit), respectively. The oral and dermal LD_{50} for isobutyric acid is used for isobutyric anhydride. Data are available for the anhydride via the inhalation route indicating a low toxicity with an LC_{50} value of >5.1 mg/L.

Both the acid and anhydride forms are considered moderate to severe eye irritants. Isobutyric acid is a moderate to severe skin irritant and is corrosive to skin. Isobutyric anhydride is not a skin irritant unless it comes in contact with water and hyrolyses to isobutyric acid (a moderate to severe skin irritant). Based on clinical signs observed in the LC50 study (e.g. rales, nasal secretions, weight loss) airborne isobutyric acid or isobutyric anhydride can cause irritation of the upper respiratory tract. Repeated inhalation exposures would likely exacerbate the irritative effects. Although reported as a non-sensitizer, sensitization data are not available.

Repeated exposures to moderate to high concentrations of isobutanol (the metabolic precursor of isobutyric acid) are well tolerated in rats. In a 90-day inhalation study, rats were exposed to isobutanol at 0, 250, 1000, and 2500 ppm. A reduced response to an external stimulus was noted in the exposed animals. Repeated exposures did not exacerbate these transient effects. There was no evidence of neurotoxicity based on functional observational battery (FOB), quantitative motor activity, neuropathy and scheduled-controlled operant behavior endpoints. Slight increases in red blood cell count, hematocrit, and hemoglobin parameters were reported in the 2500 ppm female rats. A 13-week oral gavage study was conducted with isobutanol with dose levels of 0, 100, 316, and 1000 mg/kg. Hypoactivity, ataxia, and salivation were noted in the 1000 mg/kg dose groups after dosing. In addition slight decreases in body weight gain and feed consumption was noted in the first two weeks of the 13-week study in the 1000 mg/kg dose group. The 100 and 316 mg/kg dose groups were unaffected.

The developmental/reproductive toxicity for isobutyric anhydride and isobutyric acid have been met for the purposes of the OECD SIDS program. An inhalation two-generation reproductive toxicity study conducted with isobutanol (up to 2500 ppm) did not cause any parental systemic, reproductive, or neonatal toxicity when administered for two generations via whole-body exposure. No adverse developmental effects were noted in rats or rabbits exposed to 10 mg/L isobutanol during gestation.

Isobutyric acid is not mutagenic in bacteria *(Salmonella typhimurium*, *Bacillus subtilis*, or *Escherichia coli*). An *in vivo* mouse micronucleus test conducted with isobutanol administered once orally to male and female NMRI mice at doses up to 2000 mg/kg body weight did not produce any chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis (spindle poison effect).

Environment

The preferred physical property values for isobutyric anhydride are: melting point –53.5 ^{0}C, boiling point 181.5 ^{0}C, density 0.9535 g/m^3, vapor pressure 5 hPa (at 50^{0}C) and 1.20 hPa (at 25°C), log Kow 1.24, aqueous solubility 16030 mg/L. The preferred physical property values for isobutyric acid are: melting point -47 ^{0}C, boiling point 153-155 ^{0}C, density 0.95 g/m^3, vapor pressure 19.6 hPa, log Kow 0.94, aqueous solubility 167,000 mg/L, Henry's law constant 8.85x10^{-7} atm-m^3/mol, and pKa 4.84-4.86. These compounds are liquid at 25°C and are very water-soluble. Under environmental conditions, based on its pKa, the acid is expected to exist primarily in its dissociated form. Neither compound is expected to be volatile.

Calculated atmospheric photo-oxidation half-lives were 5.7 days for isobutyric anhydride and 4.6 days for isobutyric acid. Isobutyric anhydride is unstable in water with half-lives of 2 - 17 minutes at environmentally relevant pH values pH 4 to 9 (23°C). Isobutyric acid is the hydrolysis by-product.

Level III fugacity modeling results indicate that isobutyric acid (which is representative of isobutyric anhydride) will primarily partition to soil (45.3%) and water (45.7%).

Biodegradation testing cannot be performed for isobutyric anhydride. Isobutyric acid rapidly biodegrades under anaerobic conditions (100% in 3 days). Manometric respirometry studies conducted for 30 days for the analog compounds propionic, n-butyric, and pentanoic acids showed biodegradation of 74, 58, and 72% ThOD, respectively. In addition, a modified MITI test (OECD 301C) with n-butyric acid reported 72% ThOD in 5.8 days. Collectively, these data with analog compounds support the conclusion that isobutyric acid is rapidly biodegradable. This conclusion is further supported by unverifiable BOD5 test with isobutyric acid. Fish bioconcentration factors of <2 to 3.16 were calculated for isobutyric acid. Based on the reactive nature of isobutyric anhydride, its tendency to hydrolyze in aqueous media, and the low log Kow value of the acid (0.94) one can conclude that isobutyric acid is not expected to bioaccumulate.

Aquatic toxicity data are only presented for isobutyric acid, due to the rapid hydrolysis of isobutyric anhydride in water. Since there is only aquatic invertebrate data available for isobutyric acid, data for analogous compounds are presented as well. The analogous compounds used were propionic acid ($C_3H_6O_2$, pKa 4.88) and pentanoic (valeric) acid ($C_5H_{10}O_2$, pKa 4.84). In fish *(Pimephales promelas*) the 96-hour LC_{50} values are 51.8 and 77 mg/L for propionic acid and pentanoic acid, respectively. Isobutyric acid was tested in Daphnia magna with the 48-hour EC_{50s} value of

51.25 mg/L. In green algae (*Scenedesmus subspicatus*) the 96-hour EC_{50} value is 42.9 mg/L for propionic acid and using *Selenastrum capricornutum*, a 96-h EC50 of 10.7 mg/L was reported for pentanoic acid. The pH was not controlled in any study after test initiation. In all studies, at least at higher concentrations, pH in the test medium was reduced to as low as 4.4 to 5.8 during the test. However, since pH was not a controlled variable in any test, effects on toxicity attributable to pH fluctuations cannot be discerned. Furthermore, with a pKa of 4.84-4.86, it is not likely that the acute aquatic toxicity of butyric acid will be dependent upon pH at environmentally relevant pH values (6 to 8). The toxicity of isobutyric acid (unbuffered) to fish, invertebrates and green algae is expected to range between 10.7 and 77 mg/L based on data for isobutyric acid and its analogs.

Exposure

Both isobutyric anhydride and isobutyric acid are manufactured in closed-systems in the sponsor country, and transported in tank cars, thus releases to the environment are anticipated to be minimal. Exposure of workers in processing facilities is likely to be limited by recommended personal protective equipment, its very distinct disagreeable odor, and because of the strong irritative properties of isobutyric anhydride. General population exposure is not anticipated, as isobutyric anhydride is not used in consumer products. Most isobutyric acid manufactured is consumed as an industrial intermediate in the production of other chemicals, such as isobutyronitrile and sucrose acetate isobutyrate. The major consumer use of isobutyric acid is as an approved additive in various foods, but in terms of total pounds manufactured, this is a very low percentage use. General population exposure to isobutyric acid may occur via its artificial and natural presence in foods. Environmental sources include fugitive emissions during its production and use, the exhaust of motor vehicles, and in vegetable oils and animal fluids. Isobutyric acid is an important metabolite in the breakdown of carbohydrates, fats and proteins. Isobutyric acid may arise from natural fermentation processes occurring in sediment and is a natural component of fruits, grains, and essential oils.

RECOMMENDATION

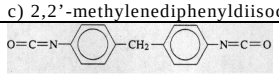
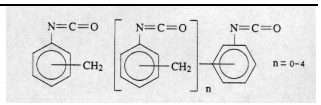
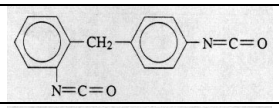
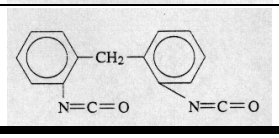
The Isobutyric Acid/Isobutyric Anhydride Category is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

These chemicals possess properties indicating a hazard for human heath (dermal, respiratory, and eye irritation) and the environment. Although these hazards do not warrant further work as they are related to transient effects or acute toxicity 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.	26447-40-5
Chemical Name	Methylenediphenyl diisocyanate ('MDI')
Structural Formula	Mixture of monomeric, oligomeric and polymeric MDI.

CAS-No.	101-68-8 (a); 5873-54-1(b); 2536-05-2 (c)	26447-40-5	9016-87-9
Chemical Name	Monomeric MDI a) 4,4'-methylenediphenyldiisocyanate b) 2,4'-methylenediphenyldiisocyanate c) 2,2'-methylenediphenyldiisocyanate	MDI (generic)	Polymeric MDI
Structural formula a)			
b)			
c)			

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The predominant commercial product covered by the term MDI is the liquid reaction mixture produced from methylene di-aniline. It comprises 4,4'-MDI and its oligomers with small amounts of the other monomers 2,4-MDI and 2,2'-MDI. It is commonly termed 'polymeric MDI' also called 'generic', 'crude' or 'non-isomer specific' MDI. A relatively small proportion is converted to monomeric MDI (essentially 4,4'-MDI) by purification. The data-set on this 'generic MDI' covers also the testing results on the other MDI analogues.
The category approach is considered justified since the substances have closely related composition i.e. excess of monomeric MDI as well as comparable –NCO content that are considered as the primary determinants of (eco)toxicity.

Human Health

There are few data available on the toxicokinetics and fate of MDI in humans. Urinary 4,4'-methylenedianiline, measured after acid hydrolysis, has been suggested as a biomarker for short-term exposure to MDI. 4,4'-methylenedianiline (4,4'-MDA), released by hydrolysis of plasma or haemoglobin, has been suggested as a biomarker of intermediate and long-term exposure to MDI. No information is available on the toxicokinetics of MDI following oral exposure in animals.
Contradictory results have been obtained with respect to dermal exposure. Eventually, a dermal absorption of 1% is taken – as reasonable worst case estimate - to use in dermal exposure calculations.
With respect to inhalation exposure, there is reliable data regarding distribution/excretion in experimental animals. In biomonitoring studies haemoglobin adducts and urine metabolites of MDI were determined. From the data generated to date, it is not possible to state categorically that the MDA measured in the majority of studies investigating levels in

blood and plasma represents a metabolite of MDI. The results of the inhalation metabolism / toxicokinetics / distribution study implicate that a proportion of the MDI dose is converted to metabolites via the intermediary formation of an amine group which is rapidly acetylated. However, it is not possible from the current data to elucidate the mechanisms in the biological transport and transformation of MDI. Further studies using biologically relevant *in vitro* systems are ongoing Additional studies are being designed to investigate metabolism of formed conjugates and any role of free or bound MDA in MDI transformation.

Assessment of the available acute toxicity data indicates that inhalation exposure to respirable aerosols of MDI results in toxicity confined predominantly to the respiratory tract. A well-conducted animal study gives a LC_{50} (4 h, rat) of 490 mg/m^3. The limited data available from animal studies indicate that MDI is of low oral and dermal acute toxicity, with an oral LD_{50} (rat) > 10,000 mg/kg and dermal LD_{50} (rabbit) > 10,000 mg/kg.

MDI is a known skin and eye irritant. The toxicity studies, mechanistic studies, and human data indicate that MDI causes irritation of the respiratory tract. A RD50 (mice) due to pulmonary irritation of 32 mg/m³ was found. An acute irritant threshold concentration of 0.5 mg/m³ was estimated from rat studies based on most sensitive (and reversible) endpoints in bronchoalveolar lavage fluid.

MDI has also a skin sensitising potential. Animal studies indicate that MDI is a strong allergen. A few human case reports describe allergic contact dermatitis due to MDI exposure. MDI is a well-established respiratory sensitiser in animals and humans. Animal studies have shown that respiratory sensitisation can be induced by skin contact with MDI. The quantitative relationships between exposure (concentration, duration, rate of exposure, route of exposure) and incidence of sensitisation have not been established. No threshold level for sensitisation could be determined. Extensive information is available on the mechanism of hypersensitivity. Cross-reactivity with other isocyanates has been described in several publications.

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure. Well-conducted short-term and long-term inhalation animal studies indicate the respiratory tract to be the target organ of respirable MDI aerosol. The reported NOAELs for chronic toxicity (inhalation, rat, 2 years) are 0.23 and 0.2 mg/m³ (final NOAEL = 0.2 mg/m³); LOAEL being 1 mg/m³. The reported NOAEL for short-term toxicity is 1.4 mg/m³; the LOAELs for short-term toxicity being 2 mg/m³ and 1 mg/m³; and a LOEL being 1.1 mg/m³. At present, the NOAEL used for short-term toxicity is 0.5 mg/m³ (for this estimation the $LOAEL_{(acute, rat)}$ of 0.7 mg/m³, based on a transient dysfunction of the pulmonary epithelial barrier, was taken into account).
The effect of long-term exposure of MDI on the respiratory system of humans has been described in several studies. Long-term exposure to MDI tends to cause restriction of pulmonary function and decline in pulmonary diffusing capacity. In addition to reports of cases of asthma, hypersensitivity pneumonitis, pleuritis, and progressive fibrosing alveolitis it may be concluded that chronic exposure to even low levels (mostly undetermined or below 0.05 mg/m³) of MDI carries a risk of respiratory disease.

From the body of available data it is concluded that MDI does not have genotoxic properties. Conflicting results were obtained in *in vitro* test systems. The results, from a recently performed *in vivo* micronucleus test, indicate that aerosolized, inhaled MDI at concentrations as high as 118 mg/m³ air (a concentration high enough to produce portal-of-entry-specific toxic effects, including statistically significantly increased lung weights) did not induce cytogenetic damage *in vivo*.

In a well-conducted chronic toxicity/carcinogenicity animal inhalation study tumours in the lungs were found, without adverse effect on the distribution and incidence of tumours apart from these lung tumours. In another long-term animal inhalation study a single bronchio-alveolar adenoma was found at 2.05 mg/m^3 MDI. There are two hypotheses concerning the oncogenesis of MDI: 1° oncogenesis on the basis of irritation through epigenetic mechanisms, 2° oncogenesis resulting from the formation of MDA (4,4'-methylenedianiline). A NOAEL of 0.2 mg/m³ is established for inflammatory and other non-neoplastic pulmonary changes. No carcinogenicity studies are available using the oral or dermal route of exposure. There is inadequate evidence of carcinogenicity in humans and limited evidence in experimental animals.

No fertility nor multigeneration studies are available for MDI. Data from (sub)chronic toxicity studies (Reuzel et al., 1994b, 1994a) did not reveal clear substance related and/or significant impairment of organs of the reproductive

system of the male and female. Taken altogether, these studies were considered too limited to allow a determination of a NOAEL for fertility. Pre-natal inhalation toxicity testing in rats indicates the absence of selective toxicity to the development (no findings indicate any specific developmental effects at exposure levels below those that caused maternal toxicity). The reported $NOAEL_{(developmental)}$ for monomeric MDI is 3 mg/m³/day and the $NOAEL_{(developmental)}$ for polymeric MDI: 4 mg/m^3/day. No data on reprotoxicity are available in humans.

Environment

Vapour pressure is < 0.005 Pa; water solubility and log Kow could only be obtained by HPLC method due to high reactivity of the substance with the water; nevertheless, the values yielded are not relevant for predicting environmental fate.

Atmospheric half-life is estimated to be of 1.331 days. Hydrolysis of the isocyanate group under conditions of low dispersion results in the formation of polyureas and polyurethanes (PUs) (i.e. both insoluble and inert compounds) and traces of MDI and methylenedianiline (MDA). Under conditions of high dispersion a substantial amount of MDA may be formed as initial breakdown product. However, MDA in the presence of MDI is rapidly transformed further to polyureas/PUs. Biodegradation tests with MDI and derived oligoureas showed that these substances are not biodegradated by micro-organisms. Two long-term studies showed that MDI is not accumulated by biota (algae, aquatic plants, aquatic invertebrates and fish).

A rather extensive package of environmental tests is available including acute and (sub)chronic tests on fish, aquatic invertebrates, algae, plants, soil dwelling organisms and microorganisms. These tests are however confounded by the rapid hydrolysis of MDI.
In all these tests no effect was observed despite the high loads involved (nominal concentrations range between 100-3000 mg/l or /kg). Absence of effect was observed with all members of substance category tested. This is obviously due to the fact that actual exposure of the test organisms takes place to predominantly polyureas/PUs and only traces MDI and MDA. One exception concerned testing where MDI had been dispersed in test medium by high speed shearing. The observed lethal effects on both fish and cladocerans are assumed to be due to the formation of substantial amounts of MDA and this study is considered irrelevant for the hazard assessment of MDI and the production under field conditions of its breakdown product MDA.

Exposure

MDI is produced in closed, industrial systems. These activities take place in a relatively small number of sites (in total 11 in Europe for the year 1996). MDI is mainly used as industrial intermediate in the manufacture or application of polyurethanes. Smaller amounts are processed to 'prepolymers'. Worldwide production was about 2,500 kilotonnes MDI per annum in 1996 (from which approximately 790 ktpa in Western Europe). MDIs are sold to numerous down-stream users (ca. 3,600 in EU).

MDI is used for the production of PU foams (69%) and coatings, adhesives, sealants and elastomers (26%). Other uses are thermoplastic PUs and PU fibers. MDI is also used as grouting agents in rock consolidation or sealing of water leaks in tunnels or geotechnical construction works. There is also use in the production of particle board (bonding of wood) and mould cores for the foundry industry.

In conclusion, human exposure to MDI may occur by inhalation of vapours and aerosols or through skin exposures at workplaces where MDI is produced, or MDI-containing products are used, or at home doing some do-it yourself jobs.

RECOMMENDATION

Human Health: The chemicals in this category are candidates for further work

Environment: The chemicals in this category are currently of low priority for further work

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment: no further work is needed because MDI is not expected to cause harm to the environment given the absence of any observed effect in ecotoxicity tests.

Human health: The chemical is a candidate for further work. Hazardous properties have been identified for this substance (local effects after repeated inhalation, irritation and sensitisation). In an assessment performed in the European Union in the context of the EU Existing Substances Regulation, both occupational and consumer exposure was identified. Other OECD countries may wish to perform an exposure assessment for humans and if necessary a risk assessment. Based on the outcome, further testing for fertility of MDI could be considered as a post-SIDS activity.
Note: further metabolism/toxicokinetic/distribution studies are currently on-going.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	5131-66-8(29387-86-8) 29911-28-2 (35884-42-5) 88917-22-0 20324-33-8 and 25498-49-1
Chemical Name	Propylene Glycol n-Butyl Ether (PnB) Dipropylene Glycol n-Butyl Ether (DPnB) Dipropylene Glycol Methyl Ether Acetate (DPMA) Tripropylene Glycol Methyl Ether (TPM)
Structural Formula	$[CH_3\text{-}CH_2(OH)\text{-}CH_2\text{-}O]_n\text{-}(R)$ Where n = 1, 2, or 3; and R = alkyl (methyl or butyl) Note: In the case of n =1, the structures shown represent the predominant (alpha) isomers. For n=2 or 3, carbon atoms next to ether linkages may be either primary or secondary, leading to isomeric mixtures.

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The category contains four structurally related propylene glycol ethers:

Propylene Glycol n-Butyl Ether (PnB, 5131-66-8, major ("alpha") isomer, 29387-86-8 isomeric mixture)
Dipropylene Glycol n-Butyl Ether (DPnB, 29911-28-2 major isomer or 35884-42-5 isomeric mixture))
Dipropylene Glycol Methyl Ether Acetate (DPMA, 88917-22-0 isomeric mixture)
Tripropylene Glycol Methyl Ether (TPM, 20324-33-8 one of the isomers and 25498-49-1 isomeric mixture)

The alpha (secondary alcohol) form is kinetically favored during synthesis. PnB is available as the isomeric mixture in which the alpha isomer is the predominant isomer (ca. 95%. DPnB, DPMA and TPM are commercially produced as mixtures of isomeric components in which the internal ether linkages may be adjacent to either primary or secondary carbon atoms. Thus, for DPMA and DPnB the commercially produced products may contain up to 4 such isomers. In the case of TPM, the commercially produced product may contain up to 8 such isomers.

Data for these propylene glycol ethers are supplemented with data from three propylene glycol ethers that are closely related to the category members in molecular structure, physicochemical properties and toxicity and thus extend the category. These compounds are:

Propylene Glycol Methyl Ether (PM; CAS No. 107-98-2)
Propylene Glycol Methyl Ether Acetate (PMA; CAS No. 108-65-6)
Dipropylene Glycol Methyl Ether (DPM; CAS No. 34590-94-8 isomeric mixture and 20324-32-7 major isomer)

PM and PMA were reviewed at SIAM 11 and DPM was reviewed at SIAM 12. All were assigned as low priority for further work.

Human Health

As a class, the propylene glycol ethers are rapidly absorbed and distributed throughout the body when introduced by inhalation or oral exposure. Dermal absorption is somewhat slower but subsequent distribution is rapid. Most excretion for PGEs is via the urine and expired air. A small portion is excreted in the feces.

This category of propylene glycol ethers (PGEs) exhibits low acute toxicity by the oral, dermal, and inhalation routes. Rat oral LD50s range from >3,000 mg/kg (PnB) to >5,000 mg/kg (DPMA). Dermal LD50s are all > 2,000 mg/kg (PnB, & DPnB; where no deaths occurred), and ranging up to >15,000 mg/kg (TPM). Inhalation LC50 values were higher than 5,000 mg/m3 for DPMA (4-hour exposure), and TPM (1-hour exposure). For DPnB the 4-hour LC50 is >2,040 mg/m3. For PnB, the 4-hour LC50 was >651 ppm (>3,412 mg/m^3), representing the highest practically attainable vapor level. No deaths occurred at these concentrations for any of the four new category members. PnB and TPM are moderately irritating to eyes while the remaining category members are only slightly irritating to non-irritating. PnB is moderately irritating to skin while the remaining category members are slightly to non-irritating. None of the category members are skin sensitizers.

In repeated dose studies ranging in duration from 2 to 13 weeks, few adverse effects were found even at high exposure levels and effects that did occur were mild in nature. By the oral route of administration, NOAELs of 350 mg/kg-d (PnB – 13 wk) and 450 mg/kg-d (DPnB – 13 wk) were observed for liver and kidney weight increases (without accompanying histopathology). LOAELs for these two chemicals were 1000 mg/kg-d (highest dose tested). Dermal repeated-dose toxicity tests have been performed for all of the category members but DPMA. For PnB, no effects were seen in a 13-wk study at doses as high as 1,000 mg/kg-d. A dose of 273 mg/kg-d constituted a LOAEL (increased organ weights without histopathology) in a 13-week dermal study for DPnB. For TPM, increased kidney weights (no histopathology) and transiently decreased body weights were found at a dose of 2,895 mg/kg-d in a 90-day study in rabbits. By inhalation, no effects were observed in 2-week studies in rats at the highest tested concentrations of 3244 mg/m^3 (600 ppm) for PnB and 2,010 mg/m^3 (260 ppm) for DPnB. TPM caused increased liver weights without histopathology by inhalation in a 2-week study at a LOAEL of 360 mg/m^3 (43 ppm). In this study, the highest tested TPM concentration, 1010 mg/m^3 (120 ppm), also caused increased liver weights without accompanying histopathology. Although no repeated-dose studies are available for the oral route for TPM, or for any route for DPMA, it is anticipated that these chemicals would behave similarly to other category members.

One and two-generation reproductive toxicity testing has been conducted in mice, rats, and rabbits via the oral or inhalation routes of exposure on PM and PMA. In an inhalation rat study using PM, the NOAEL for parental toxicity is 300 ppm (1106 mg/m^3) with decreases in body and organ weights occurring at the LOAEL of 1000 ppm (3686 mg/m^3). For offspring toxicity the NOAEL is 1000 ppm (3686 mg/m^3), with decreased body weights occurring at 3000 ppm (11058 mg/m^3). For PMA, the NOAEL for parental and offspring toxicity is 1000 mg/kg/d. in a two-generation gavage study in rats. No adverse effects were found on reproductive organs, fertility rates, or other indices commonly monitored in such studies. In addition, there is no evidence from histopathological data from repeated-dose studies for the category members that would indicate that these chemicals would pose a reproductive hazard to human health.

Regarding developmental toxicity, all category members but DPMA have been tested by various routes of exposure and in various species at significant exposure levels and show no frank developmental effects. Due to the rapid hydrolysis of DPMA to DPM, DPMA would not be expected to show teratogenic effects. At high doses where maternal toxicity occurs (e.g., significant body weight loss), an increased incidence of some anomalies such as delayed skeletal ossification or increased 13th ribs, have been reported. Commercially available propylene glycol ethers showed no teratogenicity.

The weight of the evidence indicates that propylene glycol ethers are not likely to be genotoxic. *In vitro*, negative results have been seen in a number of assays for PnB, DPnB, DPMA and TPM. Positive results were only seen in 3 out of 5 chromosome aberration assays in mammalian cells with DPnB. However, negative results were seen in a mouse micronucleus assay with DPnB and PM. Thus, there is no evidence to suggest these propylene glycol ethers would be genotoxic *in vivo*. In a 2-year bioassay on PM, there were no statistically significant increases in tumors in

rats and mice.

Environment

Category members are all liquids at room temperature and all are water-soluble. Log octanol-water partition coefficients (Log Kow's) range from 0.309 for TPM to 1.523 for DPnB. Calculated BCF's range from 1.47 for DPnB to 3.16 for DPMA and TPM, indicating low bioaccumulation. Henry's Law Constants, which indicate propensity to partition from water to air, are low for all category members, ranging from 5.7 x 10^{-9} atm-m^3/mole for TPM to 2.7 x 10^{-9} atm-m^3/mole for PnB. Fugacity modeling indicates that category members are likely to partition roughly equally into the soil and water compartments in the environment with small to negligible amounts remaining in other environmental compartments (air, sediment, and aquatic biota). Propylene glycol ethers are unlikely to persist in the environment. Once in air, the half-life of the category members due to direct reactions with photochemically-generated hydroxyl radicals, range from 2.0 hours for TPM to 4.6 hours for PnB. In water, 3 of the 4 new category members and all 3 existing members are "readily biodegradable" under aerobic conditions. (DPMA degraded within 28 days (and within the specified 10-day window) but only using pre-adapted or "acclimated" inoculum.) In soil, biodegradation is rapid for PM and PMA. Acute aquatic toxicity testing indicates low toxicity for both ethers and acetates. For ethers, effect concentrations are > 500 mg/L. For acetates, effect concentrations are > 151 mg/L.

Exposure

According to the Chemical Economics Handbook (SRI International, 2000), in 1999, approximately 810 million pounds (368 thousand tonnes) of all propylene glycol ethers were produced worldwide. The US accounted for 285 million pounds (130 thousand tonnes), Europe 472 million pounds (215 thousand tonnes), and Japan 53 million pounds (24 thousand tonnes). In the USA, a production volume of 340 million pounds (155 thousand tonnes) of all propylene glycol ethers is estimated for 2004. In 1999, production of PnB, DPnB, and TPM was 23, 10.5 and 6 million pounds (10, 4.8 and 2.7 thousand tonnes), respectively. Modern production methods result in alpha isomer content in excess of 95% and beta isomer content less than 5% for the mono-propylene glycol ethers. Estimated 2004 production for these specific ethers is 29, 14 and 7 million pounds (13, 6.4 and 3.2 thousand tonnes) respectively. These production volumes agree fairly well with the Inventory Update Rule (IUR). 1993 production information for DPM acetate was 1-2 million pounds (0.5 – 0.9 thousand tonnes). The four propylene glycol ethers comprising this category are used in the manufacture of a wide variety of industrial and commercial products, including surface coatings (paints and varnishes), cleaners, inks, resins, cosmetics, and as inert carrier solvents in pesticide formulations. Exposures to these propylene glycol ethers are likely to occur by both the inhalation and dermal routes for workers and consumers.

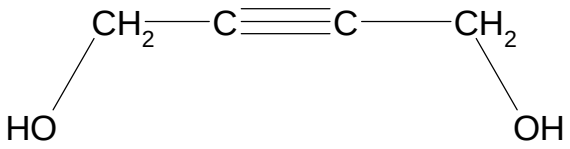
RECOMMENDATION

The chemicals in this category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemicals in this category are currently of low priority for further work. Some of the chemicals in this category possess properties indicating hazards to human health (skin and eye irritation). Although this hazard does not warrant further work (as it is related to non-adverse, reversible, transient effects), it should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-65-6
Chemical Name	But-2-yne-1,4-diol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In animals butynediol is absorbed via the oral and dermal routes of exposure; absorption via the lungs is demonstrated recently in an acute inhalation toxicity study.

Specific investigations about toxicokinetic behaviour and metabolism are not available. It may be anticipated, however, that in a first metabolic step butynediol is enzymatically activated to the corresponding aldehyde carbonic by alcoholdehydrogenase. Cytochrome P450-dependent metabolism can not be excluded, because a low increase of aminopyrine demethylase activity was detected.

Assessment of the available data on acute toxic effects indicate that in the rat butynediol is toxic by inhalation (LC 50 of 0.69 mg/l/4 h) and by oral ingestion and harmful following dermal absorption (LD 50 values oral: 132-176 mg/kg bw, and dermal: 659-1240 mg/kg bw). Human data on acute toxicity are not available. Butynediol has demonstrated corrosivity to skin and eyes of rabbits. Human data on local irritancy/corrosivity are not available. In man, two cases of contact allergy caused by butynediol have been described. Animal data on three Magnusson Kligman tests demonstrate that the substance shows a weak sensitization potential. There is no information available on respiratory sensitization.

An oral 28-day study on rats revealed toxic effects on liver, kidney and hematopoietic system at doses from 10 mg butynediol/kg bw/d. The dose of 50 mg/kg bw/d caused mortality in males and females. Histopathology showed congested internal organs, pulmonary oedema and severe changes in liver and kidneys, which included diffuse hepatic parenchymal necrosis, accompanied by reactive mononuclear cells and granulocytes, fatty changes, as well as renal tubular degeneration and interstitial mononuclear cell infiltration in the kidney. An oral NOAEL of 1 mg/kg bw/d was derived from the oral 28-day study. A preliminary concern on neurotoxicity from an oral 6-month study with reduced reliability was not confirmed by the results from a 30-day inhalation study on rats that included a battery of examinations on the neurofunction and motor activity and histopathology of the nervous system.

Indications of local toxic effects on the respiratory tract were observed on 30-day liquid aerosol exposure to rats: Epithelial changes of the nasal cavity at 100 mg/m³ and above, tracheal inflammation at 25 mg/m³, and metaplasia and inflammation of the larynx at 5 mg/m³ and above. The NOAEC for systemic toxicity was 25 mg/m³; the NOAEC for local effects on the respiratory tract was 0.5 mg/m³. Inhalation exposure on 5 days to butynediol aerosol resulted also in inflammation and metaplasia of the laryngeal mucosa at concentrations of 25 mg/m³ and above. The liver and kidney were also affected by repeated inhalation exposure on 5 days at a concentration of 300 mg/m³. Additionally this concentration caused some treatment-related deaths, growth retardation and, in unscheduled deaths only, toxic effects on the spleen, thymus and gastrointestinal tract.

There is no information on the health effects in humans of repeated exposure to butynediol.

The bacterial mutation assays did not reveal a genotoxic potential. An in vitro chromosomal aberration assay gave an equivocal result. In vivo however, a bone marrow micronucleus test was negative up to toxic doses. Altogether, there is no relevant concern with respect to germ cell mutagenicity of butynediol. There are no experimental data on cancerogenicity available.

There are no human data available on toxicity for reproduction. The available animal data from studies with rats do not indicate a specific toxic potential of butynediol adverse to reproduction and/or development including any teratogenic effects by the oral route. Moreover, there are no indications for substance-related interference with spermatology and/or estrous cyclicity. An oral NOAEL/fertility of 40 mg/kg bw/d was derived from a one-generation study according OECD Guideline 415 and an oral NOAEL/developmental toxicity of 80 mg/kg bw/d was obtained from a study according to OECD Guideline 414.

Environment

But-2-yne-1,4-diol is a solid substance (melting point 58 °C) with a water solubility of 750 g/l at 20 °C, a vapour pressure of 0.17 Pa at 20 °C and a log Kow of -0.73 at 25 °C .

There are no data available about hydrolysis of but-2-yne-1,4-diol. From the molecular structure of the compound it can be concluded that hydrolysis is not a relevant degradation process. According to the fugacity model of Mackay (level 1), the main target compartment is the hydrosphere (> 99.9 %). The calculated Henry's law constant of $2 \cdot 10^{-5}$ $Pa.m^3/mol$ at 20 °C indicates a low potential of volatilization from water.

In the atmosphere, but-2-yne-1,4-diol will react with the photochemically produced hydroxyl radicals. Based upon atmospheric concentrations of 5 · 105 OH/cm3, the atmospheric half-life of but-2-yne-1,4-diol has been estimated to be 11 hours. From the spectroscopical data available for but-2-yne-1,4-diol, direct photolysis is not to be expected. But-2-yne-1,4-diol is readily biodegradable (OECD 301 E, 100 % after 5 days).

There are no experimental results on bioaccumulation available. The measured log Kow of -0.73 does not indicate a potential for bioaccumulation. The estimated Koc-value of 1.64 l/kg also indicates no potential for geoaccumulation.

In short-term ecotoxicity tests available for fish, amphibia, invertebrates and algae the following effect values were found: *Pimpehales promelas*: 96h-LC_{50} = 53.6 mg/l; *Xenopus laevis*: 96h-LC_{50} = 15.5 mg/l; *Daphnia magna*: 48h-EC_{50} = 26.8 mg/l, *Scenedesmus subspicatus*: 72h-E_bC_{50} = 483.7 mg/l. Long-term studies are not available. Applying an assessment factor of 1000 to the lowest effect value of 15.5 mg/l results in a PNECaqua of 15.5 µg/l.

Exposure

The maximum annual EU production volume of but-2-yne-1,4-diol is 200,000 metric t. 98% of this amount is used as an internal intermediate. According to the producers, hydrogenation to butanediol and butenediol are the main application areas. Less than 2% of the production volume of but-2-yne-1,4-diol are not processed at the production sites but used as an external intermediate for the production of flame retardants or as a corrosion inhibitor and pickling agent in metal surface. Besides this, but-2-yne-1,4-diol is reported to serve as an intermediate for the synthesis of polyols, insecticides, pharmaceuticals and auxiliaries for the paint and textile industry.

According to European Product Registers but-2-yne-1,4-diol is contained in a large number of products. Some of them may be available to consumers and contain but-2-yne-1,4-diol in concentrations up to 5 %. The most frequent product types are cleaning agents, conserving agents and metal surface treatment agents.
Releases of but-2-yne-1,4-diol into the environment are to be expected during production and processing with waste water and, to less extent, exhaust gases. Further releases are to be expected through the use in metal surface treatment and of cleaning agents.

RECOMMENDATION

Environment: The chemical is of low priority for further work.

Human Health: The chemical is a candidate for further work

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment:

The chemical possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute aquatic toxicity, which may become evident only at very high exposure levels, they should nevertheless be noted by chemical safety professionals and users.

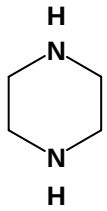
A comprehensive risk assessment has been performed in the European Union in the context of EU Regulation 793/93. From the comparison between estimated exposure levels from all life-cycle steps with the Predicted No Effect Concentrations it is deduced, that but-2-yne-1,4-diol represents, based on the present data basis, no risk to the environment. There is therefore at present no need for further testing or gathering of exposure information.

Human Health:

The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health. Due to the use pattern of the substance, member countries are invited to perform an exposure assessment, and if necessary a risk assessment for human health:

Note: An occupational risk assessment performed in the European Union in the context of the EU Existing Substances Regulation reveals concern for several toxicological endpoints.
Regarding respiratory tract irritation, risk reduction measures are considered to be necessary for those exposure scenarios in which but-2-yne-1,4-diol is handled as a solid substance (production and further processing; further processing to formulations). Concern is expressed for repeated inhalation exposure (both scenarios) and for acute inhalation exposure (only production and further processing).
In addition to its substantial irritation potential (skin, eye, respiratory tract) but-2-yne-1,4-diol has proved to be a weak skin sensitizer. Concern has been derived for the exposure scenarios with but-2-yne-1,4-diol itself and preparations with a but-2-yne-1,4-diol concentration of greater than 1%.
For but-2-yne-1,4-diol, occupational exposure limits are not reported. Based on the conclusion of the risk assessment for worker it is recommended to establish an occupational exposure level at EU level.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-85-0
Chemical Name	Piperazine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In pigs, piperazine is readily absorbed from the gastrointestinal tract, and the major part of the resorbed compound is excreted as unchanged piperazine during the first 48 hours. The principal route of excretion of piperazine and its metabolites is via urine, with a minor fraction recovered from faeces (16 %). In humans the kinetics of the uptake and excretion of piperazine and its metabolites with urine appear to be roughly similar to that in the pig, and the nature and extent of conversion to metabolites has not been determined.

Piperazine has demonstrated a low acute toxicity (LD_{50} = 1-5 g/kg bw) by the oral, dermal, and subcutaneous route of administration to rodents, whereas adequate inhalation toxicity data have not been found. However, there are findings of EEG (electroencephalogram) changes in 37 % of 89 children administrated 90-130 mg/kg piperazine (two doses during one day), corroborated by a proposed GABA (γ-aminobutyric acid) receptor agonism exerted by piperazine. Since clinical symptoms of neurotoxicity may occur after exposure to higher doses, a LOAEL of 110 mg/kg piperazine base for acute neurotoxicity in humans after acute exposure is proposed.

Piperazine, as concentrated aqueous solution, has strongly irritating properties with regard to skin, and should be regarded as corrosive with respect to the eye. Exposure to piperazine and it salts has been demonstrated to cause allergic dermatitis as well as respiratory sensitisation in humans. As shown by the LLNA, piperazine has a sensitising potential in animals. Although piperazine is clearly sensitising, no NOAEL can be set for this effect from the present database.

A NOAEL of 25 mg/kg/day of piperazine for liver toxicity in the beagle dog has been chosen after repeated exposure. A LOAEL of 30 mg/kg/day of piperazine for neurotoxicity is proposed based on documentation of (rare cases) of neurotoxicity from human clinical practice. Neurotoxicity also appears in other species (e.g., rabbits, dogs, cats, tigers, and horses), but not in rodents.

For reproductive effects of piperazine, there is a NOAEL of 125 mg/kg/day for effects on fertility, i.e., reduced pregnancy index, decreased number of implantation sites, and decreased litter sizes in rats. The teratogenic properties have been investigated in rats and rabbits in adequate studies. In rabbit, such effects may be elicited at a dose level that is also toxic to the mother animal. The maternal LOAEL is 94 mg/kg/day, and the NOAEL 42 mg/kg/day piperazine base. In the rat study, there were decreases in body weight of both dams and offspring at the top dose (2100 mg/kg/day piperazine base), but there were no signs of any malformations.

The genotoxic properties have been investigated both *in vitro* (in the Ames test, in a non- standard study on

saccharomyces cervisiae and in Chinese hamster ovary cells) and *in vivo*, a micronuclei assay on mice, all with negative results. There are no solid indications of a carcinogenic effect of piperazine, either in animal studies, or from the investigation on humans. In view of lack of genotoxic action, it appears unlikely that piperazine poses a carcinogenic risk.

Environment

Piperazine has a vapour pressure of 44 Pa (at 24.2 °C), the solubility in water is 150 g/l (at 20 °C) and the partition coefficient (n-octanol/water) is log P_{OW} -1,24 (at 25 °C). For calculations in the EUSES the lowest possible log P_{OW} is –1, in the SIMPLETREAT model the lowest possible log P_{OW} is 0, therefore these values are also used.

At neutral pH piperazine is positively charged, it would therefore theoretically bind to soil particles and humus, which are most commonly negatively charged. There is one adsorption study available, resulting in Kd values between 7.9 and 20 mL/g. These results indicate that sorption of piperazine to soil is not correlated to the organic carbon content of the soils. For sewage treatment plants, the distribution was calculated with SIMPLETREAT, resulting in distribution to the water phase.

Piperazine can be assumed to be rapidly photolysed in the atmosphere, the half-life was calculated to be 0.8 hours. In natural water it is considered to be stable towards photolysis. From non-standard studies it can be expected that piperazine is hydrolytically stable under environmentally relevant conditions. Piperazine is not readily biodegradable but can be considered to be inherently degradable.

There is no considerable potential for bioaccumulation, a BCF of < 3.9 for *Cyprinus carpio* is reported.

Short-term effect studies on aquatic organisms are available for algae, aquatic invertebrates and fish. For algae (*Selenastrum capricornutum*) the NOEC (72 h growth inhibition test) is determined to be > 1000 mg/l. For *Daphnia magna* the EC_{50} 48 h is 21 mg/l and for fish (*Poecilia reticulata*) the LC_{50} 96 h is > 1800 mg/l. A long-term study for *Daphnia magna*, which is the most sensitive of the species tested in short term studies, results in a NOEC (21 d semi static reproduction study) of 12.5 mg/l.

Exposure

In 1999, three plants in Europe produced piperazine. The United States and Japan are known to produce piperazine and export to the EU. The tonnage (production + import – export) of piperazine handled within the EU in 1997 was < 5000 tonnes.

Piperazine, as such or as salts, is mainly used as an intermediate in chemical industry including production of pharmaceuticals. Piperazine, as such or as salts, is used also for human and veterinary medicinal drugs, as formulation in gas-washing (scrubbers), and as a catalyst in urethane production.

Releases to the environment can be expected during production, processing and formulation of the substance as such or as salts, and during the use and disposal of products containing piperazine.
Sources of potential human exposure are at workplaces producing or handling piperazine or its salts.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

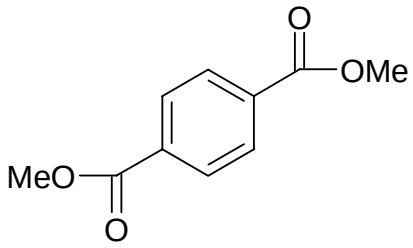
Human Health:

The chemical possesses properties indicating a hazard for human health. Due to the use pattern of the substance member countries are invited to perform an exposure assessment, and if necessary a risk assessment for human health. Note: A risk assessment performed in the EU in the context of the EU Existing Chemicals Regulation has concluded that there is a need for limiting the risks for workers, especially considering skin and respiratory sensitization, but in some scenarios also due to neurotoxicity and reproductive toxicity.

Environment:

Although this chemical possesses properties indicating a low hazard for the environment, in a risk assessment performed in the EU in the context of the EU Existing Chemicals Regulation, risks were identified at a local level from gas washer processing and other industrial sites. Other countries are invited to perform an exposure assessment, and if necessary a risk assessment for the environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	120-61-6
Chemical Name	Dimethyl Terephthalate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

Data for dimethylterephthalate (DMT) is available for all SIDS health endpoints. However, for reproductive and developmental toxicity, the available data on DMT is not considered sufficient to support a conclusion that these endpoints have been completed. As a result, additional data from terephthalic acid (TPA) is being presented to support the conclusion that the reproductive and developmental toxicity endpoints have been completed. The use of TPA data for health endpoints is acceptable due to the principle that DMT metabolizes to form TPA.

Human Health

Results from acute toxicity studies via the oral, dermal and inhalation routes indicate that DMT is of a low order of toxicity. Oral acute toxicity studies in rats reported LD50s of 4,390 to >6,590 mg/kg. Inhalation and dermal LC and LD50s in rats and guinea pigs were >6 mg/L and >5,000 mg/kg, respectively. In several animal studies, DMT is indicated to be slightly irritating to both the skin and eyes. Available data indicate that DMT is not considered to be sensitizing in guinea pigs.

Numerous repeat dose studies have been conducted via oral (gavage and dietary) and inhalation routes of exposure. Studies range in duration from 2-13 weeks via the oral route and up to six months for inhalation administrations. Collectively, the data indicate that the primary target organ is the urinary tract due to DMTs metabolism to TPA and the formation of renal crystals or calculi and their sequelae on the soft tissues. In a 14-day feeding study in rats a NOEL based on decreased body weights was seen in males at 660 mg/kg/day (0.5% in diet) and in females exposed to 1277 mg/kg/day (1.0% in diet) (Chin et al, 1981). In the same study, a NOEL for induction of urinary calculi was 1320 mg/kg (males) and 1790 mg/kg females (1.5% in diet). In a 96-day feeding study in rats, a NOEL, based on decreased body weight gains, of 313 mg/kg/day (0.5% in diet) and a LOAEL of 636 mg/kg/day (1% in diet) was determined. However, in this study, there was no evidence of urinary calculi (Krasavage et al., 1973). Thus, the formation of urinary calculi and its secondary effect on soft tissues occurred at a minimum DMT exposure length of 14 days at a dietary concentration of 1.5% for males (1,890 mg/kg) and 2% in females (2,290 mg/kg). Based on urinary solubility of Ca-TPA, normal human urine would become saturated with Ca-TPA at a TPA concentration of approximately 8-16mM. Assuming an average volume of urine excreted by humans is 1.5 L/day and that DMT is metabolized entirely to TPA, then the amount of DMT that would have to be absorbed to produce 8mM minimum saturating concentration of TPA is 2,400 mg/kg/day. Inhalation repeat dose studies do not show the primary urinary effect observed in the oral studies, however, following 90-days of exposure via the inhalation route, a NOAEL of 16.5 mg/m^3 was determined for the following effects: mild and transient clinical effects-nose rubbing, preening, and

blinking. In the same study, a LOAEC of 86.4 mg/m^3 was established.

Given the weight of evidence, DMT does not appear to be mutagenic or genotoxic in numerous *in vitro* (bacterial and mammalian systems) and several *in vivo* studies. In addition, DMT was not deemed to have carcinogenic effects in a two year feeding study in male and female rats and female mice, but equivocal evidence was noted in male mice.

In developmental toxicity studies, two on DMT and one on TPA, there is no evidence of developmental toxicity. In inhalation studies, the NOAEC for DMT was 1 mg/m^3 and for TPA it was 10 mg/m^3 (both were the highest dose tested). In a gavage study on DMT, a NOAEL of >1000 mg/kg was determined. In a 115-day oral feeding study to assess the reproductive toxicity potential of DMT, a NOEL of 636 mg/kg/day (1.0% in diet; highest dose tested) was determined for parental effects while the NOEL for offspring was 152 mg/kg/day based on reduced pup weights at weaning. This effect was likely due to exposure to DMT through lactation and having access to the mother's food and hence it is a primary toxicity of DMT. Since this study's methodology varies from the current OECD guidelines, data from the DMT metabolite TPA is used to support this endpoint. In a one-generation reproduction feeding study on TPA, postnatal growth weight and mortality effects were observed in pups. The NOAEL for maternal toxicity and for the F1 offspring was 0.5% (240 to 307 mg/kg), while the NOAEL for reproductive effects was >5.0% (2480-3018 mg/kg) TPA in the diet. The adverse effects observed in the offspring in this study appear to be the result of maternal toxicity and the formation of renal and bladder calculi found in the weanling animals.

Environment

The physical-chemical properties of DMT include a melting point of 141^{0}C, a vapor pressure of 0.01 mmHg at 25^o C, a water solubility of approximately 19 - 37mg/l, a partition coefficient of log Kow 2.25 and a flash point of 153 ^{0}C. Overall, DMT undergoes slow abiotic hydrolysis (half-life 321 days), has a photo-oxidation half-life of weeks, and stability in surface and ground water with half-lives of weeks. However, the potential for significant environmental releases are low and the material is classified as readily biodegradable (84%, MITI test).
This chemical is moderately toxic to fish (96h LC50 = 9.6 mg/L), daphnids (48h LC50 = 30.4 mg/L), and green algae (72h EC_{50} biomass = 27.6 mg/L; 72h EC_{50} growth rate >32.3 mg/L). However, it is not expected to bioaccumulate in fish and is not expected to biomagnify via food chains. Using an assessment factor of 100 and the fish toxicity value, a PNEC of 0.096 mg/L is derived.

Exposure

Dimethyl terephthalate is produced (2004 world nameplate capacity estimate 4,936,000 tonnes or 1.09E10 pounds) in closed systems and used primarily within its own manufacturing facilities as a building block in the synthesis of polyethylene terephthalate plastics. It is also used as an intermediate to manufacture dioctyl terephthalate. When transported, it is shipped in bulk containers. Human exposures are in general very minimal and limited. The main occupational exposure concern in processing is that of direct physical burns due to accidental dermal contact to DMT in its molten state. Consumer exposure is possible via residual levels of less than 1 ppm DMT in PET-polymers.

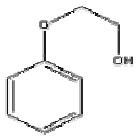
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

No recommendation for further work.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	122-99-6
Chemical Name	Ethylene Glycol Phenyl Ether
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Studies in rats and rabbits indicate that ethylene glycol phenyl ether (EGPhE) is rapidly absorbed after oral administration and excreted in the urine, either as unchanged material or 2-phenoxyacetic acid. The most reliable LD50 values for the rat after oral administration are 1,386 and 2,563 mg/kg bw in fasted males and females (respectively), and 2,937 and 4,013 mg/kg bw in fed males and females, (respectively). isSigns of acute toxicity include a slight to severe reduction of activity, decreased reflexes and labored respiration. Rats treated with high doses appeared comatose before death or recovery. A dermal LD50 value of 14,300 mg/kg bw was observed in rats. EGPhE is not irritating to human skin, but is slightly irritating to rabbit skin, and irritating to rabbit eyes. Contact with up to 5% EGPhE in petrolatum is not sensitizing to human skin.

Dermal administration of up to 500 mg/kg bw/day EGPhE (the highest dose tested) for 90 days had no effect in rabbits other than erythema at the test site. The oral (gavage), repeated-dose 90 day NOAEL in rats is 80 mg/kg bw/day. In this study, 400 mg/kg bw/day for 90 days was associated with kidney toxicity and changes in grooming behavior. Rats orally administered 2000 mg/kg bw/day exhibited toxicity to red blood cells and other effects associated with this phenomenon (decreased number of circulating red blood cells, decreased red blood cell hemoglobin, and kidney inflammation). Compared to the rat, the rabbit is more sensitive to the hemolytic effects of EGPhE (hemolysis is noted in rabbits orally treated with $\geq$ 100 mg/kg bw/day EGPhE for 10 days).

EGPhE tested negative for mutagenicity in an Ames test conducted in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 (in the absence and presence of metabolic activation). EGPhE also tested negative in an *in vivo* cytogenicity study in the rat and a mouse micronucleus test. Other *in vitro* chromosomal aberrations and gene mutation assays were also negative.

Minimal tubular atrophy of the testes was observed in 1/15 control male and 3/15 male rats orally treated with 2000 mg/kg bw/day EGPhE for 90 days. Moderate tubular atrophy associated with a reduction of spermatozoa in the epididymal tubules also was found in one high dose male. . The ability of EGPhE to cause testicular toxicity in 6-week old male mice was also reported. The animals were administered up to 2000 mg/kg of EGPhE by gavage, 5 days/week for 5 weeks. EGPhE had no effect on weights of testes, combined weights of the seminal vesicles and coagulating gland, or morphology of the testes, seminal vesicles or coagulating gland.

A 2-generation continuous breeding, oral feeding study in CD-1 mice with EGPhE resulted in NOAELs of 400 mg/kg bw/day for both parental animals and offspring. EGPhE was associated with decreased body weight (in males at 4000 mg/kg/day and in both males and females at 2000 mg/kg/day) and increased liver weight (males and females at both 2000 and 4000 mg/kg/day). Decreased absolute weight of seminal vesicles was noted in males treated with 2,000

mg/kg bw/day, but not 4,000 mg/kg bw/day. Developmental toxicity was seen in offspring of mice treated with 2,000 mg/kg bw/day, which had lower birth weights, and F1 weanlings exposed to 4,000 mg/kg bw/day test material, which had lower birth, weaning and mating weights than controls and high lethality rates. Decreased numbers of live pups per litter as well as decreased proportion of live pups were born. A lower percent of the high dose animals (60%) had a fifth litter compared with 90% in the controls.

A developmental toxicity study in rabbits resulted in no teratogenicity or developmental toxicity when administered dermally at doses up to 600 mg/kg bw/day from gestation days 6-18. This concentration induced hemolysis and death in 5/25 dams, but appeared to have no adverse effect on the remaining maternal animals. Two other studies showed some evidence of developmental toxicity; in one of the studies, the dose was administered subcutaneously and the reliability of the second study (an oral study) could not be verified.

Environment

EGPhE is a high boiling liquid (boiling point 245.2°C) with a very low vapor pressure (0.000134 hPa at 20°C). It has a melting point of 14°C, a water solubility of 28.9 g/l and a log octanol/water partition coefficient of 1.16. The photodegradation half-life is 3.9 hrs. Like other glycol ethers, EGPhE possesses no functional groups in its molecular structure that are readily subject to hydrolysis in the presence of water. The Henry's law constant is calculated to be 1.55×10^{-8} atm.m^3/mole at 25°C. Level III fugacity modeling assuming equal distribution to the various compartments indicates mass balances of 0.685% to air, 46.3% to water, 53.0% to soil and 0.0867% to sediment compartments. Although the material preferentially partitions to water and soil when released into the aqueous environment, it is readily biodegradable, and based on the log partition coefficient of 1.16, has a very low potential to bioaccumulate.

Adequate acute toxicity tests in fish and aquatic invertebrates show that EGPhE is of low toxicity to these species (LC/EC50 values are 344 and 488 mg/l, respectively). The 16-hr IC_{50} value for bacteria (sewer microorganisms) is 1,650 mg/l. Since the highest concentration used in the algal toxicity test (500 mg/l) did not have an effect on cell biomass, the EC50 value in algae is greater than this value.

There are no data on chronic toxicity of EGPhE to aquatic organisms or toxicity of EGPhE to terrestrial plants.

Exposure

In the U.S., EGPhE is produced by a single manufacturer using a continuous reactor, distillation column and storage tanks. Annual production is about 6.4 thousand metric tons in the U.S. EGPhE is used primarily as both a solvent and as an industrial intermediate, but it also has other uses in cosmetics as an antibacterial agent and some consumer products. Exposure is limited during manufacture by the enclosed nature of the process and the low volatility of EGPhE. Because the material is transported, used in product formulations and industrial application, used as a solvent, and may be present in some consumer products, there is some potential for widespread exposure. The material has been detected in the effluents of sewage treatments and effluents from chemical manufacturing facilities. Exposure can occur via ingestion, dermal absorption, and inhalation (to a lesser extent based on low volatility). Because EGPhE biodegrades and photodegrades readily it is not expected to persist in the environment and remain present in significant concentrations, thereby contributing significantly to environmental exposure.

RECOMMENDATION

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

Human Health: This chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

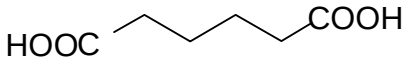
The chemical possesses properties indicating a hazard for human health (eye irritation – which is reversible - and developmental toxicity at high doses associated with maternal toxicity). Based on data presented by the Sponsor country, exposure is controlled in the occupational setting. Due the wide dispersive use, member countries are invited to perform an exposure assessment and if then indicated, a risk assessment, especially for consumers. 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.

Note: EGPhE may be evaluated further under the EU Biocides Directive. This will include exposure assessment on operators (occupational) and by-standers (consumers)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	124-04-9
Chemical Name	Adipic Acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In limited studies in animals and humans it was shown that adipic acid is absorbed after oral administration, partially metabolized to various metabolites and CO_2 which are excreted via urine and breath, resp. None of the studies was conducted according to GLP.

Adipic acid is of very low acute toxicity. The oral LD_{50} in rats in a study similar to OECD TG 401 is approximately 5560 mg/kg bw. Clinical signs at lethal doses included acute dilatation of the heart and acute congestive hyperaemia, ulceration of glandular stomach (bleeding-corrosive gastritis), intestinal atony, pale liver and reddening of intestinal mucosa. The LD50 for mice was reported to be 1900 mg/kg bw. In an inhalation test similar to OECD TG 403 in rats neither mortality nor symptoms were observed during and after 4 hour exposure to 7700 mg/m^3 of adipic acid. Reduced appetite and activity were the only effects reported following occlusive dermal administration of 7940 mg/kg bw of adipic acid to 2 rabbits for 24 hours.

In rabbits, 50 % adipic acid suspensions were slightly irritating to the intact skin and moderately irritating to scarified skin. The neat material was a severe eye irritant in rabbits, with symptoms being reversible within 16 days. Respiratory irritation in animals is not sufficiently examined. Workers exposed over an extensive period (av. 9.2 years) complained of respiratory irritation at adipic acid concentrations of 0.47-0.79 mg/m^3. Due to the acidic character of the substance, a local irritation potential is plausible.

Despite the wide dispersive use of adipic acid, only very few cases of skin or respiratory tract sensitisation reactions are reported in humans. A sensitisation study in animals according to validated guidelines is not available. Overall, sensitisation is not expected for adipic acid.

There is no repeated inhalation toxicity study with histopathological examination of the nose available. Systemic effects after repeated inhalation have not been investigated in fully valid studies. There are no studies on repeated dermal application available. In a limited 2-year oral study adipic acid was of low repeated dose toxicity, however it was not tested according to modern standards. The NOAEL was 1 % for male rats (approx. 750 mg/kg bw/day) and higher doses (3 and 5 %) caused body weight retardation with no indication of specific target organ toxicity. The NOAEL for female rats was 1 % (approx. 750 mg/kg bw/day), the highest dose tested in females. In one volunteer no overt toxic symptoms were seen after oral administration of 7 g adipic acid per day for 10 days.

A variety of mutagenicity tests in vitro and in vivo have failed to demonstrate that adipic acid possesses genotoxic potential. A number of good quality Ames tests in *Salmonella typhimurium* similar to OECD TG 471 and an examination of chromosome damage in human lung cells in culture produced negative results. In gavage studies in male rats it did not induce chromosome damage in the bone marrow or dominant lethal mutations in a dose-response or time-trend pattern.

Adipic acid was not carcinogenic in a limited two-years feeding study where male rats were fed with up to 5 % (3750

mg/kg bw/day) adipic acid and female rats with 1 % (750 mg/kg bw/day).

No specific studies on fertility have been conducted. In a two-year feeding study in rats histopathological examination of testes, ovaries, and uterus revealed no evidence of an adverse effect on the reproductive organs up to the highest doses tested (males approx. 3750 mg/kg bw/day, females approx. 750 mg/kg bw/day). Based on the available data there is no reason to expect specific reproductive toxicity of adipic acid.

Adipic acid was not embryo- or fetotoxic and not teratogenic up to the highest tested doses of 288, 263, and 250 mg/kg bw/day via oral administration to rats, mice, and rabbits, respectively. In none of these studies signs of maternal toxicity have been observed and the highest dose was well below the limit dose of 1000 mg/kg bw which would be a precondition for a fully valid negative study. In view of the low systemic toxicity of the compound, however, this endpoint seems to be adequately covered despite the limitations of the studies.

Environment

Adipic acid is a white, crystalline solid with a melting point of 152 °C, and a boiling point of 337.5 °C. The density of the solid is 1.36 g/ml at 25 °C. The vapor density in relation to air is 5.04. The vapor pressure is 9.7 Pa at 18.5 °C. The measured log K_{ow} is 0.093 at 25 °C. The solubility in water is 23 g/l at 25 °C. The flash point is 196 °C, the auto flammability (ignition temperature) 420 °C. Decomposition starts at 230 °C. pKa values of 4.34 and 5.44 indicate that under environmental conditions adipic acid is largely deprotonated.

With regard to its chemical structure adipic acid is not expected to hydrolyze under environmental conditions. According to a Mackay calculation level I the favorite target compartment of the substance (uncharged molecule) is water with 97 %. It has to be considered, that at very low concentrations of adipic acid expected in the environment, the substance is mostly present as anion (i.e. deprotonated). As anions are neither subject to volatilization nor to adsorption, the hydrosphere is also the target compartment for the deprotonated molecule. The Henry's law constant of 9.7×10^{-7} Pa m^3 mol^{-1} (Bond method) and of 8.8×10^{-2} Pa m^3 mol^{-1} (ratio of vapor pressure versus solubility) at 25 °C indicates that the compound has a low potential for volatilization from surface waters. The calculated half-life of adipic acid in air due to indirect photodegradation is $t_{1/2}$ = 2.9 days.

Adipic acid is readily biodegradable (MITI, comparable to OECD TG 301C: biodegradation 68 - 90 % after 14 days, OECD TG 301B: 91 % after 28 days, closed bottle test OECD TG 301D: 83 % after 30 days).
The bioconcentration factor BCF = 3 for adipic acid calculated from the octanol-water partition coefficient indicates that there is only a low potential for bioaccumulation in aquatic organisms. With a calculated K_{oc} value of 22, adipic acid can be regarded as a substance without geoaccumulation potential.

Concerning the toxicity of adipic acid to aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The lowest valid effect data on acute fish toxicity was > 1000 mg/l for *Danio rerio* (96 h-LC_{50}) (pH 7.4 – 7.7). With *Daphnia magna* a 48 h-EC_{50}-value of 85.6 mg/l was observed. As the pH in the test solutions was in the range of 4 (500 mg/l) to 7.7 (15.6 mg/l), pH related effects on the daphnids cannot be excluded. In an algae growth inhibition test with *Desmodesmus subspicatus* the 96 h-E_bC_{50} was 26.6 mg/l and the 72 h-E_bC_{50} was 31.3 mg/l. The pH for the concentration of the EC50 was 6.0 at test begin and 8.2 after 96 h. Therefore, it can be concluded that the effects found in this study are likely not caused by pH effects. No tests are available on chronic toxicity of adipic acid.

Based on the acute aquatic toxicity data on three trophic levels (fish, *Daphnia*, algae), a Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000. Using the lowest acute effect concentration, the 96 h-EC_{50} of 26.6 mg/l of *Desmodesmus subspicatus*, a $PNEC_{aqua}$ of 27 µg/l was determined.

Exposure

Adipic acid is manufactured from a mixture of cyclohexanol (93 %) and cyclohexanone (7 %) by oxidative ring cleavage using concentrated nitric acid. Alternatively, it is manufactured from cyclohexane by catalytic oxidative ring cleavage. The global adipic acid manufacturing volume was estimated to be 1.8 million tonnes in 1995, and the manufacturing capacity amounted to 2.3 Mio tonnes in 1996 (USA 0.78 Mio. t/a, Japan 0.1 Mio. t/a, and Western

Europe 0.92 Mio. t/a). In 2000, the global manufacturing volume is estimated to be about 2.7 Mio. tonnes by 19 adipic acid plants (Brazil 1, Canada 1, China 3, France 1, Germany 2, Italy 1, Japan 2, Korea 1, Singapore 1, Ukraine 1, United Kingdom 1, USA 4).

Adipic acid is a basic chemical but is also used in consumer products. The most important product manufactured from adipic acid is nylon 66 (up to 70 % of the production). In foodstuffs adipic acid is used e.g. as a dietetic food additive, as acidulating agent for gelatine and jams, and as a neutralizing agent and buffer, in concentrations up to 10,000 mg/kg foodstuff. Adipic acid is present in marketed preparations registered in the product registers of Switzerland, Sweden, Denmark, Finland and Norway.

The exhaust gases of the manufacturing plant of the Sponsor company are lead to a thermal exhaust purification plant. Exhausts from the manufacturing and processing areas, where particulate adipic acid might occur, are led to air filters. Waste from the manufacturing and processing of adipic acid is incinerated in an incinerator for hazardous wastes. Wastewater is lead to a wastewater treatment plant. No adipic acid is detected in its effluent (detection limit 20 µg/l).

No information is available on the occurrence of adipic acid in the hydrosphere. Adipic acid was detected in soil samples (215 - 568 and 2,050 µg/kg). Adipic is formed in the atmosphere by photooxidation. Atmospheric concentrations vary from 0.9 ng/m^3 to 9 µg/m^3 (background to urban smog). Adipic acid is a component of tobacco smoke. It was detected in particle emissions from wood and foliage combustion. Adipic acid occurs in beet juice, ripe fruits of Morinda citrifolia, and rice straw, indicating biotic formation.

In the Sponsor company, regular surveys in the working area for any possible exposure to a dangerous substance at different work situations and appropriate control measures are performed. To protect workers from exposure several precautionary and protective measures are taken by the Sponsor company. Since exposure of manufacturing workers to adipic acid is unlikely to occur, no workplace measurements are available. In another company in the sponsor country there is no exposure of manufacturing workers either. Due to filling operations there was observed a dust concentration of 1 mg/m3 (8 h TWA) in the storage area. However, in another country data exist indicating occupational exposure potential.

Based on the ready biodegradability and the low bioaccumulation potential of adipic acid, a significant indirect exposure of the general public via the environment is not expected.

RECOMMENDATION

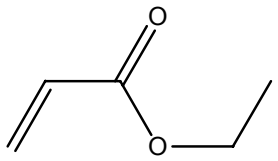
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health
The chemical possesses properties (eye and respiratory tract irritation) indicating a hazard for human health. Although these hazards do not warrant further work, they should nevertheless be noted by chemical safety professionals and users, especially at the workplace.

Environment
The chemical possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure level, they should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	140-88-5
Chemical Name	Ethyl Acrylate (2-Propenoic Acid, Ethyl Ester)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Ethyl acrylate is readily absorbed from the gastrointestinal tract and upper respiratory tract. Rapid metabolism occurs by two primary routes, carboxylesterase mediated hydrolysis of the ester linkage to acrylic acid and ethanol, and conjugation with glutathione. Both pathways serve to detoxify ethyl acrylate. Approximately 60% of the administered dose is excreted within 8 hours as CO_2.

Ethyl acrylate is slightly toxic following acute oral, dermal and inhalation exposure: LD_{50} rat (oral) = 1120 mg/kg body weight; LC_{50} rat (inhalation; vapor; 4 hour exposure) = 2180 ppm (9 mg/L); LD_{50} rabbit (dermal) = 3049 mg/kg body weight. In standard primary irritation studies, ethyl acrylate is a strong skin and eye irritant. Ethyl acrylate is considered likely to be a sensitizer and exposure to ethyl acrylate may result in cross-sensitization with other acrylates and methacrylates.

Repeated-dose studies confirm the irritant properties of ethyl acrylate with localized irritation, often severe, occurring at the site of contact for oral dosing, including forestomach tumors following chronic gavage dosing, and metaplasia or atrophy of the olfactory epithelium following inhalation exposure at concentrations greater than 5 ppm (0.02 mg/L). Repeated dose studies indicate that systemic toxicity, manifested primarily as body weight reduction, from oral or inhalation exposure to ethyl acrylate for periods up to 2 years, is minimal. No systemic toxicity was observed in oral (gavage or drinking water) studies below approximately 100 mg/kg/day for 90 days or 2 years. The LOAEC for systemic toxicity (decreased body weight) following 2 years of inhalation exposure was 75 ppm (0.31 mg/L) and the NOAEC for systemic toxicity was 25 ppm (0.10 mg/L). Nasal irritation, a site of contact effect, occurred at this concentration. The NOAEC for nasal irritation after 2 years of exposure was 5 ppm. Except for localized irritant effects, repeated exposure to ethyl acrylate in animal studies did not result in overt toxicity or specific organ toxicity.

Ethyl acrylate was not mutagenic to bacteria (*Salmonella* reverse mutation assay) *in vitro* and was not clastogenic in *in vivo* mouse micronucleus assays. Positive mutagenic activity in some *in vitro* assays occurred only at concentrations resulting in significant cell death. These assays are, therefore, considered inadequate for evaluation of the mutagenic potential of ethyl acrylate. Overall, ethyl acrylate is considered to pose no mutagenic hazard based on the available data.

Ethyl acrylate was not carcinogenic following exposure via inhalation at the highest concentration of 75 ppm (0.31 mg/L) or via drinking water at the highest concentration of 2000 ppm. Although forestomach tumors were observed in chronic gavage studies conducted by the National Toxicology Program (NTP), use of these studies for classification of ethyl acrylate carcinogenicity was determined by NTP to be scientifically unjustifiable. This was based on the conclusion that the forestomach tumors are not considered relevant and were seen only when ethyl acrylate was administered by gavage at high concentrations that induced marked local irritation and cellular proliferation. Therefore, ethyl acrylate was not considered to be carcinogenic in experimental animals; these same data were used in 1986 by IARC to classify ethyl acrylate in category 2B. Ethyl acrylate is scheduled for reevaluation by IARC.

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.

Ethyl acrylate had no effect on reproductive organs following repeated exposures via oral or inhalation routes for up to 2 years. In a well-conducted inhalation study exposing pregnant rats from gestation day 6 to 20, maternal and fetal body weights were reduced only at the highest concentration and no developmental toxicity or teratogenicity was observed. The NOAEL for maternal and fetal toxicity was 100 ppm (0.41 mg/L) and the LOAEL was 200 ppm (0.82 mg/L). The NOAEL for developmental toxicity and teratogenicity was 200 ppm (0.82 mg/L), the highest exposure concentration tested. Based on the available animal studies, ethyl acrylate is not toxic to reproduction or development and is not teratogenic.

Environment

The water solubility of ethyl acrylate is 15 g/L (25°C) and specific gravity is 0.9234 g/cm^3 at 20°C. The measured log Kow is 1.18. The vapor pressure is 38 hPa at 20°C. The melting point is – 71.2°C and the boiling point is 99.4°C.

Ethyl acrylate is photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 11.8 hours (calculated). The hydrolysis rate of ethyl acrylate is pH dependent with hydrolysis rates of <1% and <2% after 28 days at pH 3 and pH 7, respectively. The hydrolysis half-life at pH 11 is 182 minutes.

Distribution modeling using Mackay Level I indicates that the main target compartment will be air (90%) with the remainder partitioning into water (10%). Fugacity model level III calculations with 100% of the ethyl acrylate release to air (from Toxic Release Inventory data) gives comparable results; the levels are: 94% (air), 5.6% (water), <1% (soil) and <0.1% (sediment).

A low bioaccumulation potential is expected based on the partition coefficient and other physical/chemical parameters. Ethyl acrylate attained 57.3% degradation within 28 days in a closed bottle test according to OECD Test Guideline 301 D. In a CO_2-Headspace test according to ISO 14593 (identical to OECD Test Guideline 310) ethyl acrylate was readily biodegradable (96% degradation after 28 days).

Ethyl acrylate is acutely toxic to aquatic organisms. The 96-hour LC_{50} for rainbow trout was 4.6 mg/L (measured), the 48-hour EC_{50} for *Daphnia magna* was 7.9 mg/L (measured) and the 96-hour EC_{50} value (growth rate) for algae (*Selenastrum capricornutum*) was 5.5 mg/L (measured). In a 21-day chronic study with *Daphnia magna*, the EC_{50} for mortality was 0.5 mg/L and the NOEC was 0.19 mg/L (measured).

Exposure

The production volume of ethyl acrylate is estimated to be 50,000 to 100,000 tonnes per year in Europe and 250,000 to 500,000 tonnes per year in North America. Ethyl acrylate is produced and primarily used in closed systems. Its principle use is for the production of homopolymers and copolymers with other monomers (e.g. acrylic acid and its salts, amides, etc.), which are then used in a variety of products including paints, binders, polishes and adhesives.

Environmental releases are minimal. In 2001, US TRI reporting indicated that virtually all ethyl acrylate releases were to the air compartment (185,000 pounds).

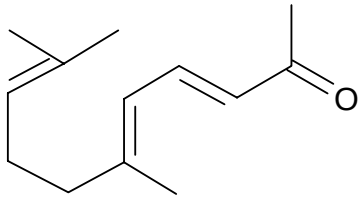
Extensive occupational exposure monitoring records are available which indicate that 8 hr TWAs for a variety of operations are below the regulatory/guideline values. End-use consumer products contain only trace levels of acrylic acid and esters (as a result of polymerization). Therefore, consumer exposure to acrylate monomers is low.

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

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (possible skin sensitization; skin, eye and nasal 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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	141–10–6
Chemical Name	Pseudoionone
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Pseudoionone has an acute oral mammalian LD_{50} (rat and mouse) above 2000 mg/kg bw, with most values greater than 5000 mg/kg bw. The acute dermal LD_{50} (rabbit) is above 5000 mg/kg bw. No inhalative or intraperitoneal toxicity data have been located.

Pseudoionone is severely to moderately irritating to the skin down to concentrations below 10%, based on studies in rabbit and guinea pig, but an 8% solution in petrolatum was not irritating to human volunteers. Pseudoionone produced transient irritant reactions of the eyes in a rabbit study. In a sensitisation test the reactions were judged to be of an irritant rather than a sensitising nature; however, a maximisation test with 8% pseudoionone in human volunteers resulted in 9 out of 108 subjects (8.3%) showing positive reactions.

The 28-day subchronic oral NOAEL of 50 mg/kg bw/d is based on minor, reversible effects (salivation kidney and liver weight gains) up to the highest dose of 1000 mg/kg bw/d. The same effects were observed in a one-generation reprotoxicity study in rat leading to a NOAEL for parental systemic toxicity of 120 mg/kg bw/d and a NOEL of 40 mg/kg bw/d, respectively.

Pseudoionone was not mutagenic in two bacterial Ames tests with and without metabolic activation nor in an *in vivo* OECD 474 mammalian micronucleus test. No carcinogenicity data have been located.

In a one-generation reproductive toxicity study in rats with an average exposure of 60 days for females and of 106 days for males, 120 mg/kg bw/d is the parental systemic toxicity NOAEL based on salivation, kidney and liver weight gains. Development of pups was unaffected up to the highest dose of 360 mg/kg bw/d leading to a developmental NOAEL of 360 mg/kg bw/d. Due to an increased rate in pup deaths during days 1–4 *post partum* in the highest dose group, the reproductive toxicity NOAEL is 120 mg/kg bw/d. A single application by gavage of 960 mg pseudoionone/kg bw to pregnant hamster dams caused no adverse effects on foetal development, in spite of reduced maternal bodyweight gain.

In several *in vitro* or *ex vivo* studies, pseudoionone was shown to have a potential for cytotoxicity at comparatively high concentrations.

In conclusion, the overall mammalian toxicity of pseudoionone is considered to be low. However, based on animal data, pseudoionone is a skin irritant and a weak eye irritant, and based on human data, there is a potential for sensitisation.

Environment

Pseudoionone is a liquid at room temperature, with a melting point of –75 °C, a boiling point of 265.4 °C, vapour pressure of 0.001741 hPa (20 °C), water solubility of 97 mg/l and a $logP_{OW}$ of 4.0. It has no ionisable groups at environmentally relevant *p*H. Due to the calculated $logK_{OC}$ values of 2.84 and 3.46 pseudoionone is predicted to adsorb moderately to organic carbon in soils and sediments. Based on standard Mackay distribution models, pseudoionone will mainly remain and be degraded in the environmental compartment of emission. Pseudoionone has no hydrolysable bonds. When exposed to atmospheric oxygen, pseudoionone is liable to slow autoxidation, but in case of exposure over large surfaces, *e.g.*, on cleaning rags, it may even self-ignite. The total atmospheric half-life due to indirect photodegradation is estimated at approximately 10 minutes. Based on the experimental $logP_{OW}$ and on QSAR-modelled $logK_{Ow}$ and BCF values (240-500), pseudoionone has a potential for bioaccumulation.

Pseudoionone attained 62% ready biodegradability in an OECD 301F test but failed the 10-day-window criterion; additional reports support aerobic biodegradability. Pseudoionone was not biodegradable under anaerobic conditions in an ISO 11734 test, being toxic to the sludge at the test concentration of 122 mg/l.

Pseudoionone was moderately toxic in acute aquatic ecotoxicity tests, with EC_{50} and LC_{50} values for freshwater fish, daphnids, green algae and cyanobacteria consistently between 1 and 10 mg/l : *Leuciscus idus*, 96-hour-LC_{50} = 4.64 mg/l, *Daphnia magna*, 48-hour-EC_{50} = 3.7 mg/l and *Scenedesmus subspicatus*, 72-hour-EbC_{50} = 1.11 mg/l respectively ErC_{50} = 2.02 mg/l, all data nominal concentrations. Pseudoionone had low toxicity to activated sludge with an EC_{50} > 1000 mg/l in a 30-minute OECD 209 test, moreover, it was not inhibitory in the ready biodegradability test at 45 mg/l. In contrast, it was toxic to anaerobic sludge bacteria at 122 mg/l and the LOEC to cyanobacteria was 3 mg/l. Based on very summary data for marine larvae and crustaceans, pseudoionone was toxic respectively inhibitory at unspecified low concentrations.

In a chronic and reproductive test with the common soil and sediment nematode *Caenorhabditis elegans* the NOEC of pseudoionone was a relatively high 100 mg/kg sediment (dry weight) for growth and egg production and 400 mg/kg for fertility, while the respective EC_{50} values were 2490, 821 and 1537 mg/kg. Pseudoionone showed juvenile-hormone-like activity in a number of insect species when applied topically at 10–80 µg per larva, which corresponds to a relatively weak effect in comparison with other terpenoids. Pseudoionone was toxic by oral uptake to mosquito larvae with an LC_{50} of 10.15 µg/l diet but it had no effect on honeybees at unspecified concentrations <1% in food. No avian data have been located.

Pseudoionone has been detected in a number of flowering plants and one mould, where it was made likely to be both a precursor and a metabolite of the common carotenoid lycopene. No phytotoxicity data have been located. Some sources show moderate toxicity towards certain fungi, moulds and bacteria, however, these data are difficult to quantify or to relate solely to the activity of pseudoionone.

In conclusion, pseudoionone is not readily biodegradable due to missing the 10-day window criterion, but expected to easily meet the criterion for inherent biodegradability, also based on a test with a closely related substance. Pseudoionone shows moderate toxicity towards aquatic and micro-organisms and low toxicity towards a common soil and sediment nematode. It has weak juvenile-hormone activity in several insects. There is an absence of toxicity studies examining terrestrial plants. However, pseudoionone has been identified as a biochemical intermediate and a metabolite in several plants. On the other hand, there may be some toxicity against fungi and bacteria.

Exposure

In Switzerland approximately 72 % of the produced pseudoionone are used on-site and processed in closed systems. Approximately 26 % are transferred by rail to a plant of the same group in Switzerland and processed in closed systems as well. Less than 1.5 % are shipped in barrels to three other companies. A similar situation applies to the coproducer in Germany.
Worldwide, approximately 40,000 tonnes pseudoionone per annum are estimated by industry to be produced. 99.9% of synthetic pseudoionone is used as an intermediate in the synthesis of vitamins A, E and K_1, of carotenoids and of terpenoid compounds. In addition, pseudoionone appears naturally in plants as an intermediate in the biosynthesis

and a metabolite in the degradation of lycopene. Lacking quantitative data, the amount of pseudoionone appearing from natural sources cannot be estimated, but it may be rather high.

Chemical production workers in the two production sites in Switzerland and in Germany and the main recipient companies are rarely exposed to pseudoionone, due to closed synthesis. Where direct contact is possible, *e.g.*, during sampling, filling of transport containers or maintenance work, standard occupational hygiene measures limit exposure. Some of the industrial pseudoionone is released to the atmosphere. Minor amounts are expected in industrial wastewater, no measured environmental concentrations have been located.

Pseudoionone is listed as a food ingredient in the European Union, but not in the United States, hence the public in the EU may be exposed to pseudoionone as an ingredient of food and beverages; while no quantitative data have been located, the actual use in food must be minimal. The use of pseudoionone as a fragrance compound in cosmetics was forbidden in the EU due to the sensitising potential and pseudoionone is only tolerated as an impurity at less than 2% in pure ionone fragrance compounds, hence exposure through cosmetics must also be minimal.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

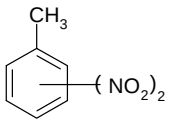
Human Health:

The only hazards identified are irritation to skin and slight irritation to eyes as well as sensitisation. Given the main use as a chemical intermediate and the low content of the substance in consumer products in the Sponsor country, the substance is considered to be 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 a hazard for the environment. 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	25321-14-6
Chemical Name	Dinitrotoluene (isomers mixture)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Dinitrotoluene (DNT) is a technical mixture containing approximately 80% 2,4-dinitrotoluene, appr. 20% 2,6-dinitrotoluene and < 5% 3,4-, 2,3- and 2,5-DNT. The toxicological profile of the DNT mixture well reflects the properties of the pure main isomers. Data on the pure 2,4- and 2,6-isomers are presented here only if they provide relevant additional information.

In humans Dinitrotoluene (DNT, technical grade) is absorbed following dermal and inhalative exposure and is rapidly metabolized and excreted in urine.

There are no acute inhalation studies on technical grade DNT and the 2,4-isomer available. LC_{50} of the 2,6-isomer, is reported to be 0.36 mg/l, however, this isomer accounts only for about 18% of technical grade DNT. No acute dermal studies on technical grade DNT and the 2,6-isomer are available. The acute dermal toxicity of 2,4-DNT, the main component of technical grade DNT, is relatively low with an LD_{50} greater than 2500 mg/kg bw in rats. Technical grade DNT is moderately toxic following oral administration to rats, with LD_{50} values of 268 to 660 mg/kg bw reported. After a 24-hour occlusive application DNT is not irritating to the skin (interior side of the ear) of rabbits. Although DNT has been reported to induce slight irritation to the eye of one rabbit, the effect is reversible within 7 days, and therefore DNT is not considered to be an eye irritant in humans.

There are no data available to evaluate the sensitizing potential of technical grade DNT. The 2,4-DNT isomer showed no sensitizing properties in a guinea pig maximization test, whereas 2,6-DNT gave a mild positive response. Patch tests or photo-patch tests in 10 or 5 healthy humans showed no allergic potential of DNT (unspecified isomer), whereas a single case of positive photo-patch test reaction was reported for a worker with skin problems.

There are no inhalative or dermal repeated dose studies on technical grade DNT or on the 2,4-/2,6-DNT isomers available. Chronic feeding of technical grade DNT to rats led to hematological changes (especially methemoglobinemia), and toxicity to liver, kidney, adrenal glands and testes in rats. At the lowest administered dose of 3.5 mg/kg bw/day signs of hepatotoxicity became obvious. No NOAEL can be derived for repeated dose toxicity.

Technical grade DNT is mutagenic in bacterial test systems in the presence and absence of metabolic activation, but it shows no mutagenic or genotoxic activity in mammalian cells *in vitro*. Technical grade DNT shows no mutagenic activity in the mouse bone marrow micronucleus assay and in mouse dominant lethal and spot tests. However, a distinct activity of DNT to induce DNA repair in the liver of rats is reported. Additionally, DNA binding properties in various rat organs, mainly rat liver were demonstrated for 2,4-DNT and 2,6-DNT isomers. Gut flora may play an important role in activation of DNT to reactive metabolites. Overall, technical grade DNT shows the potential to induce genotoxic changes *in vivo*.

Technical grade DNT shows hepatocarcinogenic properties in rats. In a long-term feeding study liver tumors were dose dependently induced in male rats from the lowest administered dose (3.5 mg/kg bw/day) and in female rats from 14 mg/kg bw/day. In an initiation-promotion liver foci assay DNT showed tumor promoting activity, however, only weak initiating properties. The pure 2,4- and 2,6-DNT isomers also induced liver tumors in rats. Additionally, the 2,4-isomer was shown to induce tumor formation in the renal tubular epithelium of male mice. After long-term feeding of technical grade DNT to rats (104 weeks) increased incidences of abnormally small testes and increased ovary weights were observed at 14 mg/kg bw/day. A daily dose of 35 mg/kg bw DNT led to testicular degeneration and hypospermatogenesis after 52 weeks of exposure. The NOAEL for changes on reproductive organs was 3.5 mg/kg bw/day in this study. Technical grade DNT did not negatively affect fertility in dominant lethal assays. Overall, impairment of male rat fertility after chronic exposure of toxic doses cannot be excluded.

In pregnant rats, administration of technical grade DNT by gavage on gestation days 7-20 did not induce teratogenic/developmental effects even at dose levels, which produced significant maternal toxicity. The NOAEL for teratogenic/developmental toxicity can be determined to be 150 mg/kg bw/day.

In humans, heavy DNT exposure causes signs of methemoglobinemia, which are reversible 2-3 days after removal from exposure. Signs of disturbances in liver function and exposure-dependent nephrotoxic effects directed to the tubular system were additionally found in exposed workers. Single findings in studies without reliable exposure data and/or only small numbers of significantly exposed workers indicating increased incidences of hepatobiliary or urothelial cancer in occupationally DNT exposed workers do not permit a conclusion on the carcinogenicity of DNT in humans. Preliminary observations pointing to an increased risk of ischemic heart disease or to an adverse effect on the human male reproductive system could not be confirmed by further studies.

Environment

Dinitrotoluene (DNT) is a technical mixture containing approximately 80 % 2,4-dinitrotoluene (121-14-2) and 20 % 2,6-dinitrotoluene (606-20-2). To a lower content also the isomers 2,3-DNT (1.3 %), 2,5-DNT (0.5 %) and 3,4-DNT (2.4 %) are contained in the technical mixture. DNT is an orange-yellow substance of characteristic odour with a melting point of 56 - 59°C and boiling point of 250 °C. With a density of 1.52 g/cm³ at 15 °C DNT is heavier than water. The water solubility was determined to 166 mg/l for 2,4-DNT and 145 mg/l for 2,6-DNT at 25 °C. A vapour pressure of 0.016 Pa for 2,4-DNT and of 0.032 Pa for 2,6-DNT was measured at 25 °C. For the isomers mixture a log Kow of 2.00 was calculated.

In the atmosphere DNT is degraded by photochemically produced OH radicals. The half-life is calculated to be ca. 84 days. In surface waters, from photodegradation measurements a half-life of 1 day was derived for (predominantly) direct photolysis under the radiative conditions of latitude 40 °N. In surface waters, with regard to the geographical conditions in Germany and the low light intensity in natural water bodies, the half-life of 2,4-DNT for direct photolysis is calculated to be 20 days in a natural water body (surface layer: 6.5 days).

DNT is not expected to hydrolyze in the environment due to the lack of hydrolyzable groups.

Biodegradation was tested under aerobic and anaerobic conditions. In organic soil a DT50 for 2,4-DNT of 7 days and a DT90 of 191 days was determined. In an aquatic ready test (aerobic) according the OECD TG 301C, 0 % biodegradation was reported after 14 days. Thus DNT is not readily biodegradable. In a test system under anaerobic conditions, performed according to EPA-Guideline No. 796.3140, 0 % biodegradation was observed within 56 days. DNT can be primary biodegraded and also mineralized by selected adapted bacteria cultures under specific conditions. However, under environmental conditions where no adaptation of the microorganisms can be assumed, no biodegradation of DNT is expected.

According to the Mackay fugacity model level I, the favorite target compartment of DNT is water with 97 - 98 %. The calculated Henry's law constant (0.0094 Pa m^3/mol at 25 °C) proves a low potential for volatilization from surface waters.

DNT bioconcentration factors measured in fish are in the range of 0.6–21.2 indicating no significant

bioaccumulation potential.

K_{oc} values were calculated with PCKOCWIN v1.66 (K_{oc} = 371) and with the TGD equation for nitrobenzenes (K_{oc} = 123). These results indicate a low to medium sorption potential of DNT onto the organic phase of soil or sediments. A test on leaching from three different type of soils is available for 2,4-DNT. After 2 days of leaching no 2,4-DNT was found in the leachates.

Concerning the acute toxicity of DNT towards aquatic species, experimental results for the trophic level fish are available. The acute toxicity determined for fish (*Oryzias latipes*) was 27 mg/l (48h-LC50). Acute toxicity data available for the single isomers of the technical mixture show that the toxicity of 2,4- and 2,6-DNT is in the same order of the toxicity found for the technical mixture. However, the other isomers are about an order of magnitude more toxic to fish than the main isomers. With the model of concentration additivity a LC_{50} of about 17 mg/l can be estimated for the technical mixture which is in good agreement with the experimentally determined value.

With *Daphnia magna* acute tests with different DNT-isomers were performed according to standard procedures or similar methods. Also for *Daphnia* it is shown that the isomers 2,3-, 2,5- and 3,4-DNT are about an order of magnitude more toxic than the 2,4- and 2,6-isomers. Assuming that the toxicity of the technical mixture can be explained by the additive toxicity of the single isomers a 48h-EC_{50} of about 23 mg/l can be estimated for the technical mixture.

For algae, tests available for the different isomers show that the toxicities of the 2,4- and 2,3-isomers are more similar than the toxicities of the 2,4- and 2,6-DNT. As 2,4-DNT seems to be the most toxic isomer to algae, it can be concluded that the toxicity of the isomeric mixture for this trophic level can be described using the data for 2,4-DNT.

The effect values from short-term tests for the technical DNT are:
Oryzias latipes: 48 h-LC_{50} = 27 mg/l (measured)
Pimephales promelas: 96 h-LC_{50} = 17 mg/l (estimated from the toxicity of the single isomers)
Daphnia magna: 48 h-EC_{50} = 23 mg/l (estimated from the toxicity of the single isomers)
Selenastrum capricornutum: 96 h-E_rC_{50} = 2.6 mg/l (2,4-DNT, regarded as representative for technical mixture)
Chlorella pyrenoidosa: 96 h-E_rC_{50} = 0.9 mg/l (2,4-DNT, regarded as representative for technical mixture)
Microcystis aeruginosa: 96 h-EC_{50} = 0.08 mg/l (2,4-DNT, regarded as representative for technical mixture)

Reliable tests on chronic toxicity towards fish, *Daphnia,* algae and blue-green algae are available as well. The lowest effect values were obtained with the 2,4-DNT:
Oncorhynchus mykiss : 90 d-NOEC = 0.27 mg/l (e) (growth)
Daphnia magna : 21 d-NOEC = 0.02 mg/l (e) (reproduction)
Scenedesmus subspicatus : 48 h-E_rC_{10} = 1.9 mg/l (n)
Scenedesmus pannonicus): 96 h-E_rC_{10} = 0.32 mg/l (n)
Microcystis aeruginosa: 96 h-E_rC_{10} = 0.056 mg/l (n)

It can be concluded that the toxicity of the technical mixture is also covered by these data.

For terrestrial organisms reliable experimental data are available with plants and earthworms. The most sensitive plant species was *Brassica rapa* with a 14 d-EC_{50} of 6.5 mg/kg soil dry weight (nominal) using the proposed guideline of the German BBA. For the earthworm *Eisenia fetida* a 14 d-LC_{50} of 668 mg/kg soil dry weight (nominal) was determined with the OECD TG 207.

Following the EU Technical Guidance Document, for the derivation of the PNECaqua an assessment factor of 10 is chosen since long term tests for three trophic levels for DNT isomers are available. Using the lowest determined concentration, the *Daphnia magna*-NOEC of 0.02 mg/l (effective), a $PNEC_{aqua}$ of 2 µg/l is derived.

Exposure

DNT is manufactured by nitration of toluene (or nitrotoluenes) producing a mixture of approximately 80 % 2,4-DNT and 20 % 2,6-DNT. Several nitroaromatics, including DNT isomers, occur as byproducts of 2,4,6-trinitrotoluene

(TNT) manufacturing. The global production capacity of DNT is about 1.6 Mio. t/a.

About 99 % of DNT are used for polyurethanes, as an intermediate for toluylenediamine (TDA) and toluylenediisocyanate (TDI). Bayer processes > 99 % of the DNT to TDA. About 1 % of the global DNT production is used in other applications: E.g. the manufacturing of TNT and propellants, as an intermediate in the production of dyes and for staining ofrefractory bricks.DNT is contained in preparations registered in Nordic countries but not in the Swiss product register. The new EU Directive 2003/34/EC (EU 2003) bans the use of DNT in consumer products in the EU market.

Manufacturing and processing (including filling) of DNT at the Sponsor company are executed in closed systems. Due to 2 step treatment of the exhausts from DNT manufacturing and processing, from the Bayer sites no relevant amount of DNT is emitted into the atmosphere. At the Bayer sites, waste from the manufacturing and processing of DNT is disposed off in an incinerator for hazardous wastes. The wastewater is treated to recover DNT and remove traces of DNT. The effluent concentrations of both isomers (2,4- and 2,6-DNT) were below the detection limit (< 85 µg/l and < 4 µg/l) (Σ for both isomers). No information is available from other sites.

In the river Elbe, the concentrations of 2,4-DNT and 2,6-DNT decrease significantly from the Czech border to the North Sea, indicating that there is no relevant DNT source in the corresponding catchment area. 2,4-DNT is not thought to be relevant for the river Rhine. There are no data on DNT in the air. DNT occurs at former munitions manufacturing sites.

Surveys of the workplaces have been performed also according to German Technical Guidance TRGS 402. In Germany there is no workplace limit concentration for 2,4-DNT. For 2,6-DNT there is a TRK-value (Technical Guidance Concentration) of 0.05 mg/m3. At all Bayer plants the exposure of workers is well below this limit.

In humans, DNT isomers have a half-life time of 1-3 hours. 24 h after exposure DNT is completely eliminated. The levels of all DNT isomers in blood are measured at least once a year in each worker of the Bayer AG DNT manufacturing and processing plants as part of the Bayer health surveillance program. In 2000 – 2002, the DNT isomer levels in blood were below the limit of detection (5 µg/l blood).

DNT is used as an industrial intermediate e.g. for polymers, explosives, and some other chemicals. Since DNT is chemically converted in the production chain e.g. during hydrogenation and phase separation, final products are thought to be virtually free of DNT. Residual levels of DNT in the Bayer isocyanates are below the detection limit of 100 ppm. Due to these products, no exposure occurs in the consumer area.

At an emission of < 25 kg/year into the atmosphere, a quantitatively relevant human dose can be excluded. Exposure of the population via the hydrosphere is considered to be minimal. Based on the very low emissions of DNT into air and water by the Bayer manufacturing and processing plants, a significant indirect exposure of the general public via the environment or via the food chain is not expected.

RECOMMENDATION

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

Environment: The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

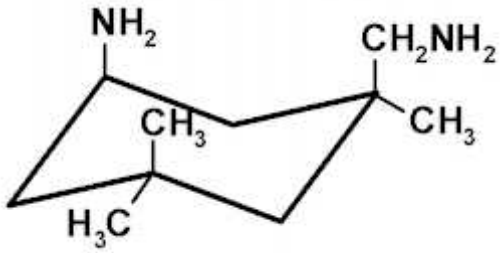
Human Health:

Technical grade DNT possesses properties indicating a hazard for human health (moderate acute toxicity, toxic after prolonged exposure, mutagenic and carcinogenic properties, influences on fertility in toxic doses possible). Based on data presented by the Sponsor country, exposure from production and processing as chemical intermediate is well controlled in occupational settings and is anticipated to be low for consumers, 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, e.g. indirect exposure of the general public from munitions dumps or former munitions sites.

Environment:

The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor company, exposure from production and processing as chemical intermediate is low. However, in addition to the use as chemical intermediate some direct uses of DNT have been identified. Therefore, an exposure assessment and, if then indicated, an environmental risk assessment is recommended. Countries may desire to investigate any exposure scenario not presented by the Sponsor Country, e.g. exposure from munitions dumps or former munitions sites.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2855-13-2
Chemical Name	3-Aminomethyl-3,5,5-trimethylcyclohexylamine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information available on toxicokinetics and metabolism of 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

There is only one valid but limited acute toxicity study of 3-aminomethyl-3,5,5-trimethylcyclohexylamine available. The LD_{50} after oral application to male rats is 1,030 mg/kg bw and the kidney is the potential target organ. Valid acute inhalation or dermal studies are not available.

Based on a limited skin irritation study with rabbits and rats, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is deemed to be a strong irritant (duration of the exposure not reported) and corrosive after repeated application. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is corrosive to the eyes of rabbits when tested according to OECD TG 405.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine was found to induce dermal sensitisation when tested according to OECD TG 406 in guinea pigs. From a number of publications there is evidence that frequent occupational exposure to 3-aminomethyl-3,5,5-trimethylcyclohexylamine may lead to the development of allergic contact dermatitis in humans. Since there is only one publication on possible airway effects of 3-aminomethyl-3,5,5-trimethylcyclohexylamine (describing a single human case) no definite conclusion can be drawn on respiratory sensitisation.

From two 14-day inhalative exposure studies with rats no NOAEL could be determined. At the first study's LOAEL of 18 mg/m^3, degeneration/necrosis in the olfactory epithelium of the nose were observed. Trachea, larynx and lungs were affected at 200 mg/m^3 and above (degeneration/necrosis, hyperplasia, squamous metaplasia). At the LOAEL of the follow-up study, i.e. at 2.2 mg/m^3, reversible minimal to mild degeneration of respiratory nasal mucosa in the anterior dorsal nose was observed. In a subchronic drinking water study according to OECD TG 408, the administration of 150 mg/kg bw/day led to reduced absolute and relative kidney weights in male and female rats (histopathology being indicative for tubular nephrosis), while 59 mg/kg bw/day (males) and 62 mg/kg bw/day (females) were determined as a NOAEL.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine was not mutagenic in bacteria and mammalian cell systems *in vitro* (Ames test according to Directive 84/449/EEC B.14 (1984) and HPRT test according to OECD TG 476 (1984)). It did not induce chromosomal aberrations in CHO cells *in vitro* in a test performed in accordance with OECD TG 473

(1981). *In vivo* mouse micronucleus tests (one performed according to OECD TG 474 (1983) for the induction of micronucleated polychromatic erythrocytes were clearly negative. From all *in vitro* and *in vivo* tests performed there is no evidence that 3-aminomethyl-3,5,5-trimethylcyclohexylamine has a mutagenic or clastogenic potential.

No studies have been performed on the toxicity of 3-aminomethyl-3,5,5-trimethylcyclohexylamine to reproduction. Data from an oral 90-day study in rats according to OECD TG 408 did not reveal any adverse effects on the male and female reproductive organs.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine did not show any teratogenic or embryofetotoxic effects in a gavage study with rats performed in accordance with OECD TG 414 (2001) up to and including the highest tested dose level of 250 mg/kg bw/day. The NOAEL for maternal toxicity was 50 mg/kg bw/day, effects at 250 mg/kg bw/day were reduced food consumption and reduced body weight gain. The NOAEL for developmental toxicity is 250 mg/kg bw/day.

Environment

3-Aminomethyl-3,5,5-trimethylcyclohexylamine has a melting point of 10 °C, is miscible with water and has a vapour pressure of 0.02 hPa at 20 °C. The measured log K_{ow} is 0.99 (23 °C). The pKa of approximately 10.4 characterises the substance as a moderate base.
According to a Mackay Level I model calculation, the main target compartment for 3-aminomethyl-3,5,5-trimethylcyclohexylamine will be water (99.8 %), followed by sediment and soil (both 0.08 %). It has to be considered that under environmental relevant pH conditions the substance is available as cation and therefore the prediction of the environmental distribution using the data for the uncharged molecule is not appropriate. The calculated Henry's law constant of 0.000446 Pa m^3/mol indicates very low volatility from surface waters. Dissociation in aqueous solution will further reduce the volatility. With a calculated K_{oc} of 340.4 l/kg, the sorption potential to soil or sediment organic matter is expected to be moderate. However, as in the environment the substance is available as cation, binding to the matrix of soils with high capacities for cation exchange (e.g. clay) cannot be excluded.

In the atmosphere, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is rapidly removed by reaction with hydroxyl radicals with a calculated half-life of 0.2 days. In water, it is expected to hydrolyse at a low rate under environmental conditions ($t_{1/2}$ > 1 year at 25°C). Photolytical degradation in surface waters is expected to be of minor importance due to the chemical structure. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is not readily biodegradable (OECD 301A: 8 % 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 hrs. The log K_{ow} value of 0.99 indicates a low bioaccumulation potential.

The lowest valid acute test results of aquatic testing determined for fish, daphnids, and algae were as follows: *Leuciscus idus:* 96-h LC_{50} = 110 mg/l; *Daphnia magna:* 48-h EC_{50} = 23 mg/l; *Scenedesmus subspicatus:* 72-h ErC_{50}> 50 mg/l; 72-h E_bC_{50} = 37 mg/l

Long term aquatic toxicity data are available for two trophic levels: *Daphnia magna:* 21-d NOEC = 3.0 mg/l; *Scenedesmus subspicatus:* 72-h E_rC_{10} = 11 mg/l; 72-h E_bC_{10} = 3.0 mg/l

An assessment factor of 50 was applied to the lowest of two long-term results covering two trophic levels. The PNEC of 0.06 mg/l for aquatic organisms was calculated from the NOEC for *Daphnia* = 3.0 mg/l.

Exposure

The production volume of 3-aminomethyl-3,5,5-trimethylcyclohexylamine is approximately 35,000 t/year world wide. Production sites are in Germany and the U.S.A. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is used as a chemical intermediate to produce hardeners for epoxy resins and coatings, and is also directly used as a hardener. It has large applications in epoxy-based self-levelling and trowelable flooring systems, and various civil engineering applications such as paving, concrete protection and repair. Other applications include coatings for superior corrosion protection of metal, adhesives and anchoring compounds. It is further used in the production of non-

crystalline speciality polyamides, as a chain extender in polyurethanes and as an intermediate in dyes.

Releases into the environment may occur during production of 3-aminomethyl-3,5,5-trimethylcyclohexylamine as well as from processing, formulation and use as an epoxy resin hardener. Available information indicates that in Germany release from production into waste water treatment plants is < 13,000 kg/year. The predicted environmental concentrations are of low toxicological significance.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine is used in a number of consumer products, mainly hardeners for paints, adhesives, and floor covering materials at various concentrations up to > 50%. Due to the low vapour pressure, exposure by inhalation is unlikely to occur.

Workplace measurements from the U.S. production site indicate a median concentration during 8-hr working shifts of <0.01 mg/m³ 3-aminomethyl-3,5,5-trimethylcyclohexylamine. No specific monitoring data for 3-aminomethyl-3,5,5-trimethylcyclohexylamine are available for the two German production sites. Exposure relevant operations are sampling, loading connections, cleaning operations, and leaks, all of which are low in duration and / or frequency. Exposure is controlled by measures like leak detection systems or exhaust ventilation as well as by personal protection equipment, which is depending on the job. No additional information is available on processing, formulation and use as an epoxy resin hardener.

RECOMMENDATION

The chemical is currently of low priority for further work

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

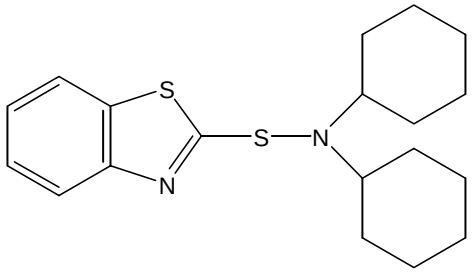
Human Health:

The chemical possesses properties (sensitisation, corrosive effects) indicating a hazard for human health. In view of the magnitude of the potential for effects, consumer products are considered to be adequately labelled and occupational exposure is controlled sufficiently in the Sponsor country to ensure safe handling, 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 for the environment. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure levels, they should nevertheless be noted by chemical safety professionals and users.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	4979-32-2
Chemical Name	N,N-Dicyclohexyl-2-benzothiazolesulfenamide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute toxicity of N,N-dicyclohexyl-2-benzotazothiazolesulfenamide (DCBS) is low. The oral LD_{50} in rats is greater than 1,000 mg/kg and the dermal LD_{50} in rabbits is more than 2,000 mg/kg. This chemical is moderately irritating to skin and slightly irritating to eyes but no sensitizing to skin.

In an oral study with rats according to the OECD combined repeated dose and reproductive/developmental toxicity screening test [TG 422], the major toxicities were found in clinical observation and histopathological examination in kidneys. Salivation in males at 400 mg/kg bw/day and decreased locomotor activity in females at 100 and 400 mg/kg bw/day were noted. Histopathological examination revealed hyaline droplets in the renal tubular epithelia in males and fatty degeneration of the renal tubular epithelia in females at 100 and 400 mg/kg bw/day. In addition, adrenal enlargement with vacuolation of the adrenocortical cells and atrophy of spleen in females at 100 and 400 mg/kg bw/day were observed. A NOAEL for repeat dose toxicity was established at 25 mg/kg bw/day for both sexes.

In the above screening test [OECD TG 422], the toxic effects were revealed in females and pups at the dose of 400 mg/kg bw/day. There was a decreased number of corpus lutea accompanied with decreases in the number of implantation sites and litter size. Three dams died on the expected delivery day or on the following day. All dams at 400 mg/kg bw/day lost their litters at delivery or by day 4 of lactation. There were no effects on the mating and fertility, and morphogenesis in pups at and below 100 mg/kg bw/day. A NOAEL for reproductive/developmental toxicity was established at 100 mg/kg bw/day.

The genotoxic potential of this chemical was mostly negative with and without an exogenous metabolic activation system in bacteria as well as mammalian cells, while the cytogenetic effect was judged to be positive in *in vitro* tests without an exogenous metabolic activation because of a slight increase of polyploid cells and induction of micronucleus cells. However, this chemical did not induce cytogenetic effects in an *in vivo* bone marrow chromosome test although a standard method was not used. The weight of evidence suggests this chemical may not be genotoxic *in vivo*.

Environment

DCBS is a white powder with a water solubility of 1.9×10^{-3} mg/L at 25 °C, a melting point of 99 °C at 1013 hPa and a vapour pressure of $< 7.0 \times 10^{-5}$ Pa at 100 °C. A measured log Kow value is > 4.8a high bioaccumulation potential. DCBS has a high bio-concentration potential (steady-state BCF is 6,000 with Japanese carp). This chemical is hydrolysed in water and its half-lives at 25 °C have been measured as 4.92 day at pH 4.0, 18.6 days at pH 7.0 and 112 days at pH 9, producing two major metabolites (dicyclohexylamine and 2-mercaptobenzothiazole). However actual hydrolysis rates are uncertain since the test was conducted above the

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.

water solubility limit. Environmental distribution using a Mackay level III model indicates that if the substance is released into water or soil it tends to remain its in original compartment whereas if released into air the substance is distributed into air (42.8 %) and soil (52.9 %). This substance is not readily biodegradable. In the atmosphere the substance is indirectly photodegraded by reaction with OH radicals with a half-life of 2.26 hrs. One of the degradation products, 2-mercaptobenzothiazole is non-volatile and not readily biodegradable whereas dicyclohexylamine is non-volatile but readily biodegradable in the environment.

In acute toxicity tests with fish, daphnids and algae, no effects were observed at the limit of solubility of the substance [96 h LC50 of > 0.0344 mg/L (*Orizias latipes*, OECD TG 203); 48 h EC50 of > 0.0314 mg/L (*Daphnia magna*, OECD TG 202, Immobilisation); 72 h EC of > 0.0118 mg/L (*Selenastrum capricornutum*, OECD TG 201, both biomass method and growth rate method) were reported].
Also in chronic toxicity tests with daphnids and algae, no effects were observed at the limit of solubility of the substance. A 21 d NOEC of >= 0.0331 mg/L (*Daphnia magna*, OECD TG 211, reproduction) and a 72 h NOEC of >= 0.0118 mg/L (*Selenastrum capricornutum*, OECD TG 201) were reported.

Exposure

Annual production volume of DCBS in Japan was about 1,900 tonnes in 2000-2003, and there is no information on import and export volumes.
In Japan, DCBS is solely used as an accelerator of vulcanization and is completely reacted in the vulcanizing process. During vulcanisation processes and the use of rubber products, some degradation products (e.g. mercaptobenzothiazole: CAS No. 149-30-4 or di(benzothiazoyl-2)disulfide: CAS No. 120-78-5) may appear and they can be released into the environment. It is reported that during the vulcanization the unstable sulphur-nitrogen-bond of DCBS is split with the intermediate formation of mercaptobenzothiazol radicals. Products resulting from the process are the basic amines, benzothiazole derivatives and further reaction products. As further degradation products, benzothiazole, 2-methylbenzothiazole and 2-benzothiazolone and 2-methylthiobenzothiazole are reported.
Occupational exposures at production sites may occur by the inhalation route during bag filling operation. No actual workplace concentration data was available. Workers wear dust respirator and body-covering clothing and local exhaust ventilation system is operated during the filling process.

RECOMMENDATION

The chemical is a candidate for further work.

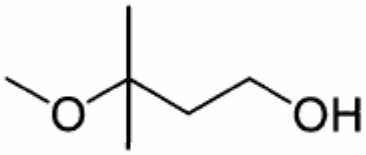
RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health
The chemical possesses a hazard for human health (repeated dose toxicity). An exposure assessment and, if necessary risk assessments for workers and consumers should be performed taking into account possible breakdown products.

Environment
The chemical did not show any adverse effects in several acute and chronic toxicity tests with aquatic organisms, but shows a high bio-concentration potential. During the use of the substance several degradation products are formed which possess properties indicating a hazard for the environment. These degradation products are present in many rubber products and a release to the environment is possible. An exposure assessment, and if necessary a risk assessment for the environment of the degradation products should be performed. The currently on-going assessment of di(benzothiazoyl-2)disulfide (CAS No. 120-78-5), of N-cyclohexylbenzothiazole-2-sulfenamide (CAS No. 95-33-0) and of the sulfenamide accelerator category should be taken into account.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	56539-66-3
Chemical Name	3-Methoxy-3-methyl-1-butanol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics, metabolism or distribution.

In an acute dermal toxicity study with 3-methoxy-3-methyl-1-butanol (MMB) at 2000 mg/kg bw, there was no death, clinical sign or abnormality at necropsy in SD rats. The acute dermal LD_{50} was considered to be more than 2000 mg/kg bw. In an acute oral toxicity study [OECD TG 401], Crj:CD SD rats (5 animals/sex/dose) were given MMB by gavage at 0, 2000, 3200, 4000 or 5000 mg/kg bw for males and females. Deaths were found in males and females at 4000 mg/kg and higher. No changes in body weight were recorded for rats that died. The LD_{50} values were estimated to be 4500 and 4300 mg/kg bw in males and females, respectively. There is no available information on acute inhalation toxicity.

The undiluted MMB showed slight irritation to the skin after prolonged exposure in rabbits. MMB was moderately irritant to rabbit eyes. There was no evidence of sensitisation of MMB in guinea pigs.

In a repeated dose toxicity study, Crj:CD(SD)IGS rats (5 animals/sex/dose) were given MMB by gavage at 0 (vehicle: distilled water), 15, 60, 250 or 1000 mg/kg bw/day. The administration period was 28 days and the recovery period was 14 days after administration. There were no MMB-induced changes in general condition, body weight gain, food consumption, hematological findings, necropsy findings and histopathological findings. A decrease in chloride in males and females at 1000 mg/kg bw/day and increases in A/G ratio and inorganic phosphorus in males at 1000 mg/kg bw/day were detected. An increase in relative weight of the kidneys in males at 250 (11%) and 1000 mg/kg bw/day (15%) and in females at 1000 mg/kg bw/day (16%), and an increase in relative weight of the liver in males (10%) and females (13%) at 1000 mg/kg bw/day after the administration period and in males at 1000 mg/kg bw/day (7%) after the recovery period were detected. The NOAELs for repeated dose toxicity were considered to be 60 mg/kg bw/day for males and 250 mg/kg bw/day for females.

In a reverse gene mutation assay [OECD TG 471], MMB was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537, and TA 1538 or in *Escherichia coli* WP2 uvrA either with or without an exogenous metabolic activation. In a chromosomal aberration test [OECD TG 473], MMB did not induce structural chromosomal aberrations or polyploidy either with or without an exogenous metabolic activation.
There is no available information on carcinogenicity.

In the reproduction/developmental toxicity screening test [OECD TG 421], Crj:CD(SD)IGS rats (12 animals/sex/dose) were given MMB by gavage at 0 (vehicle: distilled water), 8, 40, 200 or 1000 mg/kg bw/day. Males were dosed for 47 days and females were dosed from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. Increases in absolute and relative weights of the kidney in males at 200 mg/kg bw/day

and higher and relative weight of the liver and kidney in females at 1000 mg/kg bw/day were detected. No effects of MMB on reproductive and developmental parameters were observed. No external or internal malformation was found in pups at any dose. The NOAELs were considered to be 40 mg/kg bw/day in males and 200 mg/kg bw/day in females for general toxicity and 1000 mg/kg bw/day for reproductive and developmental toxicity in rats.

In a developmental toxicity study, Crj:CD(SD) female rats (25 animals/dose) were given MMB by gavage at 0 (vehicle: deionized water), 250, 500 or 2000 mg/kg bw/day on days 6-15 of gestation. Decreased motor activity, excess salivation, ataxia, muscle flaccidity and loss of righting reflex at 2000 mg/kg bw/day and decreases in body weight gains and food consumption at 250 mg/kg bw/day and higher were observed in dams. Fetal body weights were decreased at 2000 mg/kg bw/day. No increases in embryonic/fetal deaths and fetal malformations were detected after administration of MMB. Increases in skeletal variations and delayed ossification were found at 2000 mg/kg bw/day. The NOAELs were considered to be less than 250 mg/kg bw/day for maternal toxicity and 500 mg/kg bw/day for developmental toxicity in rats.

Environment

3-Methoxy-3-methyl-1-butanol (MMB) is a colourless liquid with a water solubility of 100 g/l at 25 °C, a melting point of lower than –50 °C, a boiling point of 173 °C at 1013 hPa, a vapour pressure of 1.25 hPa at 25 °C and a density of 0.927 g/cm^3 at 25 °C. Based on the measured log Kow value of 0.18 bio- or geoaccumulation of this chemical is unlikely. Environmental distribution using a Mackay level III fugacity model suggests that when MMB is released into air or water, it remains in the original compartment whereas when released into soil, 29.4 % is distributed into air, 9.3 % into water and 61.3 % remains in soil. A ready biodegradability test showed that MMB failed to meet a criterion for ready biodegradability (biodegradation rate = 50% after 28 days), however complete biodegradation was observed in an inherent biodegradation test. A study on hydrolysis indicates that MMB is stable in water. In the atmosphere MMB is indirectly photodegraded by reaction with OH radicals with a half-life of 1.1 days.

Ecotoxicity data on this substance are available for aquatic species from three trophic levels. In an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum*, open system), acute toxicity results of 72 h ErC_{50} >1,000 mg/L and 72 h EbC_{50} >1,000 mg/L were obtained. For daphnids, a 48 h EC_{50} of > 1000 mg/L was reported (OECD TG 202, *Daphnia magna*, static). For fish (OECD TG 203, *Oryzias latipes*, semi-static) a 96 h LC_{50} > 100 mg/L is available.

Regarding chronic toxicity to algae, a 72 h NOEbC of 1,000 mg/L (OECD TG 201, *Selenastrum capricornutum*, open system) was reported. In daphnids, an 21 d EC_{50} of >100 mg and a 21 d NOEC of 100 mg/L were reported (OECD TG 211, *Daphnia magna*, semi-static).

Exposure

The annual production volume of 3-methoxy-3-methyl-1-butanol (MMB) in Japan is ca. 10,000 tonnes in 2002. In 2002, ca. 2000 tonnes of this substance were exported from Japan.

MMB is synthesized from methanol and iso-butylene (C4 fraction of cracked naphtha) in a closed system in the Sponsor country. MMB is used as a solvent for paints, inks, fragrances (ca. 70%), and as a synthetic intermediate for detergents for industrial use (ca. 30%).

Although no monitoring data for MMB at the production site is available, significant emission of MMB into the environment is unlikely because well-controlled waste water treatment is in place and measures to prevent exposure to air are being taken during the production process.

Since MMB has a moderate vapour pressure and is miscible with water or organic solvents, occupational exposure through inhalation of the vapour and dermal route is possible. At the production site, workers who operate sampling and analysis, drum filling, lorry tank filling may be exposed to this chemical. The workers wear protective gloves and goggles during these operations. At user sites where this chemical is used as a solvent occupational exposure is possible, although no information is available. Since end-use products (paint, detergents) contain MMB, exposure to

consumers and the environment is expected. Monitoring data at production site or user sites are not available. No exposure standard value for this chemical was located.

RECOMMENDATION

The chemical is currently of low priority for further work

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

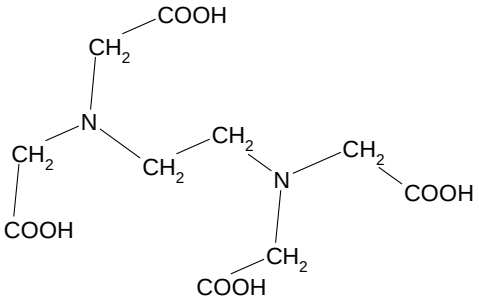
Human Health:

The chemical possesses properties indicating a hazard for human health (eye irritation, skin irritation after prolonged exposure). Although 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 based on its low hazard profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	60-00-4
Chemical Name	Edetic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

EDTA is a strong chelating agent and its toxicological profile is mainly based on this property. There are no oral toxicokinetic studies or skin absorption studies with EDTA itself or its tetrasodium salt available. According to the dissociation equilibrium of edetic acid administration of different sodium salts will result in dependence on the intestinal pH-value to the formation of various anionic species of EDTA. It can be assumed that the oral and dermal absorption of the free acid and of sodium salts of EDTA is comparable to the measured low absorption of $CaNa_2EDTA$. It is poorly absorbed from the gastrointestinal tract (a maximum of 5% was detected in the urine). Only 0.001% of $CaNa_2EDTA$ is absorbed after dermal application. After intake EDTA is not or scarcely metabolized and excreted as a chelated complex via urine following glomerular filtration and tubular secretion. In whatever salt EDTA is administered it is likely to chelate metal ions in vivo.

Animal data show that acute oral toxicity is low. In two tests on rats LD50 values of >2000 mg/kg were reported. No data are available for acute dermal toxicity. The data on acute inhalation toxicity are not valid to be used for hazard assessment. A 50% aqueous preparation of edetic acid resulted in a mild irritation of the skin after a 20 hour exposure time. Instillation of solid edetic acid to the rabbit eye resulted in strong but reversible irritant effects.

In a Magnusson Kligman Test with Na_2EDTA 30% of the guinea pigs showed a positive response after a first challenge and 10% after a second challenge. There are only two reports on single cases in humans demonstrating positive skin results. Based on the fact that EDTA is being used in industry and consumer products for many decades in high quantities the substance is considered as non-sensitising to humans. No adverse acute or chronic respiratory health effects from exposure to EDTA or Na_4EDTA have been observed in workers.

For systemic effects studies with administration of H_4EDTA or of its salts such as Na_2EDTA, Na_3EDTA and Na_4EDTA were considered as relevant information because these compounds are dissociated under physiological conditions (pH 7 - 9) into the sodium cations and the respective anionic species of edetic acid ($HEDTA^{3-}$) depending on the pH-dependent dissociation equilibria of edetic acid. Taken together, any conclusions on EDTA will be derived from consideration of the overall available data base. From repeated dose toxicity experiments (90 day feed male rats, 2 year bioassay both sexes rats and mice) a NOAEL of 500 mg/kg/d for Na_2EDTA and Na_3EDTA could be derived. Range finding studies with higher dose levels revealed diarrhoe, emanciation, loss of body weight and sometimes parakeratosis in oesophagus and forestomac as well as decreased hemoglobin and hematocrit levels.

Bacterial mutation tests are negative, but mutations and DNA damage were found in mouse lymphoma cells after exposure to very high concentrations. For somatic cells in mice (bone marrow cells) negative results with respect to the endpoints micronuclei, aneuploidy and sister chromatid exchanges were described. In germ line cells negative results were obtained for induction of structural chromosomal aberrations in spermatogonia, for induction of aneuploidy in primary and secondary spermatocytes, and also for induction of dominant lethals. A positive result was obtained in a micronucleus test with spermatids, indicating that aneugenic effects may be induced in specific phases of spermatogenesis (late spermacytoge-nesis). The effect was bound to the use of an extremely high dose in the LD_{50} range. Since the induction of aneuploidy is based on a threshold mode-of action, the potential for induction of aneuploidy will not be expressed at low doses. Altogether, EDTA and its sodium salts have a low mutagenic potential at extremely high doses. On the basis of the various negative findings and the assumption of a threshold mode-of action for aneugens, it can be concluded that EDTA and it sodium salts are no mutagens for man.

Epidemiological studies are not available for evaluation of the carcinogenic potential of EDTA. A diet study of Na_3EDTA for possible carcinogenicity was conducted in Fischer 344 rats and B6C3F1 mice. The studies on both species showed no treatment related tumors. Taking into account the negative results of the cell transformation assays and the low mutagenic potential expressed only at extremely high dose levels it can be concludet that there is no concern on carcinogenic properties of EDTA.

Concerning reproductive toxicity, valid data from human experience are not available. Data from animal studies with $CaNa_2EDTA$ did not give evidence for adverse effects on reproductive performance and outcome for doses of up to 250 mg/kg bw/day. Studies on developmental toxicity showed a specific fetotoxic and teratogenic potential of EDTA, Na_2EDTA and $CaNa_2EDTA$; a LOAEL of 1000 mg/kg bw was determined. Increased proportions/litter and significantly lower fetal body weights are indicative for an impaired fetal development. The pattern of malformations comprised cleft palate, severe brain deformities, eye defects, micro- or agnathia, syndactyly, clubbed legs and tail anomalies. These effects were exhibited in studies using maternally toxic dose levels. The mechanism resulting in developmental effects is found to occur via zinc depletion resulting in zinc deficit. These effects are independent of whether the acid or alkali- and/or calcium salts are applied.

Environment

H_4EDTA has a water solubility of 0.4 g/l at 20 °C. As no value for the vapour pressure is known, a Henry's law constant cannot be calculated from vapour pressure and water solubility. Because of the ionic properties of the substance, it has to be assumed that volatilization from aqueous solution will not occur. Mackay level I calculations for EDTA predicts that the hydrosphere is the preferred environmental compartment (99.999 %).

Due to the ionic structure under environmental relevant pH conditions, no adsorption onto the organic fraction of soils or sediments is expected.

EDTA is resistant to hydrolysis, neither strong acids nor alkalis cause any degradation. Investigations reveal that uncomplexed EDTA is not degradable by photolysis under environmental conditions. The half-life for photolytic degradation of Fe(III)EDTA in aqueous solution under environmental conditions was estimated to 20 days. Further abiotic degradation processes as reaction with OH-radicals or singlet oxygen have (compared to the direct photolysis) very low reaction constants and are of no environmental significance.

During photolysis of Fe(III)EDTA in surface waters as well as during biodegradation of other EDTA species in treatment plants and in the environment, reaction products are formed which cause further exposure of the environment. The reaction products ketopiperazinediacetate (KPDA) and ethylenediaminetriacetic acid (ED3A) were detected in German rivers and drinking water.

Different standard OECD tests show, that EDTA is neither readily nor inherently biodegradable. There are data suggesting that under alkaline conditions EDTA complexed with Ca-ions can be biodegraded which could be relevant for certain surface waters. However, in surface waters EDTA is preferably complexed with heavy metal ions and no biological degradation is expected for these complexes. Therefore, EDTA is regarded as not biodegradable in surface waters. Monitoring of EDTA concentration in influent and effluent of several industrial sewage treatment plants results in removal rates in the range of 30 to 95 % dependent on pH, retention time, EDTA concentration and

complexation stage.

Bioaccumulation studies with fish show that EDTA has no bioaccumulation potential.

It could be shown in short-term tests on fish, that EDTA and Na-EDTA are more toxic in an uncomplexed form. This can only occur if they are available in over-stoichiometric amounts to the chelants. Under these conditions the complexing agents can cause nutrient deficiency by reducing the essential concentration of different ions. The higher the water hardness the higher is the concentration of EDTA necessary to cause a toxic effect expressed as mortality. According to the results from different ecotoxicological studies, EDTA mainly influences the pathway of metal ions. The chelating properties of EDTA present a problem to the derivation of the PNEC, because it is difficult to distinguish between intrinsic properties and effects caused by nutrient depletion and other complexation properties under test conditions. In the available tests on acute toxicity, the EDTA concentration was too high to exclude substance-unspecific effects. Generally, tests in such a high concentration range are not considered to be valid, thus it is not likely to determine a PNEC with the available short-term test results. The effect assessment of EDTA is therefore based on long-term tests. For EDTA long-term studies with fish, daphnids and algae are available. The following results were found: Danio rerio: 35 d-NOEC > 26.8 mg/l ($CaNa_2EDTA$); Daphnia magna: 21d-NOEC = 22 mg/l; Scenedesmus subspicatus: 72h-EC10 = > 100 mg/l. With an assessment factor of 10 a PNEC of 2.2 mg/l was derived from the 21 d study with Daphnia magna.

Based on environmental behaviour properties, EDTA seems not to be of concern for sediment, atmosphere and terrestrial compartment and the food chain. No formal PNEC was established for these compartments because of lack of appropriate studies.

Exposure

EDTA is mainly produced and used as acid (H4EDTA) and as sodium salt (Na_4EDTA). In lower amounts, other salts or metal complexes are produced resp. used. The environmental exposure from the different uses of all EDTA species is overlapping. In the European Union, 53,900 t/a EDTA given as H4EDTA equivalents are produced.

EDTA is used as a complexing agent in many industrial branches, e.g. household detergents, industrial & institutional detergents, photochemicals, textiles, pulp and paper, metal plating, agriculture, cosmetics, water treatment and others.

Environmental releases occur during production and use. Because EDTA is a watersoluble compound, it is mainly emitted into the waste water. When H_4EDTA and Na_4EDTA are emitted during production, use etc., the same ionic species are formed in the environment, independent of the originally used compound (acid or a salt). Therefore, the emissions from both H_4EDTA and Na_4EDTA uses have to be added.

A lot of monitoring data are available for EDTA. In German municipal waste water treatment plant effluents EDTA concentrations in the typical range of 60 – 600 µg/l were measured. In 5 out of 55 sampled plants the concentration exceeded 600 µg/l.

During an extended monitoring program, EDTA was measured in German surface waters from 1993 to 1995. EDTA concentrations > 500 µg/l were measured (2/143), while most sampling sites gave values in the range of 6 – 60 µg/l (90/143) and 60 – 500 µg/l (30/143). In 1994, the concentrations were 4.1-17.6 (∅ 8.69) µg/l in the Rhine at Lobith and 3.5-11.4 (∅ 7.7) µg/l in the Ijsselmeer at Andijk. At Lobith, the average concentrations were 7.7 µg/l in 1995, 10.9 µg/l in 1996, and 7.0 µg/l in 1997. In the Lake Constance near Überlingen, the yearly averaged EDTA concentration was 4.8 µg/l in 1989. The value decreased to 2.5 µg/l in 1994. In Swiss rivers, the EDTA concentrations are generally below 20 µg/l. In the river Glatt, maximum concentrations of about 200 µg/l were measured.

In the river Odiel near Huelva (Spain) EDTA was measured at two sites. The first sampling point is near several industrial emission sources, the EDTA concentration was 2.46 mg/l. The second site near the river mouth is influenced by sea water, the EDTA concentration was 0.599 mg/l.

RECOMMENDATION

Environment: The chemical is a candidate for further work.

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

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment:

Although EDTA does not posses properties indicating a hazard for the environment, a risk assessment performed in the context of the EU Existing Substances Regulation identified a risk for the following scenarios based on very high releases of the substance:

- for the use of EDTA in industrial detergents by large sites within dairy and beverage industry where no effective waste water treatment is applied,
- for paper pulp mills where no effective waste water treatment is applied,
- for metal plating (circuit board production),
- for releases at waste disposal sites.

Therefore, the substance is a candidate for further work. Countries are invited to perform an exposure assessment to identify possible risks to the aquatic environment caused by the use of EDTA as complexing agent.

In the EU, a risk reduction strategy is currently under discussion.

Human Health:

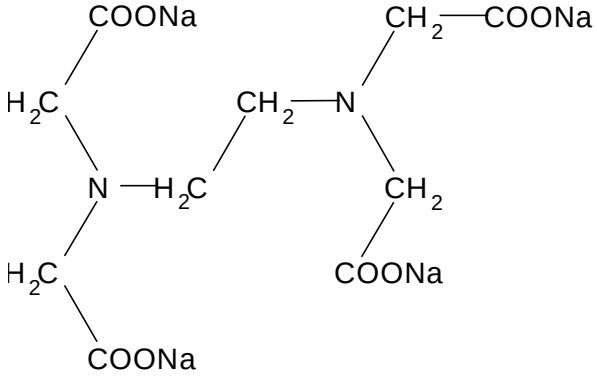
The chemical possesses properties indicating a hazard for human health (irritation, developmental toxicity). Despite of the wide disperse use of the substance the exposure of workers and consumers is low in regard to the doses producing adverse effects, and therefore the chemical is of low priority for further work.

This substance has been agreed in the European Union Risk Assessment Programme under Regulation EEC/793/93 with the following conclusion:

Consumers: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Workers: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	64-02-8
Chemical Name	Tetrasodium ethylenediaminetetraacetate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Na_4EDTA is a strong chelating agent and its toxicological profile is mainly based on this property. There are no oral toxicokinetic studies or skin absorption studies with Na_4EDTA or edetic acid available. According to the dissociation equilibrium of edetic acid administration of different sodium salts will result in dependence on the intestinal pH-value to the formation of various anionic species of EDTA. It can be assumed that the oral and dermal absorption of sodium salts of EDTA and of the free acid is comparable to the measured low absorption of $CaNa_2EDTA$. It is poorly absorbed from the gastrointestinal tract (a maximum of 5% was detected in the urine). Only 0.001% of $CaNa_2EDTA$ is absorbed after dermal application. After intake Na_4EDTA/EDTA is not or scarcely metabolized and excreted as a chelated complex via urine. In whatever salt EDTA is administered it is likely to chelate metal ions in vivo.

Animal data show that Na_4EDTA has a moderate acute oral toxicity. In three LD50 tests the acute oral toxicity for rats was found in the range of 1700 - 1913 mg/kg bw. For two other LD50 tests on rats values of > 2000 mg/kg bw are reported. In a test system similar to the inhalation hazard test there was no mortality in two tests. These data are considered sufficient for hazard assessment of acute inhalation toxicity. No data are available on acute dermal toxicity.

Treatment of the intact rabbit skin with an 80% aqueous preparation of Na_4EDTA resulted in mild or no irritation. However, treatment of the abraded skin with an 80% aqueous preparation resulted in superficial necrosis and crust formation after 8 days. According to current EU regulations, Na_4EDTA is not to be labelled for corrosivity. From the data obtained with eye tests a risk of serious damage can be deduced when the undiluted substance is instilled into the eye.

In a Magnusson Kligman Test with Na_2EDTA 30% of the guinea pigs showed a positive response after a first challenge and 10% after a second challenge. There are only two reports on single cases in humans demonstrating positive skin results. Based on the fact that EDTA is being used in industry and consumer products for many decades in high quantities the substance is considered as non-sensitising to humans.

For systemic effects studies with administration of H_4EDTA or of its salts such as Na_2EDTA, Na_3EDTA and Na_4EDTA were considered as relevant information because these compounds are dissociated under physiological

conditions (pH 7 - 9) into the sodium cations and the respective anionic species of edetic acid ($HEDTA^{3-}$) depending on the pH-dependent dissociation equilibria of edetic acid. Taken together, any conclusions on Na_4EDTA will be derived from consideration of the overall available data base. From repeated dose toxicity experiments (90 day feed male rats, 2 year bioassay both sexes rats and mice) a NOAEL of 500 mg/kg/d for Na_2EDTA and Na_3EDTA could be derived. Range finding studies with higher dose levels revealed diarrhoe, emanciation, loss of body weight and sometimes parakeratosis in oesophagus and forestomach as well as decreased hemoglobin and hematocrit levels.

Bacterial mutation tests are negative, but mutations and DNA damage were found in mouse lymphoma cells after exposure to very high concentrations. For somatic cells in mice (bone marrow cells) negative results with respect to the endpoints micronuclei, aneuploidy and sister chromatid exchanges were described. In germ line cells negative results were obtained for induction of structural chromosomal aberrations in spermatogonia, for induction of aneuploidy in primary and secondary spermatocytes, and also for induction of dominant lethals. A positive result was obtained in a micronucleus test with spermatids, indicating that aneugenic effects may be induced in specific phases of spermatogenesis (late spermacytoge-nesis). The effect was bound to the use of an extremely high dose in the LD_{50} range. Since the induction of aneuploidy is based on a threshold mode-of action, the potential for induction of aneuploidy will not be expressed at low doses. Altogether, EDTA and its sodium salts show a low mutagenic potential at extremely high doses. On the basis of the various negative findings and the assumption of a threshold mode-of action for aneugens, it can be concluded that EDTA and it sodium salts are no mutagens for man.

Epidemiological studies are not available for evaluation of the carcinogenic potential of Na_4EDTA. A diet study of Na_3EDTA for possible carcinogenicity was conducted in Fischer 344 rats and B6C3F1 mice. The studies on both species showed no treatment related tumors. Taking into account the negative results of the cell transformation assays and the low mutagenic potential expressed only at extremely high dose levels it can be concluded that there is no concern on carcinogenic properties of Na_4EDTA.

Concerning reproductive toxicity, valid data from human experience are not available. Data from animal studies with $CaNa_2EDTA$ did not give evidence for adverse effects on reproductive performance and outcome for doses of up to 250 mg/kg bw/day. Studies on developmental toxicity showed a specific fetotoxic and teratogenic potential of EDTA, Na_2EDTA and $CaNa_2EDTA$; a LOAEL of 1000 mg/kg bw was determined. Increased proportions/litter and significantly lower fetal body weights are indicative for an impaired fetal development. The pattern of malformations comprised cleft palate, severe brain deformities, eye defects, micro- or agnathia, syndactyly, clubbed legs and tail anomalies. These effects were exhibited in studies using maternally toxic dose levels. The mechanism resulting in developmental effects is found to occur via zinc depletion resulting in zinc deficit. These effects are independent of whether the acid or sodium or calcium salts are applied.

Environment

Na_4EDTA has a water solubility of 500 g/l at 20 °C. As no value for the vapour pressure is known, a Henry's law constant cannot be calculated from vapour pressure and water solubility. Because of the ionic properties of the substance, it has to be assumed that volatilization from aqueous solution will not occur. Mackay level I calculations for EDTA predicts that the hydrosphere is the preferred environmental compartment (99.999 %).

Due to the ionic structure under environmental relevant pH conditions, no adsorption onto the organic fraction of soils or sediments is expected.

EDTA is resistant to hydrolysis, neither strong acids nor alkalis cause any degradation. Investigations reveal that uncomplexed EDTA is not degradable by photolysis under environmental conditions. The half-life for photolytic degradation of Fe(III)EDTA in aqueous solution under environmental conditions was estimated to 20 days. Further abiotic degradation processes as reaction with OH-radicals or singlet oxygen have (compared to the direct photolysis) very low reaction constants and are of no environmental significance.

During photolysis of Fe(III)EDTA in surface waters as well as during biodegradation of other EDTA species in treatment plants and in the environment, reaction products are formed which cause further exposure of the environment. The reaction products ketopiperazinediacetate (KPDA) and ethylenediaminetriacetic acid (ED3A) were detected in German rivers and drinking water.

Different standard OECD tests show, that EDTA is neither readily nor inherently biodegradable. There are data suggesting that under alkaline conditions EDTA complexed with Ca-ions can be biodegraded which could be relevant for certain surface waters. However, in surface waters EDTA is preferably complexed with heavy metal ions and no biological degradation is expected for these complexes. Therefore, EDTA is regarded as not biodegradable in surface waters. Monitoring of EDTA concentration in influent and effluent of several industrial sewage treatment plants results in removal rates in the range of 30 to 95 % dependent on pH, retention time, EDTA concentration and complexation stage.

Bioaccumulation studies with fish show that EDTA has no bioaccumulation potential.

It could be shown in short-term tests on fish, that EDTA and Na-EDTA are more toxic in an uncomplexed form. This can only occur if they are available in over-stoichiometric amounts to the chelants. Under these conditions the complexing agents can cause nutrient deficiency by reducing the essential concentration of different ions. The higher the water hardness the higher is the concentration of EDTA necessary to cause a toxic effect expressed as mortality. According to the results from different ecotoxicological studies, EDTA mainly influences the pathway of metal ions. The chelating properties of EDTA present a problem to the derivation of the PNEC, because it is difficult to distinguish between intrinsic properties and effects caused by nutrient depletion and other complexation properties under test conditions. In the available tests on acute toxicity, the EDTA concentration was too high to exclude substance-unspecific effects. Generally, tests in such a high concentration range are not considered to be valid, thus it is not likely to determine a PNEC with the available short-term test results. The effect assessment of EDTA is therefore based on long-term tests. For EDTA long-term studies with fish, daphnids and algae are available. The following results were found: Danio rerio: 35 d-NOEC > 26.8 mg/l ($CaNa_2EDTA$); Daphnia magna: 21d-NOEC = 22 mg/l; Scenedesmus subspicatus: 72h-EC10 = > 100 mg/l. With an assessment factor of 10 a PNEC of 2.2 mg/l was derived from the 21 d study with Daphnia magna.

Based on environmental behaviour properties, EDTA seems not to be of concern for sediment, atmosphere and terrestrial compartment and the food chain. No formal PNEC was established for these compartments because of lack of appropriate studies.

Exposure

EDTA is mainly produced and used as acid (H_4EDTA) and as sodium salt (Na_4EDTA). In lower amounts, other salts or metal complexes are produced resp. used. The environmental exposure from the different uses of all EDTA species is overlapping. In the European Union, 53,900 t/a EDTA given as H_4EDTA equivalents are produced.

EDTA is used as a complexing agent in many industrial branches, e.g. household detergents, industrial & institutional detergents, photochemicals, textiles, pulp and paper, metal plating, agriculture, cosmetics, water treatment and others.

Environmental releases occur during production and use. Because EDTA is a watersoluble compound, it is mainly emitted into the waste water. When H_4EDTA and Na_4EDTA are emitted during production, use etc., the same ionic species are formed in the environment, independent of the originally used compound (acid or a salt). Therefore, the emissions from both H_4EDTA and Na_4EDTA uses have to be added.
A lot of monitoring data are available for EDTA. In German municipal waste water treatment plant effluents EDTA concentrations in the typical range of 60 – 600 µg/l were measured. In 5 out of 55 sampled plants the concentration exceeded 600 µg/l.

During an extended monitoring program, EDTA was measured in German surface waters from 1993 to 1995. EDTA concentrations > 500 µg/l were measured (2/143), while most sampling sites gave values in the range of 6 – 60 µg/l (90/143) and 60 – 500 µg/l (30/143). In 1994, the concentrations were 4.1-17.6 (∅ 8.69) µg/l in the Rhine at Lobith and 3.5-11.4 (∅ 7.7) µg/l in the Ijsselmeer at Andijk. At Lobith, the average concentrations were 7.7 µg/l in 1995, 10.9 µg/l in 1996, and 7.0 µg/l in 1997. In the Lake Constance near Überlingen, the yearly averaged EDTA concentration was 4.8 µg/l in 1989. The value decreased to 2.5 µg/l in 1994. In Swiss rivers, the EDTA concentrations are generally below 20 µg/l. In the river Glatt, maximum concentrations of about 200 µg/l were

measured.

In the river Odiel near Huelva (Spain) EDTA was measured at two sites. The first sampling point is near several industrial emission sources, the EDTA concentration was 2.46 mg/l. The second site near the river mouth is influenced by sea water, the EDTA concentration was 0.599 mg/l.

RECOMMENDATION

Environment: The chemical is a candidate for further work.

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

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment:

Although EDTA does not posses properties indicating a hazard for the environment, a risk assessment performed in the context of the EU Existing Substances Regulation identified a risk for the following scenarios based on very high releases of the substance:

- for the use of EDTA in industrial detergents by large sites within dairy and beverage industry where no effective waste water treatment is applied,
- for paper pulp mills where no effective waste water treatment is applied,
- for metal plating (circuit board production),
- for releases at waste disposal sites.

Therefore, the substance is a candidate for further work. Countries are invited to perform an exposure assessment to identify possible risks to the aquatic environment caused by the use of EDTA as complexing agent.
In the EU, a risk reduction strategy is currently under discussion.

Human Health:

The chemical possesses properties indicating a hazard for human health (irritation, developmental toxicity). Despite the wide disperse use of the substance, the exposure of workers and consumers is low in regard to the doses producing adverse effects, and therefore the chemical is of low priority for further work.

This substance has been agreed in the European Union Risk Assessment Programme under Regulation EEC/793/93 with the following conclusion:

Consumers: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

Workers: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-10-5
Chemical Name	Difluoromethane
Structural Formula	CH_2F_2

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Kinetic and metabolic studies in rats and mice indicate that during inhalation exposure difluoromethane is poorly absorbed (about 1%), eliminated mainly via exhalation as unchanged compound and as carbon dioxide, the major metabolite, the remaining being excreted in urine as formic acid presumably. The equilibrium in blood is reached after 2 hours of exposure.

Acute inhalation toxicity of difluoromethane is very low with no mortality in the rats after 4 hours exposure to 520,000 ppm (1,107 g/m^3). Signs of toxicity were essentially limited to a central nervous system depression at concentrations of 86,000 ppm (183 g/m^3) and above. There was no evidence of cardiac sensitization in dogs.

Repeated inhalation exposure studies have been conducted in rats exposed 6h/d, 5d/wk to difluoromethane for 4 and 13 weeks respectively at concentrations up to 50,000 ppm (1,050 g/m^3). In both studies, even at the highest concentration of 50,000 ppm, no target organ and no significant sign of any toxicity have been identified. The NOAEC was then determined at that level, about 1,050 g/m^3.

Difluoromethane has not shown any genotoxic activity both in *in vitro* and *in vivo* studies. Difluoromethane had no mutagenic effect *in vitro* in the Ames test, no clastogenic activity *in vitro* in two different mammalian cell assays. *In vivo*, difluoromethane was also negative in the mouse micronucleus assay.

In developmental toxicity studies, difluoromethane did not induce teratogenic or significant embryo-foetal toxic effects in rats and rabbits exposed up to 50,000 ppm during gestation days 7 to 16 and 6 to 18 respectively. Based on the results from the 13-wk repeated inhalation exposure study including macroscopic and histopathological examinations of the reproductive organs, the available evidence suggests that difluoromethane is unlikely to have the potential to affect fertility in rats up to 50,000 ppm. Thus, the NOAEC for fertility and developmental endpoints were both established at 50,000 ppm.

Environment

Difluoromethane is a colourless, odourless, flammable gas with a melting point of –136°C, a boiling point of –51.7°C, a vapour pressure of about 17000 hPa (25°C), a water solubility ranging from 1900 mg/l to 4400 mg/l at 20°C and 25°C respectively and a measured log Kow of 0.21 (25°C).
On the basis of its chemical properties, and according to the distribution modeling, when released to the environment the majority of difluoromethane will partition into the air compartment (99.99%). It will then degrade in the lower atmosphere by reaction with hydroxyl radicals to yield $C(=O)F_2$ as an intermediate product which will be further converted to HF and CO_2 by hydrolysis in atmospheric water. The calculated atmospheric lifetime of difluoromethane is 4.9 years corresponding to a 1/2-lifetime of 3.39 years.

Due to its structure without chlorine or bromine, difluoromethane is not expected to have an impact on the

stratospheric ozone layer (ODP = 0). Because of its low reactivity with OH, difluoromethane is not expected to contribute significantly to the formation of ground ozone (POCP = 0,2). Its Global warming potential is 650. Its contribution to the greenhouse effect can be considered as small (9 10^{-5} wm^{-2} from IPCC 2000 data).

In water, difluoromethane is not dissociated and not expected to hydrolyse owing to the lack of hydrolysable functional group in its chemical structure. It is not readily biodegradable under aerobic conditions (about 5 % of biodegradation after 28 days) and is not expected to sorb significantly to sediment based on a calculated logKoc of 1.37. Difluoromethane has a low potential to bioaccumulate in aquatic species based on a measured log Kow of 0.21. No experimental data are available on the effects of difluoromethane on organisms in the environment. Its toxicity to aquatic organisms has been estimated using QSAR method. Results from QSAR models (EPA ECOSAR and TGD) show a low acute toxicity to fish, daphnia and algae, the lowest calculated LC 50 being higher than 100 mg/l. A 16d NOEC to fish of 65.8 mg/l has been calculated using the US EPA ECOSAR program for neutral organics confirming the low toxicity of difluoromethane.

Exposure

The annual worldwide production capacity of difluoromethane is estimated to be approximately 15,000 tones.

Its main uses are in the fields of refrigeration and air conditioning. It is used as a substitute of HCFC 22 in blends with other hydrofluorocarbons in new stationary air conditioning systems (mainly small and medium size systems) and in new domestic and residential air conditioning system. A very minor use is as a refrigerant for industrial equipment (less than 2%).

Difluoromethane is manufactured in closed system. Therefore under normal manufacturing practices, emissions to the atmosphere during production are negligible. Emissions to the atmosphere mainly occur during the use of difluoromethane in stationary air conditioning systems of medium size (5 kW < power < 100 kW).

There are no aqueous streams from the production and the uses of the substance. Emissions to water are possible during handling and storage. No emission data are available but possible releases are considered to be negligible.

There is no direct consumer exposure to difluoromethane due to the fact that domestic air conditioning equipments (<5 kW) are hermetically sealed. Air conditioners of medium size are located in dedicated buildings and only maintained by professionals

RECOMMENDATION

The chemical is currently of low priority for further work.

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:

According to values estimated by QSAR models supported by available measured data on other fluorinated compounds of similar structure, the substance has a low hazard profile for the aquatic environment.
The substance predominantly partitions into the air compartment and has an important atmospheric half-life (3.4 years). Its intermediate atmospheric degradation product $C(=O)F_2$ has a lower half-life (48.5 days). No data on

toxicity for the air compartment is available for both substances. One of the final atmospheric degradation product, namely HF, has already been assessed at the OECD and the EU levels and is recommended for further work. Based on emission scenarios used by IPCC and according to the current uses of the substance, its atmospheric concentration is expected to be low. Therefore, the chemical is currently of low priority for further work.
In case of other uses of the substance in the future, e.g. use in automotive air conditioning, or higher exposure than expected, complementary investigation would be necessary, including toxicity of F32 and $C(=O)F_2$ to terrestrial plants, environmental fate and toxicity profile of $C(=O)F_2$ and contribution to the greenhouse effect of F32.

SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).[1]	770-35-4 (major isomer – Secondary Alcohol) 4169-04-4 (minor isomer – Primary Alcohol) 41593-38-8 (commercial mixed isomer product)
Chemical Name	Propylene Glycol Phenyl Ether (PPh)
Structural Formula	OH | CH_3-CH-CH-O-(C_6H_5) (major isomer) (O-C_6H_5) | CH_3-CH-CH_2- OH (minor isomer)

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Propylene glycol phenyl ether (PPh) is rapidly absorbed, distributed throughout the body, metabolized, and eliminated after oral administration. The major routes of elimination are via the urine and feces. The types of metabolites are parent ether conjugates, hydrolyzed propylene glycol, and hydrolyzed alcohol (phenol) conjugates.

Propylene glycol phenyl ether exhibits low acute toxicity by the oral, and inhalation routes. The oral LD50 in rats exceeds 2000 mg/kg (1 death from 10 subjects occurred at this highest dose tested); and the 4-hour inhalation LC50 in rats was greater than 5400 mg/m^3 (no deaths). PPh was severely irritating to the eyes but non-irritating to skin in rabbits tested and evaluated according to the Draize criteria. PPh did not cause skin sensitization when tested with guinea pigs by the Buehler method.

In repeated dose-studies ranging in duration from 4 to 26 weeks, few adverse effects were found even at high exposure levels and effects that did occur were mild in nature. In one study, PPh was administered to two generations of rats (25/sex/group) in drinking water for 26 weeks at concentrations of 0, 100, 1000, or 5000 ppm (equivalent to doses of 0, 11.3, 113, or 478 mg/kg-d) (this was a 2-generation reproductive toxicity study also discussed below). Effects were seen only at the highest exposure concentration that manifested as reduced body weights and corresponding reduced food and water consumption. No clinical signs were evident during the course of exposure and no gross or histopathological lesions were seen at autopsy. The NOAEL for this drinking water study with rats was 1000 ppm (113 mg/kg-d) and the LOAEL was 5000 ppm (478 mg/kg-day), based on body weight changes. In another repeated dose test, this time by the dermal route of exposure, rabbits (5/sex/group) received daily applications of PPh 5 days/week for four weeks (19 total applications). A slight increase in platelet counts was found that reached statistical significance in males at the high dose level. Platelet counts in females were unaltered at any dose level. No other parameters were affected other than a local thickening of the skin at the site of application. The increased platelet count in males was considered spurious since no other hematological or clinical chemistry (or any other) parameters corroborated this finding. Thus, the systemic toxicity NOAEL for PPh by the dermal route of exposure in rabbits was the highest dose tested of 1000 mg/kg-day.

In the two-generation reproductive toxicity study discussed above (rats 25 pairs/generation) treated orally with 0, 100, 1000, or 5000 ppm PPh in drinking water, no adverse effects were found on fertility, reproductive performance, or on reproductive tissues in parental generations. In offspring, reduced pup weights as well as decreased relative spleen

weights and increased relative brain weights and retarded sexual maturation were found at the high dose (but with no effect on reproductive parameters in the F1 generation once they reached sexual maturity). In a developmental toxicity study, PPh was administered daily by gavage to pregnant rabbits (15 per group) over the period of organogenesis at doses of 0, 60, 180, or 540 mg/kg-day. In the dams, the high dose of PPh caused decreased food consumption, decreased body weights, and prostration. No maternal toxicity was seen at the lower dose levels. .In fetuses, a statistical increase in the rate of total soft tissue variations was detected (septal heart defect) in the medium and high dose groups. It is possible that this may be considered coincidental because of the low incidence (1 fetus in each group), the common spontaneous occurrence of the variation in this strain of rabbit, and because statistical significance was conferred only due to the unusually low level in the concurrent control group (2.2% fetal incidence and 7.1% litter incidence versus 7.7% and 30.2%, respectively, in the laboratory historical controls). With regard to skeletal variations (predominantly an increase in 13^{th} ribs when combined with other skeletal variations), a statistical increase was detected in the high dose group. This increase in skeletal variations was considered treatment related because the incidence (approximately 10%) exceeded historical control levels. The NOAEL for maternal toxicity was 180 mg/kg-day and the LOAEL was 540 mg/kg-day, based on reduced body weight and clinical signs. The NOAEL for fetal toxicity was 180 mg/kg-day and the LOAEL was 540 mg/kg-day based on the increased incidence of 13^{th} rib buds. PPh exhibits toxicity in the developing rabbit conceptus at high doses that produce toxicity in the dam.

PPh tested negative in the Ames Salmonella assay and also was negative in an *in vitro* chromosome aberration study with human lymphocytes. In an *in vivo* mouse bone marrow micronucleus test, mice received two consecutive daily doses of 0, 500, 1000, or 2000 mg/kg-day. The high dose animals had a slightly increased incidence of micronuclei that reached statistical significance in a first assay but did not in a second (although a trend was evident). The study authors attributed this finding to hypothermia, which occurred only in the high dose animals and which has been shown with other chemicals to cause increased micronuclei as a secondary effect from hypothermia. It seems reasonable to conclude that the negative *in vitro* results and the equivocal *in vivo* results at a very high dose level that may be due to physiological stress indicate that propylene glycol phenyl ether does not pose a genotoxicity hazard at doses that would likely be encountered in the environment. PPh has not been tested for carcinogenicity.

Environment

The melting point of PPh is 11.4 ºC and the boiling point is 253 ºC. Vapor pressure is 0.029 hPa at 25 ºC and the log octanol-water partition coefficient is 1.5. Finally, water solubility is 10,000 mg/L.

If released into the environment, PPh will distribute primarily to water and soil. The log octanol-water partition coefficient (log K_{ow}) for PPh is 1.50 and the BCF is 0.776 (log BCF = -0.110). Both parameters indicate that PPh will not tend to bioaccumulate up food chains. The Henry's Law Constant, which indicates propensity to partition from water to air, is low for PPh: 4.36×10^{-7} atm-m^3/mole. Fugacity modeling (Mackay Level III) indicates that PPh is likely to partition roughly equally and predominantly into the soil and water with small to negligible amounts distributing to other environmental compartments (air, sediment, and aquatic biota).

PPh is unlikely to persist in the environment. Once in air, the half-life of PPh due to direct reactions with photochemically generated hydroxyl radicals is estimated to be 3.45 hours. In water, PPh is readily biodegraded under aerobic conditions. In a biodegradation study that measured oxygen depletion, CO_2 production, and organic carbon disappearance (OECD 301F), PPh was "readily biodegradable" by all criteria. In soil, biodegradation also is rapid. When incubated with three soil types for 25 days, PPh degraded rapidly under aerobic conditions and very little under anaerobic conditions. Under aerobic conditions, time to 50% removal usually ranged from 1 to 7 days.

Acute aquatic testing indicates a low order of toxicity for PPh. The acute aquatic toxicity in the Golden Orfe with the 96-hour LC50 was between 215 and 464 mg/L; in the Fathead minnow, the 96-hour LC50 was 280 mg/L (263 mg/L < 95%CL > 297 mg/L). The 48-hour LC50 in daphnia was 370 mg/L (321 mg/L < 95%CL > 431 mg/L). In algae, the 72-hr EC50 was 74.5 mg/L (biomass) and > 100 mg/L (growth rate).

Exposure

In 1999, approximately 16 million pounds (7.3 thousand tonnes) of propylene glycol phenyl ether was produced worldwide and this is projected to increase to 18 million pounds (8.2 thousand tonnes) in 2004. Modern production

methods result in major isomer content in excess of 85% and minor isomer content less than 15%.

A major use of PPh is as a solvent that facilitates the mixing of aqueous and organic constituents in paints, coatings, and films. PPh is used as a latex coalescent in water-based architectural and industrial coatings and adhesives, a carrier solvent for textile dyes, a solvent for inks in ball point and felt tip pens, stamp pads, and textile printing pastes, and paint remover. Due to its antibacterial properties, PPh also is used in cosmetics and soaps.

During manufacture and transport, occupational exposure potential is low due to the enclosed systems employed. For either occupational or consumer exposure, the most significant likelihood of exposure is by dermal contact or inhalation during application of paints and coatings, or application of materials for which PPh is a solvent or carrier. No occupational or other exposure limits have been established for PPh.

Individuals applying paint or other PPh-containing coatings may be exposed to this propylene glycol ether. Dermal contact through minor spills or usage contact is a source of exposure, as is inhalation from aerosol or vapor generated during application or usage.

Propylene glycol phenyl ether typically enters the environment through slow escape and evaporation from the solvent or coating system used. Spills of such products can also occur during application of coatings. Emissions to the atmosphere or surface water occurring via industrial wastes or effluents during manufacture or processing are limited by predominately enclosed processing and low volatility.

General population exposure also is possible through inhalation of ambient air containing low concentrations of PPh that may be released from industrial processes or through evaporation of coatings or other products containing it.

RECOMMENDATION

Environment: This chemical is currently of low priority for further work.

Human Health: This chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

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

Human Health:
The chemical possesses properties indicating a hazard for human health (eye irritation – which is reversible - and developmental toxicity at high doses associated with maternal toxicity). Based on data presented by the Sponsor country, exposure is controlled in the occupational setting. Due the wide dispersive use, member countries are invited to perform an exposure assessment and if then indicated, a risk assessment, especially for consumers. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Note: PPh may be evaluated further under the EU Biocides Directive. This will include exposure assessment on operators (occupational) and by-standers (consumers).

[1]Note: the commercial product is commonly referred to as CAS# 770-35-4. CAS# 41593-38-8, which is uncommon, also can refer to the commercial mixed isomer product. However, CAS# 41593-38-8 is rarely used, especially in Europe because it is not listed on EINECS. The commercial product is listed under both CAS #s because modern production methods result in the major isomer content being in excess of 85% and the minor isomer content less than 15%. The major isomer is thermodynamically favored during synthesis and consists of a secondary alcohol configuration.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7778-54-3
Chemical Name	Calcium hypochlorite
Structural Formula	$Ca(OCl)_2$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Calcium hypochlorite is a white or grayish-white powder. This substance is dissociated into calcium ion (Ca^{++}) and hypochlorite ion (ClO^-) in water. Human health effect may be caused by contact with the solid powder, the aqueous solution, or accidentally generated chlorine gas. The calcium ion can generate a strong alkaline condition at the application site. Concerning hypochlorite ion toxicity, the exposure scenarios to calcium hypochlorite are common to sodium hypochlorite (liquid) or chlorine gas which is utilized as a source of hypochlorite ions, and they are thoroughly assessed in competent/pertinent international risk assessment programmes of organizations like WHO or the EU. Substantial parts of the description on hypochlorite-ion-related effects are common to those in the assessment documents for chlorine (CAS No 7782-50-5) which is also assessed in the OECD HPV Chemicals Programme.

Most of the data for toxicity of this substance by the oral route are from studies performed with sodium hypochlorite or chlorine gas. In biological systems, characterized by pH values in the range of 6-8, the most abundant active chemical species is HOCl, in equilibrium with ClO^-. Such available chlorine is readily absorbed via the oral route and distributed into plasma, bone marrow, testis, skin, kidney and lung. Only ca. 50% is excreted mainly with the urine followed by excretion with feces. HOCl is not enzymatically metabolized.

The acute oral LD_{50} of calcium hypochlorite was 790 mg/kg in male rats. Inhalation exposures to concentrations of greater than about 500 ppm (10 min or more) may be fatal for rats. Based on human experience and control studies in volunteers, it can be concluded that the acute NOAEL for humans was considered to be 0.5 ppm (1.5 mg/m^3). In a 13-week study, male and female F-344 rats (10/sex/group) received NaClO in drinking water at level of 0.025, 0.05, 0.1, 0.2, or 0.4 %. A weight gain was significantly decreased in male rats at 0.2 and 0.4 % and in females at 0.4 %. These effects were dose related and obviously correlated with reduced water consumption. No histopathological changes attributable to the treatment were found. But an increase of AAT in the blood gave evidence of the adverse effects on the liver. Based on significant body-weight reduction at the top dose, a subchronic NOAEL of 59.5 mg/kg bw/day as free available chlorine (FAC*) (at 0.1% NaClO level in the drinking water) can be calculated for male rats. For female rats a subchronic NOAEL of 215.7 mg/kg bw/day as FAC (at 0.2 % NaClO level in the drinking water) can be calculated. A NOAEL of 950 ppm available chlorine (59.5 mg/kg bw/day) can be derived from a 13-week rat study with sodium hypochlorite in drinking water.
In a life-time guideline NTP-study, 70 male and female F344 rats and B6C3F1 mice were administered chlorine via drinking water at dose levels of 0, 70, 140 and 275 mg (equivalent to FAC)/L in buffered water. These concentrations were equivalent to 0, 4.8, 7.5 and 13.9 mg/kg bw/day for male rats and 0, 3.8, 6.9 and 13.2 mg/kg bw/day for female rats. Mean body weights of male and female rats were similar among treated and control groups at both 14-week and 66-week interim evaluations. Those of male mice were significantly lower at week 66. Dose-related decrease in water consumption was observed throughout the study in both species and sexes. Food consumption was comparable among chlorine-treated and control groups. There were no clinical findings, alterations in haematological parameters and biologically significant differences in relative organ weights attributable to the treatment at 14/15-week and 66-week interim evaluations. Survival rate in chlorine-treated groups of rats and mice were similar to those of the controls after two groups. There was no evidence for non-neoplastic lesions to be associated with the consumption of

chlorinated drinking water [NTP, 1992]. Based on these findings, a NOAEL (chronic) can be calculated to be approximately 14 mg available chlorine /kg bw/day for rats and 22.5 mg available chlorine /kg bw/day for mice.

Calcium hypochlorite is reported to be corrosive to the skin and has severe effects that can be expected from exposure to the eyes, which is ascribable to the alkalinity of calcium cation (pH=12.0 at 1 % FAC*). Moderate to severe lesions in the respiratory tract were reported after exposure to chlorine that may emerge in case of accidental misuse of hypochlorite salts. Exposure to chlorine at 9 ppm (27 mg/m^3) for 6 h/day during 1, 3 and 5 days was reported to cause epithelial necrosis, cellular exfoliation, erosion, ulceration and squamous metaplasia in the nasal passage of rats and mice. For either of Ca or Na salt, reliable skin sensitization studies are not available and case reports are available but no reliable case report could be found showing a sensitization potential in humans.

There are data from *in vitro* studies to suggest that solutions of chlorine/hypochlorite have some mutagenic potential, but it can be concluded that they are not mutagenic *in vivo*.

No carcinogenicity was observed in mice or rats exposed by inhalation to chlorine and orally to sodium hypochlorite, except some equivocal results were reported for female rats by oral route. For human carcinogenicity, no causal relationship between hypochlorite exposure and tumor incidence was observed. The observation is applicable to calcium hypochlorite.

No reproductive toxic effects were shown up to 5 mg/kg (highest dose tested) of sodium salt (equivalent to 4.8 mg/kg of Calcium salt) in a one generation oral study in rats. No evidence of adverse developmental effects were reported in animals. Moreover, epidemiological studies in humans did not show any evidence of toxic effects on reproduction and development.

{*Hypochlorite ion is predominant at alkaline pH values, while Cl_2 is mainly present at pH below 4. Therefore the concentration of chlorine in an aqueous solution is generally expressed as free available chlorine (FAC) which is the sum of Cl_2 + HOCl + ClO^-, regardless whether these species stem from dissolved gaseous chlorine or from dissolved sodium/calcium hypochlorite.}

Environment

Calcium hypochlorite is a white or grayish-white powder with chlorine like odor at ambient temperatures and pressures. Density is 2.35 g/cm^3 and vapour pressure is not applicable. This substance is a strong oxidizer. It is highly soluble in water (214 g/L). The anion of this substance dissolved in water is brought to equilibrium between active chlorine species like chlorine (Cl_2), hypochloric acid (HOCl) or hypochlorite ClO^-. The relative amounts of the components are dependent on ionic strength and pH. At the pH in the natural environment (6-8), HOCl or ClO^- is dominating (HClO: pKa = 7.53). A diluted aqueous solution of HOCl will decompose very slowly in the dark, but more rapidly in the presence of light, particularly rapidly in full sun light, by producing hydrogen chloride and oxygen. Some chlorine and chloric acid ($HClO_3$) may also develop. The physico-chemical properties indicate that chlorine released into the environment as HClO or Cl_2 is distributed into water and air. Consequently, the effects that may manifest in the natural environment are considered common to those assessed for the other source of hypochlorite.

In the natural water, in the presence of organic or inorganic compounds, the free available chlorine immediately reacts forming various chlorinated and/or oxidized by-products e.g. chloramines or chloromethanes. They are mainly distributed to the hydrosphere, but are also able to transfer to some extent to the atmosphere depending on their intrinsic properties. A potential for bioaccumulation or bioconcentration of active chlorine species can be disregarded, because of their water solubility and their high reactivity.
Valid freshwater short-term toxicity data are available only for invertebrates: the LC50 for *Ceriodaphnia dubia* is 5 µg FAC/l (FAC=Free available chlorine). Adequate standard acute tests in fish are not available, but from many reliable studies performed under intermittent exposure conditions a 96h LC50 of 60 µg TRC/L and a 168h LC50 of 330 µg TRC/L can be derived (TRC = total residual chlorine = the sum of combined and free residual available chlorine). Due to the intermittent regime (three 45 minutes pulses per day) a 96h LC50 << 60 µg TRC/l can be expected for fish in a standard test. Most lowest result for algae is reported for *Thalassiosira pseudonana* with a IC_{50} of 75 µg/L (20°C).

Regarding long-term toxicity to freshwater organisms, the lowest NOEC was 5 µg/L (*Ictalurus punctatus*, 133d, growth). In microcosm and field studies the most sensitive parameter was the density of zooplankton with a NOEC of 1.5 µg TRC/L, and zooplankton is more sensitive to chlorine than algae.
For salt water, valid short-term toxicity data are available for mollusks and for fish (*Oncorhynchus kisutch* 96 h LC50 = 32 µg TRO/L) (TRO = Total Residual Oxidant) showing comparable sensitivity. For long term toxicity the molluscs are more sensitive than fish showing a 15d NOEC of 6.2 µg TRO/L. It is impossible to delineate representative toxicity indicator figures because of the unique feature of the chemical to be tested in standard methods. However, the accumulated scientific information covering a wide range of species, temperature, application regime or field studies can be used for the hazard assessment.

Exposure

Calcium hypochlorite is a basic chemical, and used as algicide, bactericide, deodorant, disinfectant, fungicide, oxidizing agent, bleaching agent and so on. Chlorine (gas) or sodium hypochlorite (liquid) is used in far higher amounts for the same purpose. The production volume of calcium hypochlorite was estimated to be 16,940 tonnes/year in Japan in 2001, and the total nameplate capacity worldwide including the PRC was approximately 230,000 t/year in 2002.

Exposure to this substance can occur through accidental events in industry (e.g. during filling operations of chlorine gas, using procedure as bleaching agents), during transport and storage, during professional water purification and disinfection measures for swimming-pools.
There is no available official recommendation and regulation for an occupational exposure limit. However, there are some recommendations and regulations for chlorine. This product is a solid and direct contact to the powder can be irritating or corrosive. The product is therefore usually pelletted with water to avoid dust generation and to control exposure during handling or transportation.

For consumers exposure to chlorine gas can occur through accidental events during the use of this chemical for disinfection of swimming-pools and the use of hypochlorite-containing cleaning products. For example, mixing of household cleaning agents, hypochlorite and acids eventually causes chlorine release and inhalation.

RECOMMENDATION

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

Environment: The chemical is a candidate for further work

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

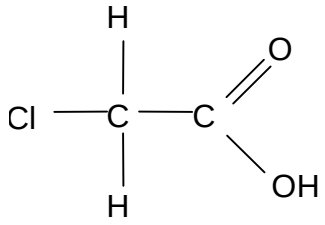
The chemical possesses properties (corrosive effects and acute respiratory toxicity) indicating a hazard for human health. Although there are some open uses, consumer exposure is sufficiently regulated under the drinking and other water acts and occupational exposure is adequately controlled in the Sponsor country to ensure safe handling, 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 substance has hazardous properties for the environments. As there are some open uses of the substance an exposure assessment and if necessary risk assessment should be performed for these uses. The formation of

chlorinated by products should be taken into account. Work to that effect is being or has been performed for sodium hypochlorite in many countries and also within the framework of the EU existing substance regulation. The action that may be taken should be common to that for sodium hypochlorite.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-11-8
Chemical Name	2-Chloro-ethanoic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The SIAR contains information on MCAA and SMCA, monocloroacetic acid and its sodium salt. For SMCA a SIAR already exists. Therefore, the present SIAP is only based on MCAA.

Human Health

Most of the studies on the toxicokinetics, metabolism, and distribution of MCAA are very briefly reported and were performed with relatively high doses. After oral exposure of rats and mice the absorption from the gastro-intestinal tract amounted to 90% and 60%, respectively. Based on the high toxicity in one inhalation study and the low molecular weight, inhalation absorption of 100% is indicated, in this limited study. Toxicity data also indicate a high and rapid absorption via the skin of rats, rabbits and humans (100%). The major metabolic pathway of MCAA is an initial formation of S-carboxymethyl glutathione, which is converted to S-carboxymethylcysteine, part of which is further metabolized to thiodiacetic acid. The other route involves hydrolysis of the carbon-chlorine bond resulting in the formation of glycolic acid, which is mainly oxidized to carbon dioxide. MCAA can inhibit different enzymes: acetate oxidation, aconitase, pyruvate carboxylase, pyruvate-dehydrogenase, a-ketoglutarate dehydrogenase and glutathione S-transferase (GST).

The acute toxicity (LD_{50}) of MCAA was between 55 and 277.5 mg/kg bw in rats after oral exposure and circa 300 mg/kg bw after oral exposure in mice. After dermal exposure to MCAA in 0.9% NaCl the LD50 for rabbits was around 250 mg/kg bw and is clearly concentration dependent. The LC_{50} after 1- and 4-hour inhalation exposure of rats was >259 and 180 mg/m^3, respectively. MCAA induced acute neurotoxic effects after exposure by different routes. Also human data indicate a high acute toxicity of MCAA.
MCAA is corrosive to the skin and eyes. Respiratory irritation was observed at 23.7 mg/m^3 in a limited study with rats. The threshold for respiratory (sensory) irritation in humans was reported to be 5.7 mg/m^3. Based on wide practical experience with MCAA in the absence of any case reports on allergy, it is concluded that no indications for sensitizing effects exist.

No suitable dermal and inhalation repeated-dose toxicity studies are available. Oral repeated-dose toxicity studies with 16-day, 13-week, and chronic exposure to MCAA were available. Within the limited study design of the 16-day toxicity studies (by gavage), the NOAEL in rats was 7.5 mg/kg bw/day, and in mice 60 mg/kg bw/day, both based on lacrimation. A NOAEL could not be derived from the results of a 13-week repeated-dose toxicity study with rats (by

gavage). Changes in the weight of the heart, liver, kidneys, and clinical chemistry values were observed at the lowest dose level tested, i.e., 30 mg/kg bw/day. An increased liver weight and decreased activity of serum cholinesterase were observed in mice exposed during 13-weeks by gavage. The NOAEL for mice was 100 mg/kg bw/day. Main target organs of MCAA after prolonged oral administration are liver in both rats and mice, and heart and kidneys in rats. In the chronic toxicity studies, effects on the nasal mucosa, growth depression, and decreased survival became more apparent. The effects on the heart disappeared at lower dose levels in repeated-dose toxicity studies with longer study duration. Based on the data available, rats appeared to be more sensitive for the toxic effects of MCAA than mice. A NOAEL of 3.5 mg/kg bw/day was derived from a 2-year drinking water carcinogenicity study in rats. At this level, no effect on survival, body weight, liver, kidneys, or (non-)neoplastic lesions was found.

MCAA does not induce point mutations or primary DNA damage in bacteria, or chromosome aberrations or DNA strand breaks in mammalian cells in *vitro*. MCAA gave positive results in several TK+/TK- assays with mammalian cells *in vitro*. *In vivo* MCAA did not induce DNA strand breaks in spleen, liver, stomach or duodenum of mice or in liver of rats.

No evidence of carcinogenic activity of MCAA was found in rats and mice after oral administration in drinking water or by gavage. A NOAEL of 3.5 mg/kg bw/day was derived from the 2-year drinking water study in rats (see above for systemic effects). At this level, no (non-)neoplastic lesions were found. Besides, no evidence for carcinogenic activity after repeated dermal exposure (during 580 days) was found in female mice. Carcinogenicity studies by inhalation exposure were not available.

A reproductive toxicity study with MCAA was not available. However, in the oral (sub)chronic repeated-dose toxicity studies with rats and mice, no effects were found on the male and female reproductive organs. With respect to developmental toxicity, in a study, aimed at the investigation of fetal cardiac teratogenicity, in rats exposed to 193 mg/kg bw/day the only effect observed was a decrease in maternal average weight gain during pregnancy. No developmental toxicity was observed in this study. Developmental toxicity of MCAA is indicated based on a limited reported developmental test with rats, on a Hydra regeneration assay, and a whole CD-1 mouse embryo culture test. Indications for effects on the heart of the embryo were found.

Environment

MCAA is a solid with a melting point of about 62 ºC. The solubilities of MCAA and the sodium salt (SMCA) in water are reported as 4210 and 820 g/l at 20 °C, respectively. The vapor pressure for MCAA is 8.7 Pa at 25 °C. The partition coefficient log P_{OW} was measured and calculated as ≤ 0.2. The acid-base constant (pKa) is 2.85 at 25 °C.

MCAA will be completely ionized at environmentally relevant pHs. MCAA hydrolyses very slowly. Direct photolysis of MCAA in air and water is not expected, because it does not absorb UV radiation above 290 nm. The photo-oxidation rate of MCAA with OH-radicals was estimated with a QSAR (DT50 of 58 days). The direct photolysis competes with the dissolution of MCAA in the atmosphere and further with wet deposition. The wet deposition of MCAA was estimated to take about 10 days. Dry deposition of MCAA from air can also take place. MCAA is readily degradable. Bioaccumulation is not expected to occur in view of the low log Kow and ionizing properties. A Henry's Law constant of $1.9*10^{-4}$ $Pa.m^3/mol$ at 20 ºC can be calculated for MCAA. The calculated Henry's Law constants indicate that volatilization of MCAA from surface water will not occur at significant levels. With regard to the adsorption of MCAA in a soil-water system, organic-water partition coefficients (Koc) of 4 and 3.16 have been calculated using the QSAR for organic acids and non-hydrophobics, respectively. Adsorption to soil is thus not expected to occur.

The available short-term EC50-values and long-term NOEC-values for daphnia and fish in neutralized medium range between 10-1000 mg/l. The short- and long-term results for algae are all < 1 mg/l, except for one EC50-value. The lowest long-term test result is the NOEC of 5.8 µg/l for *Selenastrum subspicatus*. Two NOECs for additional algae species support the lowest obtained NOEC value of 5.8 µg/l. A number of short-term toxicity studies for MCAA with bacteria and protozoa are available. The lowest observed IC50 was 16 mg/l for protozoa. A seedling emergence/growth test with three plant species resulted in a 21 day NOEC of 3.2 mg/kg dwt. A time average NOEC of 0.6 mg/kg dwt (assuming a first order rate degradation during the 21 day experiment) can be estimated based on the neutral soil DT50 value of 66 hours.

Exposure

In the European Union MCAA is produced by three companies at five different locations. Two companies have two production locations each. The total EU production volume of MCAA for 1999 was 145,000 tonnes per annum. According to industry there was no import from outside the EU in 1999. The estimated total export was about 25,000 tonnes per annum. The use volume, i.e. production and import minus export, within the EU was therefore about 120,000 tonnes per annum. Three production companies convert MCAA into the salt SMCA. MCAA is mainly used as a chemical intermediate for the synthesis of other products. Major applications of MCAA are related to the production of: carboxymethylcellulose (CMC), carboxymethyl starch, crop protection chemicals (like 2,4-D and MCPA), plastics, thioglycol acid (TGA), sodium salt of MCAA and other products such as esters and amides. SMCA is mainly used as a chemical intermediate for the production of: amphoteric surfactants (e.g. shampoos and industrial cleaning agents), pigments, dyes (indigo), printing inks, paints, lacquers and varnishes, pharmaceuticals (caffeine, vitamin B6) and CMC.

A number of minor applications of MCAA occur as well: constituent in acidic paint remover or graffiti remover, can coating for food (i.e. as modifier for resins), escharotic agent, wart remover, anti-microbial additive for food and analytical reagent.

MCAA may be released by industry into the environment during its production and processing as intermediate. The emission of MCAA will occur via air and water. However, in view of the low vapor pressure and high water solubility, MCAA is expected to end up mainly in the water compartment. MCAA may also be released by unintentional sources. For instance, MCAA can be formed (indirectly) in the atmosphere from industrial chlorinated chemicals. Besides anthropogenic sources, MCAA is also expected to be formed *de novo* in the environment.

Occupational exposure may occur in industries where MCAA is produced or is used as a raw material or as an intermediate. Routes of exposure are by inhalation and by accidental dermal contact. The presence of MCAA in consumer products was unknown in Denmark (Product Register, June 1997) but known in the US (Product Register, October 1997). MCAA was not available in the inventory of ingredients used in cosmetic products (EC, 1996). Industry does not support applications of MCAA which are not related to the use as intermediate. However, some consumer use has been identified, but this use can be considered mostly as negligible. Possible consumer exposure: MCAA was used as an anti-microbiological additive in food and as a wart remover, use of MCAA as a paint stripper or graffiti remover, and in can coatings for aqueous foodstuffs. The use of antifoliant has been discontinued.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

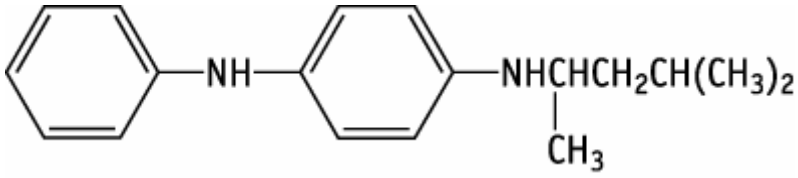
The chemical is a candidate for further work. Hazardous properties have been identified for this substance (acute neurotoxic effects, corrosive to skin and eyes, indications for effects on the heart of the embryo). In an assessment performed in the European Union in the context of the EU Existing Substances Regulation (793/93/EEC), occupational exposure and risks were identified for some scenarios. Other OECD countries may wish to perform an exposure assessment for humans and if necessary a risk assessment.

Note: In the EU the request for a developmental toxicity study depends on the risk reduction strategy. It is noted that effects were observed in developmental toxicity studies at high concentrations/dose levels. This effect at high dose levels and considering that risk reduction measures for corrosivity need to be taken in the EU, it is expected that the exposure will sufficiently be limited. Therefore, developmental toxicity will not lead to a risk for this endpoint.

Environment:

The chemical is a candidate for further work. Hazardous properties have been identified for this substance (aquatic toxicity). In an assessment performed in the European Union in the context of the EU Existing Substances Regulation (793/93/EEC) it was shown that the local PECs in surface water exceed the PNEC for MCAA at two production/processing sites. In one case the conclusion is based on monitoring data. For the other site the PEC/PNEC is >1 for the STP as well. For both sites industry has indicated that the efficiency of the local WWTP will be improved, but up to now no data are available to verify this statement. Other OECD countries may wish to perform an exposure assessment for the environment and if necessary a risk assessment. In addition in an assessment performed in the European Union in the context of the EU Existing Substances Regulation, substantial MCAA levels reported in the literature in various environmental compartments, wet deposition, surface water and soil. These regional/continental background concentrations exceed the corresponding PNEC in some cases, especially in soil. Further research is needed to investigate, quantitatively, the origin of these MCAA levels (natural versus anthropogenic).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	793-24-8
Chemical Name	N-(1,3-Dimethylbutyl)-N´-phenyl-1,4-phenylendiamine (6PPD)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No experimental data are available regarding the toxicokinetic behaviour and metabolism of 6PPD. The appearance of systemic toxicity after oral and dermal exposure shows the principal bioavailabilty of 6PPD via these routes.

The acute toxicity of 6PPD is moderate after oral administration and low after dermal application. The oral LD_{50} values in rats were 893 mg/kg bw for females and 1005 mg/kg bw for males. Signs of intoxication were hypoactivity, diarrhea, bradypnea, hypothermia and a prone position accompanied by pathological lesions in digestive organs and respiratory system. The dermal LD_{50} in rabbits was > 3000 mg/kg bw. Signs of intoxication were reduced food consumption, hypoactivity and lethargy.

The skin irritating potential of 6PPD is low. 6PPD is slightly irritating to the eye. The substance was found to induce dermal sensitization in experimental animals and humans. Positive patch-test results in humans partly may be related to para-group cross-sensitization.

The main targets identified after repeated oral intake of 6PPD by rats are the liver (increase of weight, fatty and vacuolar degeneration) and the blood cells (anemia, lymphocytopenia, and thrombocyto-sis). In studies with gavage covering exposure periods ranging from 28 to 48 days a NOAEL of 6 mg/kg bw/day and a LOAEL of 25 mg/kg bw/day can be derived based on a ca. 10 % increase in liver weight in both sexes as well as vacuolar liver degeneration in 2/12 males and salivation in males. From studies with exposure via the feed ranging from 13 weeks to 24 months a NOAEL of 75 mg/kg bw/day and a LOAEL of > 75 mg/kg bw/day can be derived both for male and female rats mainly based on anemia observed in the 13-week-study at a dose of 2500 ppm (ca. 150 mg/kg bw/day) which is higher than the top dose of 1000 ppm (ca. 75 mg/kg bw/day) tested in the chronic study. The higher NOAELs and LOAELs in feed studies are plausible taking into account the limited bioavailability of 6PPD when administered without lipophilic vehicle like corn oil used in the gavage studies.

In vitro 6PPD showed no mutagenic activity in bacterial and in mammalian cell test systems and it did not induce unscheduled DNA synthesis in primary rat hepatocytes. 6PPD showed clastogenic activity in CHL cells in vitro. 6PPD showed no clastogenic activity in the cytogenetic assay or the micro-nucleus test in vivo. Consequently the clastogenic activity reported in an in vitro test was not confirmed in vivo. In view of the clear negative finding in the in vivo test, there is no longer concern that 6PPD is likely to induce chromosomal aberrations in humans.

The underlying insufficiently documented studies with long-term application of 6PPD via diet gave no indication for a carcinogenic potential of 6PPD in rats.

In rats, up to oral doses of 100 mg/kg bw/day no impairment of reproductive performance was observed and there are no indications for teratogenic or developmental effects up to oral doses of 250 mg/kg bw/day (highest dose tested). Exposure during the gestation period demonstrated the absence of a developmental or teratogenic potential and of maternal toxicity in rabbits for doses up to 30 mg/kg bw/day (highest dose tested).

Environment

6PPD is a brown solid substance with a melting point of 50°C. 6PPD has a caluculated boiling point of 370 °C. It is nearly insoluble in water (1 mg/l at 20 °C). The vapour pressure was calculated to be 6.85×10^{-3} Pa at 25 °C. A log K_{ow} value of 4.68 was calculated. The flash point of the substance is 200 °C.

6PPD is not stable in water under environmental conditions. The half-life is less than 1 day under aerobic conditions. The major degradation products are 4-hydroxydiphenylamine, N-phenyl-p-benzoquinone monoimine and 1,3-dimethylbutylamine. The favourite target compartments of 6PPD are soil with 95 %, followed by water with 2 %, and sediment with 2 %, according to a Mackay calculation level I. The measured Henry's law constant of 1.84 $Pa*m^3*mol^{-1}$ indicates that the compound has a moderate potential for volatilization from surface waters. In the atmosphere rapid photodegradation takes place by reaction with photochemically produced OH radicals. The half-life is calculated to be 1 hour. On lighted surfaces and in the air, 6PPD will undergo direct photolysis due to absorbance of environmental UV light.

6PPD is not readily biodegradable but it is degraded rapidly in the environment. In an OECD TG 301C test on ready biodegradability, based on BOD, only ca. 2 % of 6PPD was biodegraded. Based on HPLC, ca. 92 % of 6PPD was removed within 28 d indicating that 6PPD was transformed. In another respirometer test according to OECD TG 301C 13 - 40 % of 6PPD were degraded within 28 d. In a River die-away test in Mississippi River water 6PPD was quantitatively removed (97 % within 22 h). The estimated half-lives are 2.9 h in biologically active river water, 3.9 h in sterile river water, and 6.8 h in sterile deionized water.

The calculated log K_{ow} indicates that 6PPD has a potential for bioaccumulation. 6PPD is not stable under certain environmental conditions. Bioaccumulation test results are available with some degradation products. Measured bioconcentration factors in Cyprinus carpio are in the range of < 1.2 - 23 for the degradation product N-phenyl-p-benzoquinone monoimine (concentration during incubation 6.83 µg/l or 0.683 µg/l), and in the range of < 1.7 - 17 for 1,3-dimethylbutylamine (concentration during incubation 0.2 mg/l or 0.02 mg/l). For 4-hydroxydiphenylamine a BCF of 30 was calculated. These data indicate that there is no potential for bioaccumulation of these metabolites.

In fish, the lowest acute toxicity was observed in *Oryzias latipes* during a test in accordance with OECD TG 203. A 96 h LC_{50} of 0.028 mg/l (effective concentration) was measured. In daphnids, the lowest effective LC_{50}/EC_{50} was a 48 h EC_{50} of 0.23 mg/l measured with *Daphnia magna* in a Guideline study according to OECD TG 202. In a "degradation toxicity" test with Daphnia magna, it was shown that 6PPD solution aged shortly (24 h) lost its toxicity towards *Daphnia magna*. Freshly prepared 6PPD solution exhibited a nominal 48 h NOEC of 0.25 mg/l and a 48 h LC_{50} of 0.51 mg/. Stirring for 24 h under areobic conditions at room temperature, decreased the toxicity of the test solution (containing 6PPD and degradation products) significantly. The 48 h NOEC of aged 6PPD was larger than 1 mg/l (highest exposure concentration). In a study according to the Algal Assay Procedure: Bottle Test of the US EPA with the green alga *Selenastrum capricornutum*, a 96 h $EC_{50}$of 0.6 mg/l (nominal) and a 96 h EC_{10} in the range of 0.2 mg/l were obtained.

It has to be considered that the toxicity observed in the reported studies was caused both by the 6PPD as well as by the degradation products due to the instability of the test substance.

Exposure

The total production of 6PPD is estimated to be about 130,000 t/a in 2001. 6PPD is used as rubber antidegradant which reacts as an excellent antiozonant. The main area of application is the rubber sector, with the majority of the manufacturing volume going into tyres.

Releases of 6PPD into the environment may occur from production, from use in the rubber industry and during use and disposal of rubber products.

In the Sponsor country, 6PPD is manufactured from 4-aminodiphenylamine (CAS No. 101-54-2) in closed systems. Manufacturing waste is incinerated.

6PPD is lost from rubber articles into the environment, due to tyre abrasion, evaporation from rubber surfaces, and losses from landfilled rubber wastes. There are no environmental monitoring data. Even in the vicinity of new tyres, no 6PPD was detected in the surrounding air.

In the manufacturing plant of the Sponsor company, workplace air sampling of precursors and auxiliaries, which are thought to be indicators of exposure, suggest that the exposure of workers to airborne 6PPD is negligible during manufacturing. In workplace areas of the rubber industry, most workplace concentrations were negligible (peak value of 6.6 mg/m^3). In workers of the Sponsor company no adducts with hemoglobin could be detected. 6PPD was found in 15 % of the urine samples (maximum was 1.3 µg/l urine) of 21 workers of the Italian rubber industry. In another study the concentration of 6PPD in urine samples of rubber industry workers was of < 1 to 300 µg/g creatinine (with a peak value of 580 µg/g) in 1982 to 1987.

RECOMMENDATION

The chemical is a candidate for further work

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

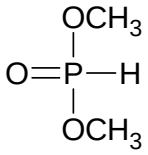
Human Health:

The chemical possesses properties indicating a hazard for human health (skin sensitization, anemia). It is therefore recommended that countries perform an exposure assessment, and, if then indicated, a risk assessment addressing exposure to workers and to humans via the environment.

Environment:

The chemical possesses properties indicating a hazard for the environment. Releases of 6PPD into the environment may occur during manufacturing in the rubber industry from the use of 6PPD as an antiozonant, as well as from the utilization of rubber products. Therefore, an exposure assessment and, if then indicated an environmental risk assessment is recommended. This should also include further investigations on identities and properties of degradation products.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	868-85-9
Chemical Name	Dimethyl phosphonate (DMP)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Dimethyl phosphonate (DMP) is rapidly absorbed via the oral and dermal routes. The main metabolic pathway in rodents is demethylation to monomethyl hydrogen phosphite (MMP) and further oxidation to CO_2. DMP was mainly eliminated via urine and expired air. Over the studied dose range between 10 and 200 mg/kg bw and 5 x 200 mg/kg bw, respectively, only little evidence of bioaccumulation or saturation of absorption and elimination was observed. The only difference in studied toxicokinetics between rats and mice was the more rapid metabolism and elimination in mice.

An inhalation LC_{50} value is not available, but an exposure of 7100 mg/m³ (concentration estimated based on air flow and net loss of material) over 6 hours was not lethal for rats, mice and guinea pigs. Clinical signs were observed in mice only, and included occasionally laboured respiration after approximately 2 hours of exposure and ptosis after 5 hours. The acute dermal LD_{50} was 681 mg/kg bw (rabbits). Signs of intoxication were depression, ptosis, labored respiration, ataxia and placidity. The acute oral LD_{50} values were: 3283 mg/kg bw for male rats, 3040 mg/kg bw for female rats, 2815 mg/kg bw for male mice, and between 2150 and 3160 mg/kg bw for female mice. Clinical signs were inactivity, weakness, prostration and shallow breathing at doses near to or exceeding the LD_{50} values. White opaque eyes were seen in male mice.

DMP is irritating to the skin and eyes of rabbits. After prolonged or repeated exposures moderate to severe irritation of skin and mucosa was observed in rats. No sensitisation studies are available.

In a repeat dose inhalation study on rats over 4 weeks, no NOAEL could be derived as increased kidney weights and keratitis were found in both sexes down to the lowest tested concentration (LOAEL: 49 mg/m³, corresponding to about 10 mg/kg bw/d). In the same study, DMP caused eye cataracts at concentrations equal to or greater 142 mg/m³, and an increase in mortality at concentrations equal to or greater 483 mg/m³.

In 13-week gavage studies on rats, decreased body weight gains were noted in females at 200 mg/kg bw/d, and for males at 400 mg/kg bw/d. At 400 mg/kg bw/d, eye changes (cataracts), and lung toxicity (inflammation, congestion, histiocytosis) occurred (NOAEL, male: 200 mg/kg bw, NOAEL, female: 100 mg/kg bw). At 375 mg/kg bw/d mortality was increased, and there were no surviving animals at 750 mg/kg bw/d. For mice the NOAEL (13 week, gavage), was 95 mg/kg bw/d, with histopathological changes in heart and liver appearing at 190 mg/kg bw/d.

In a 2-year gavage study on rats, lung effects were seen in both sexes at 100 mg/kg bw/d. At 200 mg/kg bw/d, males had cataracts and focal mineralization in the cerebellum (NOAEL, females: 50 mg/kg bw/d; LOAEL, males: 100 mg/kg bw/d, lowest tested dose in males). For female mice the NOAEL (2-yr, gavage) was 200 mg/kg bw/d (highest tested dose), whilst a NOAEL for male mice could not be derived as calcification of testis was still found at the lowest tested concentration of 100 mg/kg bw/d. An increased mortality was seen in male mice at 200 mg/kg bw/d.

In vitro data indicate that DMP has mutagenic and clastogenic potential. The available *in vivo* data are limited to the bone marrow and the results are conflicting with one study indicating clastogenicity. DMP should be regarded as having genotoxic potential *in vivo*.

DMP showed clear evidence of carcinogenicity in male F344 rats and equivocal evidence in female F344 rats. Target organs were lungs and forestomach. No evidence of carcinogenicity was observed in male and female B6C3F1 mice.

In a screening study on rats according to OECD TG 421 (gavage study), effects on fertility were seen in females at 270 mg/kg bw/d in the presence of severe general toxicity (decrease in number of females with corpora lutea and implantation sites) (NOAEL reproduction toxicity: 90 mg/kg bw/d; NOAEL general toxicity: 90 mg/kg bw/d). Focal testicular calcification was seen in mice treated orally with 100 mg/kg bw/d for 2-years, and hypospermatogenesis in rats after inhalation of 483 mg/m³ (corresponding to about 100 mg/kg bw/d) for 4 weeks. No developmental toxicity was found in rats at doses of 30 and 90 mg/kg bw/d (NOAEL developmental toxicity: 90 mg/kg bw/d).

Environment

DMP is a colourless liquid of mild odour with a melting point of < –60 °C, boiling point of 171.1 °C, density of 1.2 g/cm^3 and a vapour pressure of 1.35 hPa at 20 °C. The substance is very soluble in water with > 100 g/l at 19.5 °C. The log Kow of DMP was calculated to be –1.2.

DMP released into the atmosphere is rapidly degraded by OH-radicals with an estimated half-life of 2.9 hours. The main degradation process in water is hydrolysis. The degradation products are monomethyl phosphonate (MMP), phosphorous acid, and methanol. At pH 4 the experimentally determined half-life is about 470 h, at pH 7 it is about 3 h, and at pH 9 it is < 0.3 h.

DMP is not readily biodegradable (50 % after 28 d).

According to the Mackay Fugacity Model Level I, the main target compartments (environmental equilibrium distribution) for DMP are water (95 %) and air (5 %). The degradation product MMP will partition nearly exclusively to the water compartment based on a water solubility of 1000 mg/l, a vapor pressure of 25 Pa and a log Kow of –1.19. The calculated Henry's law constants of 0.33 Pa$*$m^{3*}mol^{-1} for DMP and of 0.002 Pa$*$m^{3*}mol^{-1} for MMP indicate a low to moderate potential for volatilization from surface waters. The calculated log Kow values (log Kow = -1.2 for DMP, log Kow = -1.19 for MMP) indicate no bioaccumulation potential. The calculated Koc values (Koc = 2.62 for DMP and 1.36 for MMP) suggest that both substances have a very low geoaccumulation potential.

Concerning the toxicity of DMP towards aquatic species, experimental results of short term tests with fish, *Daphnia*, and algae are available. During aquatic ecotoxicity tests DMP hydrolysed with half lives of several minutes to hours. Thus, during these tests, DMP itself and its degradation products MMP, methanol, and phosphorous acid were present. For testing the acute fish toxicity with *Danio rerio* a limit test with a concentration of (nominal) 100 mg/l was conducted and no effects were observed at this concentration level after 96 h. Another test with *Pimephales promelas* reported a 96 h-LC_{50} of (nominal) 225 mg/l. In a GLP study according to Directive 92/69/EEC, C.2, the EC_{50} (nominal) of *Daphnia magna* was 25 mg/l after 48 h. The geometric mean of the concentration of the hydrolysis product MMP over the exposure period was 8 mg/l. In a GLP study according to Directive 92/69/EEC, C.3, the 72 h EC_0 (nominal) of *Desmodesmus subspicatus* was >= 100 mg/l. The geometric mean of the concentration of the hydrolysis product MMP over the exposure period was 26 mg/l.

Data on long-term toxicity on aquatic organisms are not available. Valid tests on terrestrial species are not available as well.

Following the EU Technical Guidance Document, for the derivation of the $PNEC_{aqua}$ an assessment factor of 1000 is chosen since at least one short-term EC_{50} or LC_{50} value is available from each of the three trophic levels. Using the lowest determined concentration: *Daphnia magna* EC_{50} = 25 mg/l, a $PNEC_{aqua}$ of 25 µg/l is derived. This PNEC covers both the toxicity of DMPas well as the toxicity of its hydrolysis products.

Exposure

The global production capacity of DMP is estimated to be 3 000 – 15 000 t/a by about 10 producers. DMP is a basic chemical which is used industrially as an intermediate for the production of water treatment chemicals (about 50 %), pesticides and pharmaceuticals (about 20 %), flame retardants and other specialities (about 15 %), textile finishing products (about 15 %).

Consumer exposure is not known to occur in the EU. Use as a reactive flame retardant in textile finishing is reported for the U.S.

From the Bayer Chemicals manufacturing and processing site no DMP was emitted into the environment in 2000. Workplace air sampling shows that there is no relevant exposure of workers at this site.

With respect to the use as an intermediate, the exposure of consumers is considered to be not relevant. Due to the low emissions and to the hydrolysis of DMP indirect exposure via the environment is not expected.

Methyl and ethyl esters of phosphorous acid can be converted by chemical synthesis to nerve gases. Therefore the production and export of DMP is stringently controlled under the International Chemical Weapons Convention.

RECOMMENDATION

The substance is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

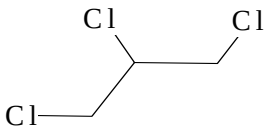
Human Health:

DMP possesses properties indicating a hazard for human health (irritating, mutagenic and carcinogenic properties, repeated dose toxicity). In the Sponsor country, exposure is controlled in occupational settings and is negligible for consumers. Countries may desire to investigate any exposure scenarios (particularly use as a reactive flame retardant in textile finishing) that were not presented by the Sponsor country.

Environment:

The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country, exposure to the environment 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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	96-18-4
Chemical Name	1,2,3-Trichloropropane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

A Concise International Chemical Assessment Document (CICAD) number 56 is available for 1,2,3-trichloropropane (TCP). In addition, an Integrated Risk Information System (IRIS) assessment has been conducted. This case is being evaluated under the OECD HPV Chemicals Programme to ensure that the SIDS required endpoints have been addressed and that robust summaries have been prepared on the relevant studies.

Human Health

The potential human exposure to 1,2,3-trichloropropane is expected to be principally *via* inhalation or ingestion. This compound was rapidly absorbed from the gastrointestinal tract, metabolized and excreted (within 60 hours) via urine (50-65%), faeces (15-20%) and breath as carbon dioxide (20%). Metabolism appears to occur faster in mice than in rats. In rats after oral administration, the major urinary metablites after 6h is a mercapturic acid conjugate (N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine). After 24h a second metabolite, a cysteine conjugate (S-(3-chloro-2-hydroxypropyl)-L-cysteine) was determined. ^{14}C activity was still found in the target organs (liver, kidney and forestomach) 60h after oral administration of [^{14}C] 1,2,3-trichloropropane. After intravenous injection in rats, one major metabolite in the bile was 2-(S-glutathionyl)malonic acid. In mice, the profile of urinary metabolites was more complex than in rats, in that the biotransformation appears to involve both conjugation with glutathione and oxidation.. One proposed pathway in the liver is the mixed-function oxidase-catalysed oxygenation of 1,2,3-trichloropropane on a terminal carbon to yield a chlorohydrin, followed by additional reactions that result in formation of the observed metabolites. A second pathway in the liver may involve the GSH transferase-catalysed formation of GSH conjugates, which either undergo additional biotransformation in the liver or are excreted in bile or plasma. Dermal absorption of 1,2,3-trichloropropane can also occur based on the results of acute dermal toxicity studies; a single prolonged exposure may result in the material being absorbed in harmful amounts.

In acute oral studies rats the LD_{50} range was from 120 to 205 mg/kg bw. Results revealed LD50 values of 205 mg/kg bw (male) and 170 mg/kg bw (female); and 120 mg/kg bw (males) and 188 mg/kg bw (females) the combined LD50 from these studies were 190 and 151 mg/kg bw, respectively. Rabbit dermal LD50 values ranged between 523 and 880 mg/kg (sexes combined). A 4-h inhalation toxicity study with rats at a concentration of 4800 mg/m^3 revealed no deaths and no significant findings at necropsy. However, other 4-h studies with rats and mice revealed an LC_{50} of about 3000 mg/m^3. The primary effects observed were irritation of the eye and nose mucosa along with liver and kidney damage. Due to the volatility of 1,2,3-trichloropropane, excessive vapor concentrations are readily attainable and may cause serious adverse effects, even death. Direct contact of 1,2,3-trichloropropane with the skin causes slight irritation or strong irritation if confined to the skin. In rabbits (24-h occlusive, intact skin) 1,2,3-trichloropropane indicated mild reversible irritation with comparable results also reported for intact and abraded skin of rabbits with a

primary index of 1.63. In contrast, in another study 1,2,3-trichloropropane was severely irritating in rabbits (24h occlusive, intact and abraded skin). In rabbits, two different standard eye irritation tests revealed that the substance was moderately irritating to the eyes of rabbits with slight variation between the two studies. Effects in one study included conjunctival irritation, conjunctival necrosis, clouding of the cornea and iris damage with all effects reversible in 2-7 days. In sensitization tests using guinea pigs, 1,2,3-trichloropropane was determined to be non-sensitizing (two acceptable studies) to very mildly sensitizing (one acceptable study).

Short and longer-term duration repeated dose inhalation studies were conducted in rats and mice. Two 9-day studies were conducted in rats and mice at 0, 80, 240 or 780 and 6, 18 and 61 mg/m^3. The primary effects in rats and mice are microscopic degeneration and inflammatory changes in the nasal olfactory mucosa. Besides nasal exudates at the lowest dose in both species, degeneration of the epithelium was observed in rats and 80 mg/m^3 and mice at 240 mg/m^3. Further nasal exostosis and fibrotic changes were detectable in rats at 780 mg/m^3, whereas mice showed nasal exostosis from 240 mg/m^3. Concentration-dependent adverse effects on nose tissues were more severe in rats than mice. In a 13-week study, male and female rats were exposed to concentrations of 0, 28, 92 and 300 mg/m^3. Body weight decreases were noted in both the mid and high dose females only. In addition, increases in liver weights were observed in males (all dose groups) and females (mid and high dose groups). Signs of respiratory tract irritation were reported at 92 mg/m^3 and higher. Hepatocellular hypertrophy was observed in male rats at all doses. Dose related focal peribronchial lymphoid hyperplasia was found primarily in males whereas splenic extramedullary haematopoiesis was observed only in females at all 1,2,3-trichloropropane concentrations. In a similar 13-week study with doses up to 9.2 mg/m^3 (1.5 ppm) reported effects include signs of irritation of mucous membranes (increase of lacrimal discharge), even at the lowest concentration of 3.1 mg/m^3 (0.5 ppm). At the highest dose an increase in lung and ovary weights was found without corresponding microscopic findings.

Repeated oral doses to laboratory animals by intubation directly into the stomach (called gavage) for up to 120 days, produced adverse effects to the forestomach, liver, kidney, spleen, nasal tissues and blood. More severe effects were found when 1,2,3-trichloropropane was administered by gavage than were observed at comparable doses with continuous exposure *via* the drinking water. The lowest observed effect levels (LOELs) for increased liver weight following 17 weeks of dosing by gavage were 8 mg/kg/day in male rats and 16 mg/kg/day in female rats; the LOELs in mice were 63 and 125 mg/kg/day for males and females, respectively. The LOELs for increased relative liver and kidney weights in the study where 1,2,3-trichloropropane was administered for 90 days to rats *via* the drinking water were higher, 17.6 and 113 mg/kg/day for males and females, respectively.

At a dose of 120 mg/kg/day, 1,2,3-trichloropropane was shown to impair the fertility of female mice in studies where the dose was given by intubation directly into the stomach. The NOAEL for a reduction in fertility was 60 mg/kg/day. 1,2,3-Trichloropropane was negative in studies examining the potential to produce birth defects or fetal death when injected into the peritoneal cavity of pregnant rats at doses up to 37 mg/kg.

Long term gavage administration of 1,2,3-trichloropropane caused cancer in multiple tissues in both rats and mice. In rats, an increased incidence of cancer was found in non-glandular stomach (no analog of this tissue exists in humans) and the oral mucosa in both sexes. Increased incidence of cancer was also found in the mammary gland in female rats, the pancreas and kidney in male rats as well as the preputial gland and clitoral gland in males and females, respectively. In mice, the main targets of carcinogenic action were the non-glandular stomach, the liver and the Harderian gland. Significant increases in tumor incidence were observed at 3 mg/kg/day and 6 mg/kg/day in rats and mice, respectively.

In vitro genotoxicity studies have demonstrated a genotoxic potential for 1,2,3-trichloropropane in the presence of metabolic activation systems. *In vivo*, DNA damage was detectable with the alkaline elution method after intraperitoneal injection of 1,2,3-trichloropropane. The major DNA adduct, *S*-[l-(hydroxymethyl)-2-(*N*7-guanyl)ethyl]glutathione, and other DNA adducts were identified in preneoplastic and neoplastic lesions of target organs.

Environment

1,2,3-Trichloropropane is a clear, colourless liquid with a boiling point of -14.7 °C and melting point of 156-157 °C. At 20 °C the relative density is 1.4 g/cm^3. The vapour pressure of 1,2,3-trichloropropane is 0.492 kPa, while the

water solubility is 1.75 g/l. The log K_{ow}, based on calculated and measured data, ranged between 1.98 and 2.54. In Mackay level I fugacity modeling, the predominant target compartment for 1,2,3-trichloropropane in the environment is air (85%) followed by water (11%). Whereas, level III fugacity modeling results with equal distribution to air, water and soil indicate the primary distribution compartment to be soil (46.7%) followed by water (34.9%), air (18.3%) and sediment (0.122%). 1,2,3-Trichloropropane released into the environment is neither hydrolysed nor readily biodegraded and might therefore remain present for extended periods. However, it can be removed from aquatic systems by evaporation and might be leached from soil into groundwater, which is due to the low soil sorption coefficients reported for this compound. Based on the low octanol/water partition coefficient and the volatility of 1,2,3-trichloropropane it is unlikely to bioaccumulate. The half-life of 1,2,3-trichloropropane in the troposphere was calculated to be 30.5 days based on reaction with hydroxyl radicals.

The acute toxicity of 1,2,3-trichloropropane was tested using a variety of aquatic species from different trophic levels. Standard guideline studies were done with algae (*Selenastrum capricornutum*) and water fleas (*Daphnia magna*) in closed test systems to assure exposure. Based on measured concentrations the EC50 values for biomass and immobility were 50 and 20 mg/l, respectively. A flow-through fish test with fathead minnow (*Pimephales promelas*) revealed an LC50.96h value of 66.5 mg/l based on effective (measured) concentrations. No data were identified on the toxic effects of this substance upon terrestrial invertebrates or higher plants.

Exposure

Based on the available information 1,2,3-trichloropropane is only manufactured as a byproduct of the production of other chlorinated compounds including epichlorohydrin. Less than about 50 000 metric tons of 1,2,3-trichloropropane is produced annually, globally, as a byproduct of epichlorohydrin. There are about 20-30 epichlorohydrin-producing facilities in North America, Europe and Asia.

The majority (>80%) of the 1,2,3-trichloropropane produced as a byproduct of epichlorohydrin is incinerated on-site. 1,2,3-Trichloropropane is used as an intermediate for the synthesis of other chemicals (e.g. pesticides) in closed systems and is used as crosslinking agent in the production of polymers such as polysulfides and hexafluoropropylene. To the best of our knowledge, TCP is no longer marketed for use in consumer product applications.

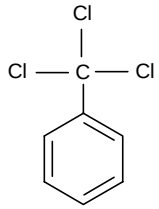
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health 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 Sponsor countries.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-07-7
Chemical Name	α,α,α-Trichlorotoluene (Trichloromethylbenzene)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

α,α,α-Trichlorotoluene hydrolyzes to hydrochloric acid and benzoic acid upon contact with moisture. It is readily absorbed from the gastrointestinal tract, distributed within the body, and excreted after metabolic transformation to hippuric acid mainly via the urine. The 4-hour inhalation LC_{50} in rats was 530 mg/m^3 for females, and >600 mg/m^3 for males. 5 of 6 rats died after a 4-hour exposure to about 1,000 mg/m^3. Clinical signs included ocular and respiratory tract irritation, dyspnea, and weight loss. The dermal LD_{50} value for rats was greater than 5,000 mg/kg bw, with sedation and poor general health from days 1 to 10 after exposure. Depending on the vehicle used, the acute oral LD_{50} values in rats were between about 700 mg/kg bw (when applied in corn oil) and 2,200 mg/kg bw (when applied as aqueous suspension). Clinical signs like sedation, dyspnea, polyuria, and weight loss were observed for several days after the oral administration of the chemical.

Under occlusive conditions, α,α,α-trichlorotoluene was irritating to the skin of rabbits. The chemical may cause severe eye irritation. The vapors are irritating to the respiratory tract.

In mice, the repeated inhalation of α,α,α-trichlorotoluene (12.8 mg/m^3 for 12 months) resulted in a high incidence of bronchitis and bronchopneumonia. In rats, repeated inhalation exposure to concentrations ≥ 48.2 mg/m³ for 4 weeks led to death, depressed weight gain, dyspnoea and gasping. Microscopically, inflammation and/or squamous metaplasia of the cells lining the nasal, tracheal, bronchial and bronchiolar epithelia were observed. No significant changes occurred in the 5.1 mg/m³ group (NOAEL). Skin irritation up to necrosis was seen after dermal treatment of rabbits with 50, 100 or 200 mg/kg bw/day of the undiluted chemical for three weeks. Histopathologically, an increased incidence of portal inflammatory cell infiltrates in the liver, and, at 200 mg/kg bw/day, bile duct proliferation was found. Pathological changes were also seen in the seminiferous tubules at 100 and 200 mg/kg bw/day. Irritation of the eyes, the skin and the respiratory tract were the main clinical signs after repeated painting of mice skin with α,α,α-trichlorotoluene. In a 28-day feeding study on rats, a NOAEL could not be determined, as mild histopathological effects on liver, kidney and the thyroid gland were still present at the lowest test concentration of 0.5 ppm in the diet (corresponding to about 0.05 mg/kg bw/day).

α,α,α-Trichlorotoluene has demonstrated a genotoxic potential in bacterial and mammalian cell systems. In non-standard *in vivo* tests, the chemical induced micronuclei in bone marrow cells of mice. Chromosomal aberrations in bone marrow cells and sister chromatid exchanges in peripheral lymphocytes have been reported in rats after repeated inhalation exposure.

α,α,α-Trichlorotoluene has induced lung tumors, skin tumors, leukemia and lymphomas in animals by the inhalative, dermal and oral routes of exposure. The available human data for α,α,α-trichlorotoluene are limited because the studies included small numbers of cancer deaths and were confounded by exposure to mixtures of chlorinated compounds. Based on the limited human data and sufficient evidence from animal studies, the combined exposures to α-chlorinated toluenes and benzoyl chloride are probably carcinogenic to humans (IARC Group 2A).

There were no fertility studies available. In a 3-week dermal study on rabbits, degeneration of the tubules in seminiferous ducts, and an increased incidence of multinucleated giant cells in the seminiferous tubules were reported at dose levels of 100 and 200 mg/kg bw/day, but not for 50 mg/kg bw/day. Pathological changes in reproductive organs were not reported in any of the carcinogenicity studies. Sufficient documentation with regard to the scope of the examinations relating to the reproductive organs was however not available, and therefore a lack of effect cannot be deduced from these studies. The effects on male reproductive organs observed in the 3-week dermal study in rabbits give some indications that α,α,α-trichlorotoluene might be toxic to reproduction. As results from further testing would not affect the most stringent exposure control measures already in place, no further tests are warranted.

In a poorly documented study, developmental effects were reported in rats at non-maternally toxic dose levels (LOAEL, fetal development = 12.5 mg/kg bw/day; NOAEL maternal toxicity = 12.5 mg/kg bw/day). Further testing is not warranted because exposure to the chemical is already strictly controlled due to its mutagenic and carcinogenic properties. Although not fully tested for reproductive and developmental toxicity, α,α,α-trichlorotoluene should be regarded as potentially toxic to reproduction because it is a genotoxic carcinogen.

Environment

α,α,α-Trichlorotoluene is a moisture/water sensitive fluid with a melting point of -4.8 °C, a boiling point of 220.7 °C, and a density of 1.37 g/cm³ at 20 °C. The vapour pressure of the substance is 0.2 hPa at 20 °C. The log Kow cannot be determined due to hydrolysis. The solubility in water is 0.1 g/l at 20 °C. The flash point is ca. 108 °C, the auto flammability (ignition temperature) 420 °C. An atmospheric half-life of about 45 days is estimated due to the reaction with hydroxyl radicals.

α,α,α-Trichlorotoluene reacts completely with water within a few minutes at 20 °C, forming benzoic acid and hydrochloric acid. Any emission into the air or into the terrestrial compartment would be affected by humidity and also results in the formation of the hydrolysis products. However, several aquatic toxicity tests have been undertaken with α,α,α-trichlorotoluene. The observed toxicity effects in these studies can be attributed to the degradation products benzoic acid and hydrochloric acid. For assessment of the environmental impact of the hydrolysis products it is referred to the validated results of the hazard assessments on benzoates and hydrochloric acid within the OECD SIDS-Program.

Hydrochloric acid is a strong mineral acid that dissociate readily in water to the hydrated protons. Hydrochloric acid will not adsorb on particulate matters or surfaces and will not accumulate in living tissues. Benzoic acid is not expected to hydrolyse.

The hydrolysis products benzoic acid and hydrochloric acid have been tested with aquatic species. Especially hydrochloric acid caused a pH shift in water which determined the impact on aquatic life. The tolerance of water organisms towards pH margin and variation is diverse. Recommended pH values for test species listed in OECD guidelines are between 6.0 and almost 9. Acute testing with fish showed 96h-LC50 at about pH 3.5 (equals about 20 mg α,α,α-trichlorotoluene), chronic testing with early life stages of fish NOECs at pH 6.0 and 5.56. Benzoic acid is not toxic (LC50 or EC50 >100 mg/l) towards aquatic organisms. The substance is readily biodegradable and non-bioaccumulative.

Acute toxicity of α,α,α-trichlorotoluene to fish (*Leuciscus idus*) was 4140 mg/l (48 h-LC_{50}) . With *Daphnia magna* an EC_{50} (24 h) of > 100 mg/l was determined. For the blue-green alga *Microcystis aeruginosa* an 8 day-EC_3 of 34 mg/l was obtained in a cell multiplication inhibition test (test solution was not neutralized). It is not expected that an algal EC_{50} obtained in a neutralized test solution would be lower than the EC_{50} for *Daphnia*. Since there are acute tests for α,α,α-trichlorotoluene from three trophic levels, an assessment factor of 1000 is applied according to EU

Technical Guidance Document to the lowest acute effect concentration (*Daphnia magna*, 24 h-EC50 of 100 mg/l). The following value is obtained: $PNEC_{aqua}$ = 0.1 mg/l

Exposure

In 2000, the world wide production capacity of α,α,α-trichlorotoluene is estimated to 80,000 metric tons by about 10 producers: Western Europe 56,000 t/a, USA 16,000 t/a, Japan 5,500 t/a, and others 2,400 t/a. α,α,α-Trichlorotoluene is an intermediate, used exclusively in the industrial production of other intermediates such as benzoylchloride, benzotrifluoride, 2,4-dihydroxybenzophenone. These intermediates are further used in the synthesis of pesticides, dyestuffs, UV absorbers and pharmaceuticals.

At the sponsor company α,α,α-trichlorotoluene is manufactured and processed in closed systems. The exhausts from manufacturing and processing (including filling) of α,α,α-trichlorotoluene are connected to absorbing units, thermal exhaust purification plants and air washing units. Thus, at the sponsor company during production and processing virtually no α,α,α-trichlorotoluene is emitted into the atmosphere. Due to the water-free production and processing processes emissions into the wastewater were not detected. The exposure of workers is below the German Technical Exposure Limit (TRK) value of 0.012 ppm (0.1 mg/m³) for α,α,α-trichlorotoluene.

A direct use of α,α,α-trichlorotoluene is not known, and α,α,α-trichlorotoluene is not listed in the Nordic and Swiss product registers as being contained in consumer products. Exposure of consumers to α,α,α-trichlorotoluene is considered negligible.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

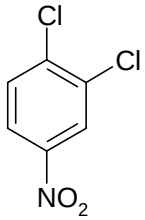
Human Health:

The chemical possesses properties indicating a hazard for human health (e.g. acute and repeated dose toxicity, irritation, mutagenicity, carcinogenicity, reproduction and developmental toxicity). In the sponsor country, the substance is solely used as an isolated intermediate with controlled transport, and exposure in occupational settings is controlled. There is no exposure of consumers. 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. The degradation products benzoic acid and hydrochloric acid have already been assessed within the OECD SIDS-Program.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	99-54-7
Chemical Name	1,2-Dichloro-4-nitrobenzene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,2-Dichloro-4-nitrobenzene is absorbed from the gastro-intestinal tract and although there are some species differences in experimental animals from the available data it can be concluded that 1,2-dichloro-4-nitrobenzene is excreted mainly via urine in the form of the mercapturic acid derivate N-acetyl-S-(2-chloro-4-nitrophenyl)-L-cysteine. Data on humans were not identified in the available literature.

There are no valid acute inhalation studies available. Based on the results of the acute dermal toxicity study with rats the LD50 is > 2000 mg/kg bw. From studies with rabbits no LD50 could be derived, the lowest Lethal Dose Level (LDLo) was 950 mg/kg bw. The acute oral toxicity in rats ranges from 625 to 950 mg/kg bw. 1,2-Dichloro-4-nitrobenzene causes the formation of methaemoglobin. Predominant signs of intoxication were lethargy, increasing weakness, collapse and coma.

1,2-Dichloro-4-nitrobenzene gave no skin irritation effects when tested for 4 hours under semiocclusive conditions according to OECD TG 404 and showed slightly irritating effects, which disappeared within 72 hours under occlusive conditions according to the method of Federal Register 38 No. 187. 1,2-Dichloro-4-nitrobenzene is slightly irritating to the eyes when tested according to OECD TG 405. 1,2-Dichloro-4-nitrobenzene was not found to induce dermal sensitization when tested according to OECD TG 406. In addition, 1,2-dichloro-4-nitrobenzene was not found to induce dermal sensitization in humans in a limited study.

The main targets identified in animal studies after repeated oral administration as well as after inhalation exposure are the haematological system and in addition the kidneys after oral application and the liver after inhalation. From a 28-day oral study performed according to OECD TG 407 a NOAEL of 4 mg/kg bw/day was derived. The NOAEL following subchronic inhalation exposure study of limited validity (limited documentation) was 0.4 mg/m³ (4 hours per day).

Changes in haematological parameters (e.g. methaemoglobinaemia, Heinz bodies) are the main target in the only available report on exposure of workers. As these findings relate to mixed exposures they cannot be clearly attributed to 1,2-dichloro-4-nitrobenzene, but would be plausible, because they were also observed in animal experiments. In the recent open literature reports of human poisoning could not be identified.

1,2-Dichloro-4-nitrobenzene exhibits mutagenic activity in *Salmonella typhimurium* but not in the HPRT test in Chinese Hamster Ovary (CHO) cells. 1,2-Dichloro-4-nitrobenzene induced chromosomal aberrations in V79 cells

with metabolic activation only at the highest concentration, which was cytotoxic. In insects (*Drosophila melanogaster*) 1,2-dichloro-4-nitrobenzene revealed no mutagenic activity in the SLRL-test after application over 3 days with slight increased toxicity, but revealed mutagenic activity following a single i.p. injection of a clearly toxic dose. 1,2-Dichloro-4-nitrobenzene showed no clastogenic activity *in vivo* in a chromosomal aberrations test with rats. Overall in non-toxic doses, there was no evidence for genotoxicity *in vivo* under the conditions tested.

Studies dealing specifically with toxicity to reproduction were not identified. The subacute study with 1,2-dichloro-4-nitrobenzene yielded no damage of the reproductive organs in rats despite clear systemic toxicity up to the maximum tolerated dose of 100 mg/kg bw.

1,2-Dichloro-4-nitrobenzene commercial grade (85% 1,2-dichloro-4-nitrobenzene and 15% 1,2-dichloro-3-nitrobenzene) caused effects on development at maternally toxic doses probably due to methaemoglobinaemia in dams and foetuses. A significant dose-response trend for variations (dilated ureters) was seen in the foetuses of the >= 30 mg/kg bw/day-groups and significant reduced body weight gain of dams at dose levels of 30 mg/kg bw/day on gd 6-10 with an even stronger effect at 100 mg/kg bw/day. Thus, 10 mg/kg bw/day was determined as the NOAEL for maternal and developmental toxicity.

Environment

1,2-Dichloro-4-nitrobenzene is a yellow substance with a melting point of 43 °C, a boiling point of 255 °C, a flash point of 155 °C, and an ignition temperature of 420 °C. With a density of 1.56 g/cm³ at 15 °C and 1.487 g/cm³ at 50 °C 1.2-dichloro-4-nitrobenzene is heavier than water. The substance is slightly soluble in water with 121 mg/l at 20 °C. The vapour pressure was determined to be 2 Pa at 25 °C. A log Kow of 3.04 at 25 °C was experimentally determined.

With regard to its chemical structure 1,2-dichloro-4-nitrobenzene is not expected to hydrolyse under environmental conditions. According to the Mackay level I fugacity model, the main target compartments for 1,2-dichloro-4-nitrobenzene are air (48 %) and water (44 %). The measured Henry's law constant of 0.82 $Pa*m^3*mol^{-1}$ indicates that the compound has a low to moderate potential for volatilization from surface waters.

In the atmosphere slow photodegradation takes place by reaction with photochemically produced OH radicals. The atmospheric half-life is calculated to be 321 days with an atmospheric concentration of 0.5×10^6 hydroxyl radicals/cm^3 as a 24 h average. 1,2-Dichloro-4-nitrobenzene will undergo direct photolysis in air due to absorbance of environmental UV light, however, the respective half-life is not known. In water, no photolysis will occur to a significant extent.

1,2-Dichloro-4-nitrobenzene is not readily biodegradable (Manometric respirometry test: biodegradation < 10 % after 21 days based on BOD; OECD TG 301 C biodegradation 0 % within 28 days, presumably due to inhibition of inoculum). 1,2-Dichloro-4-nitrobenzene is biodegradable by adapted microorganisms under aerobic conditions and by non-adapted inocula under anaerobic conditions (primary degradation). Sewage from adapted wastewater treatment plants has significant potential to primary degrade 1,2-dichloro-4-nitrobenzene (Test method "Simulation of an industrial waste water treatment plant": after 3 days 100 %).

Bioconcentration factors determined for fish were in the range of 26 – 65. A measured Koc (Koc = 417) for sediment suggests the substance to have a medium geoaccumulation potential.

Concerning the acute toxicity of 1.2-dichloro-4-nitrobenzene towards aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The acute toxicity determined for fish (*Leuciscus idus*) was of 3.1 mg/l (48 h LC_{50}) [DIN 38412 L15] and *Daphnia* (*Daphnia magna*) of 3 mg/l (24 h-EC_{50}) [DIN 38412 L11]. In the growth inhibition test with algae (*Scenedesmus obliquus)* the value 5.8 mg/l was achieved after 48 h (48 h-ErC_{50}) [OECD TG 201]. For the algae *Chlorella fusca* a value of 0.32 mg/l was found after 24 h (24 h-ErC50).
In a chronic (21 d) study with *Daphnia magna* a NOEC of 0.025 mg/l was determined for the most sensitive endpoint reproduction rate. An E_rC_{10} > 0.1 mg/l was reported for the algae *Scenedesmus subspicatus* after 48 hours
For terrestrial organisms the lowest measured 6d-EC_{50} for was 27 mg/l for the plant *Phaseolus aureus.*
Applying an assessment factor of 50 to the lowest available chronic value of 25 µg/l (21d reproduction in *D. magna*),

a $PNEC_{aqua}$ of 0.5 µg/l is obtained.

Exposure

About 36,800 tonnes of 1,2-dichloro-4-nitrobenzene were produced worldwide (excluding Eastern Europe) in 2001. 1,2-Dichloro-4-nitrobenzene is a basic chemical for the synthesis of intermediates which are further processed to herbicides, bactericides, and dyestuffs. A direct use of 1,2-dichloro-4-nitrobenzene is not known in the Sponsor country. 1,2-Dichloro-4-nitrobenzene is not contained in products registered in the Danish, Finnish, Norwegian, Swedish and Swiss Product Registers.

In the Sponsor country, 1,2-dichloro-4-nitrobenzene is manufactured and processed in closed systems. From this site the effluent concentrations was below the detection limit of 2 µg/l.
In Gemany in 1999, the 90-percentile of the 1,2-dichloro-4-nitrobenzene concentrations in the River Rhine was < 0.5 µg/l and in the River Danube < 0.02 µg/l. For the River Elbe the maximum was < 0.02 µg/l.
A non-quantifiable contamination of the terrestrial compartment by 1,2-dichloro-4-nitrobenzene might result from the application of herbicides manufactured from 3,4-dichloroaniline. This assumption is based on the observation that during the biodegradation of such herbicides 3,4-dichloroaniline is formed that in trace amounts may be oxidized biotically or abiotically to 1,2-dichloro-4-nitrobenzene. However, a significant exposure of the terrestrial compartment by this source is not expected.

Exposure is well controlled in occupational settings of the main producer in the Sponsor country and the exposure of workers is well below the workplace guidance value (ARW) of 1 mg/m^3 for 1,2-dichloro-4-nitrobenzene recommended by the German Association of the Chemical Industry (VCI).
The levels of 3,4-dichloro-aniline-adducts in blood and of 3,4-dichloro-aniline in urine of manufacturing and processing plants workers were never higher than 5 % of the tolerance values (no health effect for worker in case that value is not exceeded).

Based on the very low emissions of 1,2-dichloro-4-nitrobenzene into air and water by the manufacturing and processing plants in the Sponsor country, on the very low environmental concentrations, and on the low bioaccumulation potential, a significant indirect exposure of the general public via the environment or via the food chain is not expected.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health (principally haematological toxicity, and developmental toxicity, probably linked to methemoglobinemia) and the environment. Based on data presented by the Sponsor country, exposure to the environment is anticipated to be low, exposure is controlled in occupational settings, and exposure of consumers is not known to occur. 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.	1306-19-0 & 7440-43-9
Chemical Name	Cadmium oxide & Cadmium metal
Structural Formula	CdO & Cd

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The main reason for treating Cadmium (i.e. cadmium metal) and Cadmium oxide together stems from consideration of similar physico-chemical properties, in particular their relatively low solubility in water and from consideration of the conditions of exposure. Indeed, in occupational settings, workers are mainly exposed to cadmium oxide fumes and dust, produced when the metal is heated. The general population is exposed mainly by the oral route via food or water to cadmium (not necessarily CdO/Cd metal). However, both compounds release the biologically active form, i.e. ionic Cd^{2+} in the environment and biological tissues and so the effects can generally be treated together.

The objective of the study was not to be complete in reviewing the data on cadmium compounds but rather to focus on critical studies and endpoints. Reviews have been used in retrieving critical studies.

Human Health

While the toxicological database for cadmium (generic) is in general considerable, most of the experimental data have been produced with soluble cadmium compounds and, in human studies, the exact species involved is seldom well defined. As a consequence, incomplete data are available when specifically dealing with the fate and hazards of cadmium metal and cadmium oxide. Therefore, when necessary, use has been made of data for cadmium compounds in general.

The gastro-intestinal absorption of cadmium (generic, not specifically Cd metal or CdO) is low and subject to variations according to the source of Cd, the presence of Zn in the diet and its composition, age and physiological status of the individual: generally below 5 % (average 3%) when iron stores are adequate and may increase up to 10% when iron stores are depleted. Absorption rates after inhalation of CdO derived from animal studies range from 50 (fumes) to max. 30 % (dust, depending on particle size). In humans, figures of 10-30 % absorption rate according to particle size are derived for CdO dust. No data are available for Cd metal. From experimental studies performed with soluble Cd salts it can be deduced that percutaneous absorption is likely to be significantly less than 1 % (elemental Cd).

Cd is widely distributed and retained in the body where it accumulates throughout life. Hence, the body burden increases upon continuous exposure and the element has a biological half-life of about 10-20 years. After long-term low-level exposure, about half the body burden of cadmium is localised in the kidneys and liver, a third of the total being in the kidneys with the major part located in the cortex. In non-occupationally exposed subjects the cadmium concentration in the renal cortex is estimated between 10 and 50 ppm (2-3 fold increase in smokers). Only a small part of cadmium absorbed from long-term low level exposure is excreted: daily excretion which takes place via faeces and urine represents only 0.005-0.02% of the total body burden of the element The placenta provides a relative barrier protecting the foetus against cadmium exposure. There is some build up of cadmium in the placenta and levels are significantly higher in smokers than in non-smokers. Cadmium is found in human breast milk at low concentrations (< 1 µg/l).

The whole blood Cd (Cd-B) concentration, is a useful indicator of exposure over the last few months. After long-term high Cd exposure, an increasing proportion of blood Cd will, however, also be related to body burden. Therefore, in non-smokers and after cessation of long-term high exposure, Cd-B may also reflect body burden.

Cd urinary excretion (Cd-U, expressed as µg Cd/l, as µg Cd/g creatinine, as nmol Cd/mmol creatinine or µg Cd/ 24 h) is correlated with the body burden and has been extensively used as a biomarker of long-term exposure in human studies. Several studies have shown that in the general population, Cd-U increases with age and this increase coincides with an increased body burden. At the group level, there is a close relationship between Cd-U and kidney cortex content of the element; a Cd-U of 2.5 µg/g creatinine corresponds, at the group level, to about 50 ppm in the kidneys cortex.

Orally, LD50 values (rat and mouse) range between 72 and 296 mg/kg bw for CdO and from 890 to 2330 mg/kg for Cd metal. Acute inhalation exposure to CdO was found to produce pulmonary inflammation and oedema in experimental rats. The lowest dose (LOAEL) reported to cause mild pulmonary damage (hypercellularity indicative of hyperplasia) in experimental animals was a 3-hour exposure to 0.5 mg/m^3 CdO fumes (MMAD: 0.26-0.33 µm). In humans, it has been estimated that an 8-hour exposure to 5 mg/m^3 may be lethal and an 8- hour exposure to 1 mg/m^3 immediately dangerous for life. LC_{50} and/or CT_{50} values are available for several animal species. CT_{50} expresses the concentration x time, causing death in 50% of a defined experimental animal population. The most reliable data are on rat where the CT_{50}-values of 1 962 and 13 770 mg x min/m^3 were obtained. These results allow to conclude to the high acute toxicity of Cd(O) via inhalation in animals. Human data support this finding. A N(L)OAEL for acute dermal exposure could not be derived. However, acute effects via the dermal route are not expected to be significant as uptake appears to be very low (cf. toxicokinetics).

No specific data were located regarding the irritation potential of CdO or Cd metal on the skin, eye or respiratory tract neither in animals nor in humans. Based on the effects observed after acute and repeated inhalation exposure, it seems, however, possible that CdO (as fumes or dusts) is irritant for the respiratory tract.

A substantial body of information is available indicating that the lung, kidney and bone are the main target organs upon repeated exposure to CdO/Cd metal in occupational settings (mainly by inhalation). Environmental exposure to Cd (generic, not specifically CdO/Cd metal), mainly by the oral route, is associated with bone and kidney toxicity.

NOAELs identified from long-term inhalation tests are 0.025 mg CdO/m^3 in F344/N rats and < 0.025 mg CdO/m^3 in $B6C3F_1$ mice, exposed for 13 weeks. No study specifically using Cd metal dust or powder was located. In humans, long term inhalation of CdO fumes or dusts leads to reduced lung function and emphysema. A LOAEL equivalent to a Cd-U of 3.1 µg Cd/l is derived for CdO fume exposure. No human data are available for Cd metal dust.

Experimental and epidemiological studies indicate that the bone tissue is another target for Cd toxicity, but the mechanism is not fully understood yet. A LOAEL of 3 nmol Cd/mmol creatinine for bone effects was suggested from epidemiological studies conducted in populations exposed to Cd via the diet.

Numerous studies in several experimental species have indicated that exposure to cadmium compounds administered orally or by inhalation causes kidney damage and functional changes (reduced glomerular filtration rate, proteinuria). In workers occupationally exposed to cadmium, a Cd body burden corresponding to a Cd-U of 5 µg/g creatinine constitutes a LOAEL based on the occurrence of Low Molecular Weight proteinuria. In the general population (mainly exposed by the oral route), the most recent studies conducted in Europe indicate that renal effects can be detected for Cd body burdens below 5 µg Cd/g creatinine. The LOAEL of 2 µg/day (Cd-U) derived for increased calciuria is consistent with the view that bone and kidney effects of Cd are probably interrelated.

Cardiovascular and liver effects are not critical endpoints for CdO/Cd metal toxicity.

Evidence from experimental systems indicates a potential neurotoxic hazard for cadmium (not CdO or Cd metal specifically) in adult rats. In humans, heavy occupational exposure to cadmium dust has been associated with olfactory impairments and studies performed on a limited number of occupationally-exposed subjects are suggestive of an effect of Cd on the peripheral and central nervous systems but these findings should be confirmed. In the young age, there is some experimental indication that Cd exposure (not specifically CdO or Cd metal) can affect the

developing brain but this should be further investigated.

In bacterial systems, cadmium compounds generally fail to induce point mutations. A well conducted study on four *S. thyphimurium* strains did not show mutagenic effect of CdO. In mammalian systems, cytotoxic concentrations of cadmium compounds have been shown to cause chromosomal damage *in vitro*. Chromosomal aberrations and micronuclei in bone marrow cells have been reported after exposure of rodents to soluble Cd compounds. However, inhalation exposure to CdO (up to 1 mg CdO/m^3) did not induce micronuclei in peripheral erythrocytes in mouse. With regard to human exposure, data are conflicting but seem to indicate a genotoxic potential of Cd compounds, at least in occupational settings. Studies performed in environmentally exposed populations have suggested that cadmium compounds might exert genotoxic effects. Overall, it cannot be excluded, based on the available data, that cadmium compounds (including Cd metal and CdO) might exert genotoxic effects.

CdO induced lung tumours in rat inhalation studies. Cd metal produced local tumours when injected in experimental animals. In humans, the possibility that cadmium dust or fumes (including CdO) might cause a risk of lung cancer by inhalation is reported in several epidemiological studies but the possible contribution of confounding factors (mainly co-exposure to other carcinogens) could not be clearly defined. No study was specifically conducted with Cd metal in animals exposed by inhalation or in humans. Overall, the weight of evidence collected in genotoxicity tests, long-term animal experiments and epidemiological studies leads to conclude that CdO/Cd have to be considered at least as suspected human carcinogens (lung cancer) upon inhalation exposure. There is no indication or evidence that CdO/Cd act as carcinogens in the general population exposed by the oral route.

Effects on reproductive organs and fertility have been noted in experimental studies after exposure to CdO and Cd compounds-. The lowest values were derived in rats exposed by the oral route to $CdCl_2$ (NOAEL 1 mg Cd/kg/day) and by inhalation to CdO (NOAEL 0.1 mg CdO/m^3). Epidemiological studies do not point to an association between exposure to CdO/Cd metal and relevant effects on fertility or reproductive organs.

Regarding developmental toxicity, cadmium compounds have been reported to induce malformations primarily of the skeleton, neurobehavioral alterations and reduced body weight in offspring of animals exposed via the oral route (gavage or diet) or by inhalation, both at doses that generally produced maternal toxicity. In well conducted inhalation studies with CdO (MMAD: 1.1-1.6 µm) the NOAEL was 0.05 mg CdO/m^3 in mouse and 0.5 mg CdO/m^3 in rat. Neither the mechanism nor the critical period of cadmium-induced adverse effects in offspring due to maternal exposure are completely elucidated.

Further information is needed to better document the possible effect of low doses of Cd/CdO on the developing brain suggested in experimental animals. Based on the human data available, there is no indication of a potential developmental effect of CdO or Cd metal.

Environment

Both substances are solids. Cadmium metal exists in virtually all forms, shapes and particle sizes. CdO is commercialized as powder. Water solubilities are low: in the range of 0.19 mg Cd/L – 0.227 mg CdO/L. Vapour pressure for cadmium metal is 1 mmHg (at 394°C), for cadmium oxide: 1 mmHg (at 1000°C). Octanol-water partition coefficients are not relevant for this type of substances.

The database on the effects of soluble cadmium compounds to aquatic organisms is in general extensive. Limited data are available on cadmium oxide specifically and again far less on cadmium metal.
Besides the available limited number of standard tests on the substances, data from other soluble salts are used as well in the derivation of ecotoxicological thresholds.

The median acute LC50 values are 166 µg L^{-1} for freshwater invertebrates and 1500 µg L^{-1} for fish and amphibians (all values expressed as concentrations of cadmium ion). The median EC50 for primary producers (algae and aquatic plants) is 59 µg/l.

The lowest adverse effect concentrations of Cd in chronic studies with freshwater species range from 0.3 to >100 µg Cd L^{-1} with a tendency to find the lowest toxic thresholds for invertebrates in soft waters. The $PNEC_{water}$ of Cd was

derived with statistical extrapolation from 44 chronic NOEC values. The HC5 of this distribution is 0.38 µg/l. A safety factor of 2 is applied to reach the PNEC of 0.19 µg Cd L^{-1} (dissolved fraction). A US EPA hardness correction is applied to derive a PNEC for waters with a hardness of 100 to 40 mg $CaCO_3$/l: 0.08 µg/l. Mesocosm data indicate that this corrected PNEC is also protective down to a hardness of approximately 10 mg $CaCO_3$/l. There are no data available to correct the PNEC at a water hardness below 10 mg $CaCO_3$ L^{-1}. No further correction for bioavailability has been applied.

The lowest adverse effect concentrations in soil for plants, invertebrates or soil micro organisms vary between 2.5 and >1000 mg kg^{-1} with a tendency to find lowest thresholds for plants grown in potted soil applied with Cd^{2+} salts. The $PNEC_{soil}$ of Cd is derived by conducting a species sensitivity distribution of either NOEC values for soil microbial processes (based on soil functions) or for plant and invertebrates (species). The most conservative of these distributions (microbial processes) results in an HC5 of 2.3 mg/kg. An assessment factor of respectively 1 or 2 is applied to reach a $PNEC_{soil}$ of 2.3 to 1.15 mg/kg. The final $PNEC_{soil}$ is 1.15 mg Cd kg^{-1}. The overall database did not reveal significant trends between soil properties (pH, % clay) and Cd toxicity and similar information from studies using multiple soil types was inconsistent.

One chronic study with benthic organisms was found from which a NOEC of 115 mg kg^{-1} is derived. The $PNEC_{sediment}$ was derived applying a safety factor of 50 on this value resulting in a value of 2.3 mg Cd kg^{-1} , because other derivation methods (equilibrium partitioning) did not give satisfactory results. No correction for bioavailability was made.

The median Cd Bioconcentration Factors (BCF, L kg^{-1}_{ww}) decrease in the order algae>invertebrates>vertebrates and the water-fish Cd Bioaccumulation Factors (BAF's) are about 40 L kg^{-1}_{ww} with maximal values around 600 Lkg^{-1}_{ww}. Soil-earthworm BAF values are about 15 (dry weight concentration ratio) with values up to 150. All BCF and BAF values exhibit a pronounced decrease with increasing concentrations in the environment.

Environmental monitoring in wildlife does not suggest biomagnification of Cd. Field data of terrestrial birds (body burden Cd) do not indicate Cd poisoning, even in contaminated areas and in top predators. Pelagic birds have reported kidney Cd concentrations above acceptable values but the assessment of hazards to marine organisms was not made.

The effect of Cd on small terrestrial mammals was assessed based on monitoring data of body burden and an assessment of critical kidney Cd concentrations. A critical soil Cd concentration was derived which is 0.9 mg $kg^{-1}_{dw.}$ This value is triggered by data on moles and shrews (both carnivorous) dwelling in acid soils. This critical soil Cd concentration is below the $PNEC_{soil}$ derived from direct toxicity tests (plants, invertebrates and microbial processes) confirming the general knowledge that Cd is more toxic to mammals than to plants or invertebrates.

Exposure

Cadmium is a naturally occurring element with a ubiquitous distribution in the environment. It is found in high concentrations in zinc ores, also as greenockite (CdS) and otavite ($CdCO_3$). Natural processes e.g. volcanic eruptions are major natural source of cadmium release.

Primary cadmium is produced during the refining of other non-ferrous metals' ores, mainly zinc and to a lesser extent lead and copper. Cadmium as a by-product is here obtained by either pyrometallurgical (high temperature) or hydrometallurgical (electrolytic) production techniques. The final step in the production of high purity cadmium (>99.99%) is vacuum distillation or electrolysis. Cadmium is also increasingly being recovered from the recycling of e.g. NiCd batteries, cadmium-coated products, alloys, etc so as to obtain cadmium - so-called secondary cadmium - with a purity, quality and form that can be utilized again in industrial applications.

Cadmium oxide is produced indirectly from commercial cadmium metal.

The production of cadmium in the EU in 1996 was approximately 5808 tonnes, of which 2536 tonnes (approximately 44%) were subsequently converted into CdO.

The major uses of cadmium and cadmium oxide in the EU are in the manufacture of NiCd batteries (75%), other Cd-containing chemicals e.g. pigments (15%) and stabilizers (5%), in cadmium-plating and alloys (5%) and in miscellaneous uses (<0.01%).

Emissions to the environmental compartments are possible from the production and the use of the substances. However, the quantity of Cd actually present in the EU environment (topsoil, sediments and freshwater) exceeds by orders of magnitude the actual annual emissions. The environmental emission from Cd/CdO producers and processors only form a minor part of the total emissions of Cd in Europe. The major sources of Cd emissions at the continental scale are phosphate fertiliser application, production of iron and steel and oil combustion.

During the production or the use of Cd metal and/or CdO, the main route of potential exposure is inhalation. The potential for consumer exposure due to Cd(O) is generally non-existent or very low. Exposure by ingestion (mainly food, to lesser extent water and beverages) and possibly inhalation from environmental sources (nearby point sources) or from smoking is significant. The dietary Cd intake varies between 7-32 µg Cd day^{-1} in EU and is mainly due to consumptions of leafy vegetables, cereals and potatoes, which take up Cd from soil. Seafood may be an additional source of Cd exposure. Inhalation of Cd and direct Cd deposition onto crops are only major contributor for the general population around point sources with elevated atmospheric emissions (i.e. a minority of the production and processing sites, data resp. from 1996 and 1999). Tobacco smoking is an important source of exposure to Cd compounds that leads to a doubling of the Cd body burden in smokers.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health and Environment:
Hazardous properties have been identified for these substances both for human health (respiratory irritation, kidney and bone toxicity, possible genotoxicity, carcinogenicity and neurotoxicity) and for the environment (increased mortality and reduced growth or reproduction for organisms living in water, sediment and soil; reduced microbial functioning of micro-organisms in soils and sewage treatment plants; kidney damage in mammals and birds). In an assessment performed in the context of the EU Existing Substances Regulation, potential exposure (mainly occupational and environmental exposure) was identified and concern for kidney/bone toxicity was expressed for several sub-populations. Other OECD countries may wish to perform an exposure assessment and if necessary a risk assessment.

Further testing could be considered as a post-SIDS activity:

Human Health
Further experimental and epidemiological information is needed to better document the possible effects of low doses of Cd/CdO on neurobehavioural performances suggested in experimental animals, especially on the developing brain (prenatal and early childhood exposure). Effects on the adult nervous system should also be characterised.

Environment
Ecotoxicity testing in very soft waters (hardness below approximately 10 mg $CaCO_3$/L) needs further clarification. Moreover, more information is required to quantify the bioavailability of Cd in the sediment compartment, i.e. if it is appropriate to apply the concept that the excess simultaneously extractable metals above the free sulphide concentration predict the toxicity of Cd.

SIDS INITIAL ASSESSMENT PROFILE

CAS No. (Nos.)	107-21-1, 111-46-6, 112-27-6, 112-60-7, 4792-15-8
Chemical Name(s)	Ethylene glycol, Diethylene glycol, Triethylene glycol, Tetraethylene glycol, Pentaethylene glycol (Ethylene Glycols Category)
Structural Formula	$HOCH_2CH_2OH$, $HO(CH_2CH_2O)_2H$, $HO(CH_2CH_2O)_3H$, $HO(CH_2CH_2O)_4H$, $HO(CH_2CH_2O)_5H$

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

Category members are represented by the generic molecular structure, $HO(CH_2\ CH_2\ O)_n\ H$, where n = 1-5. All category members therefore possess two terminal hydroxy groups and the members differ from each other only in the number of oxyethylene units. Because of this it is appropriate to classify EG and the higher glycols (up to and including n=5) as a single group. At n = 6-8, absorption from ingestion decreases and certain physicochemical attributes change significantly. Adequate studies are available for most of the required SIDS endpoints for the category members. A category approach is used where experimental data are not available.

Category members ethylene glycol and the higher glycols (di-, tri-, tetra-, and penta-) are closely related in structure and have physicochemical properties which differ in a regular and expected way as a result of increasing molecular weight and consistent functionality of a relatively less stable hydroxy moiety on each end of the molecule. Thus, the hazard profile and dose response are also expected to change consistently, with decreasing potential for adverse effect with increasing molecular weight. Available data and quantitative structure activity modeling for the category for several toxicological endpoints confirm this expectation, indicating that it is reasonable to assume consistent changes in toxicological effects for the relatively few instances where experimental data for the category are lacking.

Available data and modeling confirm that as the molecular weight increases, the potential for systemic, reproductive, and developmental toxicity decreases. Available data for several ecotoxicological endpoints demonstrate that the potential for these effects is consistently low throughout the category in that the LOELs are greater than the limit dose (1000 mg/kg). Polyethylene glycol 200 (PEG 200, CAS No. 25322-68-3), which is not a category member, is a mixture of EGs (n=2 to 8, thereby containing category members and other higher molecular weight ethylene glycols) with an average molecular weight of approximately 200 and an average of 4 oxyethylene units. It has some properties similar to the category members and data from this mixture are used to support the trend that as molecular weight increases, toxicity decreases within the five-member category.

Human Health

EG, DEG and TEG are almost completely absorbed by laboratory animals via oral routes as would be expected from their total miscibility with water. As tetraEG and pentaEG are likewise completely miscible with water and are of relatively low molecular weight, it is reasonable to assume that they are likewise extensively absorbed via the oral route. The absorption estimate for inhaled EG is approximately 100 percent. No direct measures of inhalation absorption are available for DEG, TEG, tetraEG and pentaEG. In *in vivo* rodent dermal absorption studies, 1-51% of EG was absorbed. Dermal bioavailability of DEG was estimated as 9%. No direct measures of dermal absorption are available for TEG, tetraEG, and pentaEG. Since the EGs are completely soluble in water, they are expected to be well distributed throughout the aqueous tissues of the body with lower concentrations in adipose tissue; Uniform distribution has been demonstrated to a limited extent for EG. The main metabolic pathway for metabolism of the EGs is oxidation via alcohol dehydrogenases and aldehyde dehydrogenases. The main metabolites of EG are carbon dioxide, oxalic acid and glycolic acid. Identified DEG and TEG metabolites include carbon dioxide, oxalic acid and other acid metabolites. EG, DEG, and TEG may be directly eliminated by urinary excretion. Acid metabolites of EG, DEG and TEG are also eliminated in urine and may also be metabolized to carbon dioxide and eliminated in exhaled breath.

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.

Results of acute mortality studies in rodents indicate that the EGs are generally of low acute toxicity by the oral, inhalation and dermal routes of exposure with the values for reported endpoints being greater than a limit dose. Acute lethality by the oral route is greater than that for the other category members. The acute toxic effects of EG in laboratory animals and humans can include narcotic effects, metabolic acidosis and renal toxicity. Acute oral toxicity in rats (measured as LD50 in mg/kg) ranged from 5890 in EG to over 16000 in pentaEG. Tested members of the EG category have LOAELs greater than a limit dose (1000mg/kg) for repeated dose toxicity studies by the dermal, inhalation and oral routes. No adverse effects were seen in dermal studies performed with EG and tetra EG. Oral repeated dose toxicity (NOAEL in mg/kg/day) ranged from approximately 150 for EG and DEG to greater than 2000 for tetraEG and pentaEG. Studies by the oral route demonstrate that repeated oral exposure to the lower molecular weight category members (EG and DEG) induces renal toxicity. However, TEG had only minor effects on the kidney and as the number of oxyethylene units increases to four and five oxyethylene units, no renal toxicity is observed even at high doses. Due to the structural and physical similarities of pentaEG with the other category members and data for the EG mixture PEG 200, it can be reasonably assumed that pentaEG also will have low potential for repeated dose mammalian toxicity.

EG can produce skin irritation, but the other EGs tested on humans (DEG, TEG, and tetraEG) produce minimal irritation, and the human skin primary irritation index decreases with an increasing number of oxyethylene units. All category members produce only minor eye irritation. While DEG caused respiratory depression, the characteristics were not typical of a "pure" airway irritant (WIL, 2001). In a human clinical study of EG, all participants found exposure to 0.14mg/L to be irritating to the throat and exposures above 0.20mg/L could not be tolerated due to severe irritation. EG, DEG, TEG and tetraEG have not induced skin sensitization.

Mutagenicity studies in bacteria and *in vitro* mutagenicity studies in mammalian cells have been conducted for all category members. The results of the bacterial studies have been uniformly negative (± S9 activation). The results of *in vitro assays* for chromosomal aberrations and in sister chromatid exchange assays have also been uniformly negative for all category members. PentaEG was tested *in vitro* for chromosomal aberrations after the SIAM review, and the results were negative. PentaEG produced no biologically significant chromosomal damage in the mouse bone marrow micronucleus test. Evidence indicates that tetraEG causes chromosomal aberrations *in vitro*. However, results of *in vivo* genotoxicity studies have been negative (dominant lethal test) or equivocal (bone marrow chromosome aberrations in rats, peripheral blood micronucleus test in mice). In several studies conducted for EG, DEG and TEG some of which were limited, there was no evidence of carcinogenicity in animals. QSAR results from multiple models for mutagenicity *in vitro* (Salmonella, mouse lymphoma) and cancer were negative. No structural alerts were identified. Information on the genotoxicity of PEG 200 is not considered to contribute to interpretation of results for compounds in the category, due to the lack of assessment of some its components for mutagenicity.

EG, DEG, and TEG have been assessed using the Reproductive Assessment by Continuous Breeding protocol. EG and DEG produced decreased numbers of litters per fertile pair and live pups per litter. No reproductive effects were seen for TEG-exposed mice. TetraEG was negative in the rodent dominant lethal assay and repeat dosing with tetraEG for 4 weeks in rats produced no notable changes in the histopathology of the testes and epididymides. Extensive developmental toxicity data are available for EG, DEG, and TEG.. Observed effects include reduced fetal body weights and skeletal variations for EG, DEG and TEG and malformations at higher dose levels and dose rates for EG and DEG. By the oral route, DEG and TEG do not cause any developmental effects below a limit dose. There is a clear trend of NOAELs increasing with the number of oxyethylene units in the rat studies. Benchmark dose analysis indicated that the trend also held for the mouse. NOAELs for repeated oral exposure ranged from approximately 150mg/kg/day for EG (16-week study) to an estimate of over 2000 mg/kg/day for pentaEG. While studies of repeated dermal exposure to the EGs are limited, the two relevant studies indicate that these compounds are of low toxicity by the dermal route. No effect was observed in maternal animals dermally exposed to EG at 3549 mg/kg/d for 10 days and no toxicity was found in animals dermally exposed to 3360 mg/kg/d tetraEG for 13 weeks. These findings are consistent with the low dermal bioavailability determined for DEG and assumed for higher molecular weight EGs. Based on studies by different routes (oral vs. dermal), EG exposure below the limit dose results in developmental toxicity in animals only by the oral route and only when rapidly ingested (bolus).

Environment

The ethylene glycol category consists of liquids of low volatility and high water solubility. Partition coefficients (Log Kow) range from –1.20 for EG to –2.3 for pentaEG. Fish acute toxicity (measured as LC50 in mg/L) has been tested for all category members and ranges from 22800 for EG to greater than 50000 for pentaEG. The acute toxicity of the

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.

category members to invertebrates has also been tested. Toxicity to *Daphnia* (measured as LC50 in mg/L) is greater than 20,000 for all category members except tetraEG (LC50=7800 mg/L) indicating low toxicity, but the toxicity was not as uniform as in fish. Toxicity evaluations in another invertebrate, brine shrimp (A*rtemia salina)* were imprecise, but appear to be more consistent than the measured *Daphnia* toxicity values (no toxicity observed at the highest tested dose, 20g/l for EG, 10 g/l for DEG, TEG and tetraEG). Algal toxicity has been tested for EG, DEG, TEG, and PentaEG, and no toxicity was found at concentrations less than or equal to 100 mg/L. Based on the low toxicity of tested category members, it can reasonably be assumed that tetraEG likewise poses no appreciable hazard to algae. The QSAR predictions indicate that the category members should exhibit low toxicity, with trends of decreasing toxicity with increasing chain length and are supportive of the available experimental data. All evidence indicates that EG is readily biodegradable. The rate of degradation, however, decreases for other members of this category. Biodegradation of EGs may deplete levels of dissolved oxygen in receiving water-bodies near airports where these chemicals are used in high volume for deicing activities. Depletion of dissolved oxygen can result in adverse effects on aquatic organisms that may be present near points of effluent discharge. There is a limited potential for category members to bioaccumulate.

Exposure

Total global production capacity estimated for each category member in 2001 was as follows: EG- 15,841,000 metric tons; DEG- 1,584,000 metric tons; TEG- 150,000 metric tons; Tetra EG- 10,000 metric tons; and PentaEG- 3,000 metric tons.

Approximately 78% of EG is consumed in the manufacture of polyethylene terephthalate (PET) with an additional 13% used as an ingredient in automotive coolants. The largest use of DEG is in the production of unsaturated polyester resins, polyols and polyurethanes. The majority of TEG consumption is for natural gas dehydration. Commercial mixtures of tetra- and pentaEGs left over from distilling out lower boiling EG, DEG, and TEG are often processed into brake fluids, and can also be used as an aid in cement grinding.

Occupational exposure to members of the EG category is limited during manufacture by the enclosed, continuous nature of the manufacturing process. The most likely routes of occupational exposure to EG are dermal and inhalation of vapors and mists. The use with the highest potential for exposure is in deicing aircraft and runways. There is some potential for consumer exposure to lower molecular weight EGs. Consumers may come into dermal contact with EG and DEG infrequently and for short periods, when topping off radiator antifreeze in personal vehicles. Consumers may also come into dermal contact with low concentrations of EG present in a variety of commercial products and DEG in limited consumer products. Human exposure to EG in commercial products can occur through dermal contact and inhalation of air and ingestion of soil near point sources. Workplace exposure to DEG may occur during manufacture or use as an industrial intermediate. Exposure may also occur during its use as a solvent. Almost all DEG is used industrially. The most likely human exposure to TEG is in the industrial setting. The most likely route of exposure is through dermal contact (e.g., during quality control sampling). The primary uses of tetraEG, pentaEG, or mixtures containing these substances, are industrial. Therefore human exposure is most likely to occur in the work place, during such uses as a solvent, industrial extractant, plasticizer or humectant. The most likely route of industrial exposure is dermal, since tetraethylene and pentaethylene glycols possess extremely low vapor pressure(6×10^{-5} hPa or less).

RECOMMENDATIONS

Environment: The chemicals in this category are currently of low priority for further work.

Human Health: Ethylene glycol and diethylene glycol are candidates for further work. Depending upon use and exposure, member countries should assess possible risk associated with renal (EG and DEG) and/or developmental toxicity (EG) for the lower molecular weight EGs.. The remaining chemicals in this category are currently of low priority for further work.

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.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment

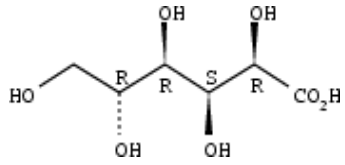
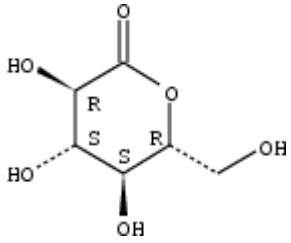
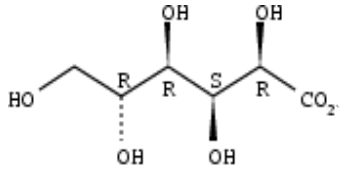
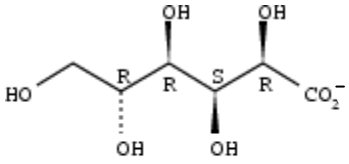
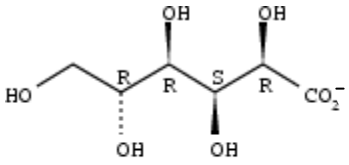
Available data for several ecotoxicological endpoints demonstrate that ecotoxicological effects due to direct exposure to ethylene glycols are unlikely to result. However, biodegradation of ethylene glycols may deplete levels of dissolved oxygen in receiving water-bodies near airports where these chemicals are used in high volumes for deicing activities. Depletion of dissolved oxygen can result in adverse effects on aquatic organisms that may be present near points of effluent discharge. Member countries (particularly Nordic countries) that use EG for deicing at airports should verify their exposure profile and risk management measures for this chemical to determine if there is a need for additional measures to be applied.

Human Health

Based on studies by different routes (oral vs. dermal) and different regimes (gavage vs. diet), EG exposure below the limit dose (1000 mg/kg/day) results in developmental toxicity in animals only by the oral route and only when rapidly ingested (bolus). Depending upon use and exposure, member countries should assess possible risk associated with renal (EG and DEG) and developmental toxicity (EG) for the lower molecular weight EGs. In this context, an additional study on dose-response for renal effects following long-term exposure to EG was completed, and the results, confirming previous chronic animal studies for renal effects, are included in the EG SIDS Dossier. An additional *in vitro* gene mutation assay for pentaEG in mammalian cells, the CHO/HPRT test, was completed to expand the genotoxicity profile of this substance, confirming the negative results for gene mutation assays for all members of the category.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	Chemical	Structural formula
526-95-4	D-Gluconic acid	
90-80-2	Glucono-delta-lactone	
527-07-1	Sodium D-gluconate	 • Na
299-28-5 18016-24-5	Calcium D-gluconate	 • 1/2 Ca
299-27-4	Potassium D-gluconate	 • K

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

Gluconate derivatives are presented as a category. Gluconic acid and its mineral salts freely dissociate to the gluconate anion and the respective cations. Glucono-delta-lactone (GDL), the 1,5-inner ester of gluconic acid, is formed from the free acid by the removal of water. On the basis of these spontaneous chemical rearrangements, glucono-delta-lactone, gluconic acid and its sodium, calcium and potassium salts can be considered as a category, with all members sharing the same representative moiety, the gluconate anion. Manufacturing and uses of the category members are also interlinked. The data summarized in this report are focused on the environmental and health effects from the gluconate anion and read-across to the lactone but do not deal with specific effects of the cations. Thus toxicological effects related to the cationic components are not part of the present report.

Human Health

Gluconic acid and its derivatives are naturally occurring substances. In mammalian organisms both D-gluconic acid and its 1,5-lactone are important intermediates in the carbohydrate metabolism. Gluconate is a metabolite of glucose oxidation. The daily production of gluconate from endogenous sources is about 450 mg/kg for a 60 kg person. A significant portion (60-85%) of parenterally administered gluconate is excreted unchanged in the urine.

The LD50 calculated after oral administration (gavage) of potassium gluconate on Wistar rats is 6060 mg/kg bw.

None of the repeated dose toxicity studies of any duration (4 weeks, 6 months, or 24 months) showed any significant toxicological effects of gluconates. Potential side effects were attributed to high doses of cation intake, evidenced by results from assays designed for the gluconate anion effect specifically. The NOAEL of sodium gluconate determined from the 28 days studies on rats was equal to 1000 mg/kg bw for males and 2000 mg/kg bw for females. These compounds are neither irritant to the eye or the skin nor show sensitizing properties.

The available in vitro and in vivo mutagenicity data with glucono-delta-lactone, sodium or calcium gluconate were negative. No carcinogenicity studies, and no inhalation toxicity data were available for any of the gluconates of the category.

SIDS testing requirements regarding reproductive toxicity were satisfied with histopathology of the reproductive organs in repeat dose studies on sodium gluconate and with developmental toxicity studies on glucono-delta-lactone. Indeed no changes were observed on the reproductive organs in 28 days oral studies with sodium gluconate (dosage up to 4400 mg/kg bw) and developmental toxicity studies on GDL on different species were all negative.

Environment

Gluconates are readily biodegradable both in aerobic and anaerobic conditions. As the sequestering tendency of gluconates decreases rapidly upon dilution or lowering pH, their chelated metal complexes are destroyed effectively and quickly by biological waste water treatment as well.

A closed bottle test for sodium D-gluconate showed that the Theoretical Oxygen Demand (ThOD) was 89% after 28 days which predicts 100% degradation; and an anaerobic study showed that 100% of sodium D-gluconate was degraded after 35 days.

Gluconic acid, its salts of sodium, potassium and calcium as well as glucono-delta-lactone are all characterised by a low vapour pressure (from 2.41e-009 hPa to 1.58e-022 hPa, estimated from the modified Grain Method), and a low octanol/water partition coefficient (estimated as -5.99 for the sodium salt, -7.51 for the calcium salt, - 5.99 for the potassium salt, -1.87 for the free acid and -1.98 for GDL). The dissociation constant of gluconic acid is in the range of 3.5 to 3.8. Because of their good water solubility (from 30 g/L for calcium gluconate to 590 g/L for sodium

gluconate) and low Log Ko/w, no bioaccumulation effects are to be expected, the substances were also shown to be readily metabolised.

Estimations from a level II/III fugacity model show that the main target compartments of gluconates are water (38.8 – 49.8 %) and soil (48.9-61.2%). The calculated Henry's law constants (1.38 x 10^{-4} $Pa.m^3$/mole for GDL, 4.74 x 10^{-8} $Pa.m^3$/mole for gluconic acid and 4.76 x 10^{-8} $Pa.m^3$/mole for sodium gluconate) indicate a low potential for volatilization and the estimated indirect photodegradation in the atmosphere with OH radicals (AOP (v1.91) program) gives a $t_{1/2}$ between 1.7 and 4.0 hours. The good water solubility and low vapour pressure designate water to be a major target compartment for these substances.

Acute toxicity to aquatic organisms (fish, daphnia, algae) was tested on sodium gluconate. In the range of concentrations tested, sodium gluconate did not show toxicity to any of the aquatic species: fish (LC0-96 hrs > 100 mg/l), daphnids (NOEC 24-48 hrs > 1000 mg/l), algae ($NOEC_r$ (24-72 h): 560 mg/l - E_rC_{50} (24-72 h): > 1000 mg/l)) The data from these studies were used for the other members of the category.

No terrestrial toxicity data for gluconates are available.

Exposure

Gluconic acid and its derivatives presented in this category are naturally occurring substances. In mammalian organisms both D-gluconic acid and its 1,5-lactone are important intermediates in the carbohydrate metabolism.

Most of these compounds are listed as permitted food additives, which may be added to all foodstuffs, following the "quantum satis" principle, as long as no special regulations restrict their use.

The manufacturing of gluconic acid is based on a fermentation process. Estimation of the worldwide industrial production per year for all the members of the gluconate category is around 65000 - 100000 tonnes. There is no production site in Belgium.

The typical industrial applications for the category are both dispersive and non-dispersive. The main non- dispersive applications are industrial cleaning, metal surface treatment, textile bleach stabiliser and aluminium processing.

When gluconates are used in wide dispersive applications such as chelating agents in cement set retarding, institutional and household cleaning, personal care products, pharmaceuticals and foodstuffs, their use might result in exposure to the environment. However, when used as sequestering agents in the building industry (concrete and mortar), the gluconate ions react with calcium ions present in the cement to form an insoluble and impermeable layer of calcium gluconate. Therefore, the gluconate is bound within the microcrystalline fibres of cement and is not free to migrate to cause any environmental pollution. Food applications could potentially contribute to spreading gluconates and glucono-delta-lactone in the environment, as these products are added in their crystalline or powder forms to food components such as meat, milk or soma at levels below 5 %w/w. However, since the final food is meant for human consumption and mostly gets ingested, there is no real potential for environmental distribution of gluconates from this application either.

Human exposure by all routes (including inhalation) is possible. Workers exposure will mainly be by inhalation and by skin contact. Consumers' exposure may be from the oral and dermal routes. Individual exposure of consumers to gluconates is expected to be limited because gluconates are mostly used as additives in the different consumer products typically in low dosages. Furthermore, Consumer exposure in personal care products, pharmaceuticals and foodstuffs applications are subject to specific regulatory provisions requiring an authorization procedure where the evaluation of the hazardous properties as well as the actual exposure is taken into account.

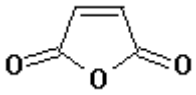
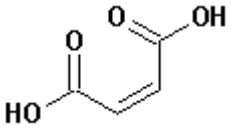
RECOMMENDATION

The chemicals in this category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemicals in this category are currently of low priority for further work because of their low hazard potential.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-31-6 110-16-7
Chemical Name	Maleic Anhydride Maleic Acid
Structural Formula	Maleic Anhydride: $C_4H_2O_3$  Maleic Acid: $C_4H_4O_4$ 

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

Maleic anhydride is readily hydrolyzed to maleic acid under aqueous conditions. As a result, these two chemicals are presented because of the conditions used to test their toxicity. The only difference may be due to the potential for maleic anhydride to form haptens by acylating with amino acids, resulting in an immunological response (dermal and respiratory sensitization).

Human Health

Maleic anhydride and maleic acid exhibit relatively low acute toxicity by the oral and dermal routes, with the oral LD_{50} of about 1.0 g/kg in rats and an acute dermal LD_{50} in the range of 1.6 to 2.6 g/kg in rabbits. Maleic anhydride and maleic acid have been reported to be severely irritating to the skin and eyes of rabbits. Maleic anhydride has been shown to be a skin sensitizer to guinea pigs and a possible respiratory sensitizer to rats. There have been a few published human cases suggesting that maleic anhydride provokes asthma in a relatively small proportion of exposed workers; however, questions have been raised about whether the asthma was related to maleic anhydride exposure. Although no sensitization data exist for maleic acid, it is not predicted to be either a skin or respiratory sensitizer.

Repeated exposure of maleic anhydride by inhalation to rats, hamsters, and monkeys have resulted in effects that were limited to the respiratory tract and eye irritation. In a four-week study, rats exposed six hours/day to 0, 12, 32, and 84 mg/m^3 (0, 3, 8, 21 ppm) maleic anhydride showed evidence of nasal, trachea, and lung irritation at all exposure levels. These effects were concentration-related and included epithelial hyperplasia and the presence of inflammatory exudates in the nasal turbinates and trachea; and epithelia hyperplasia, squamous metaplasia, and intra-alveolar hemorrhage in the lung. Increased incidence of hemorrhagic lung foci were also observed in the 32 and 86 mg/m^3 exposed groups. The LOAEL was 12 mg/m^3 (3 ppm). In a six-month inhalation study in which rats, hamsters, and monkeys were exposed to 0, 1.1, 3.3, or 9.8 mg/m^3 (0, 0.3, 0.8, or 2.4 ppm), respiratory tract and eye irritation were observed in rats and hamsters exposed to 3.3 or 9.8 mg/m^3 (0.8 or 2.4 ppm) and monkeys to 9.8 mg/m^3 (2.4 ppm),

with body weight reductions only in male rats from the high-exposure group at study termination. Hyperplastic changes in the nasal tissues, which ranged in severity from trace to mild, were present in rats at all exposure levels and in hamsters in the mid- and high-exposure levels. Metaplastic changes in the nasal tissues occurred in both rats and hamsters at all exposure levels. Both the hyperplastic and metaplastic changes in the nasal passages are considered indicative of irritation and judged to be reversible. The NOAEL for rats is 3.3 mg/m^3 (0.8 ppm) and the NOAEL for hamsters and monkeys is 9.8 mg/m^3 (2.4 ppm). Oral feeding studies with maleic anhydride have resulted in kidney damage in rats at relatively high doses ($\geq$ 100 mg/kg/day after 90 days of exposure), with the effects being more severe in males than in females. The effects appear to be largely in the tubular cells, with some effects also occurring in the glomeruli. The kidney effects are likely due to maleic acid, since maleic anhydride rapidly hydrolyzes to maleic acid under aqueous conditions and maleic acid is known to cause kidney damage with the target site being tubular cells. However, no kidney effects were observed in rats that were fed diets containing 32 and 100 mg/kg/day maleic anhydride for two years. A dietary study in dogs dosed at 0, 20, 40, or 60 mg/kg maleic anhydride, seven days a week for 90 days, showed no adverse effects related to maleic anhydride exposure, except for decreased food intake for the first few weeks in the high-dose group.

Maleic anhydride and maleic acid were both negative in bacterial gene mutation tests. A single in vitro chromosomal aberration test with and without S-9 was positive for maleic anhydride. Because there is inadequate documentation on this study, it is unclear whether the results were due to maleic anhydride or to a change in pH due to the acidic environment from the hydrolysis of maleic anhydride to maleic acid. Maleic anhydride was negative in an in vivo rat bone marrow chromosomal aberration test. Both maleic anhydride and maleic acid were not carcinogenic when given to rats in their diets for two years up to doses of 100 mg/kg/day.

In a two-generation reproductive toxicity study, rats were dosed via gavage to 0, 20, 55 and 150 mg/kg/day maleic anhydride. The NOAEL for reproductive effects is 55 mg/kg/day (highest dose tested due to parental death at 150 mg/kg/day.) However, in the parental group adverse effects (mortality, body weight changes, and respiratory irritation) were observed at 150 mg/kg/day (the highest dose tested.) In addition, there were histopathological effects in the kidneys and bladder of the parental animals (first generation only) in all treated dose groups. The LOAEL for parental effects is 20 mg/kg/day. No developmental toxicity was observed when pregnant rats were dosed with maleic anhydride via gavage to 0, 30, 90 and 140 mg/kg/day. The dams in all dose groups either lost weight or failed to gain weight between days 6 and 9 of gestation; however, this effect was not statistically significant at any interval and was reversible. As a result, the NOAEL (maternal) was determined to be 140 mg/kg/day. Negative results for reproductive and developmental toxicity of maleic acid are inferred from the rapid hydrolysis of maleic anhydride to maleic acid.

There have been been a few published human cases suggesting that maleic anhydride provokes asthma in a relatively small proportion of exposed workers. Questions, however, have been raised whether the asthma was actually related to maleic anhydride exposure.

Environment

Maleic anhydride has a melting point of 51.2 to 53.1 ^{0}C, a boiling point of 185 ^{0}C, and vapour pressures of 15.1, 37.7, and 108 Pa at 22, 30, and 40 ^{0}C, respectively. The log K_{ow} of maleic anhydride (as maleic acid) is –2.61. The water solubility of maleic anhydride (as maleic acid) was ~400 g/L at 20^{o}C.
Maleic acid has a melting point of 130-144 ^{0}C. This range is based on three entries under different conditions: 138-139 ^{o}C when crystallized from water; 130-135 ^{o}C when crystallized from alcohol, and 144^{o}C in air. The boiling point has been reported to be about 138 ^{0}C, at temperature at which decomposition occurs. This temperature is known to result in isomerization to fumaric acid. The vapor pressure of maleic acid is reported to be 4.8 x 10^{-3} Pa at 25 ^{0}C. The dissociation contants for maleic acid are at 25 ^{o}C: K_1: 1.14 x 10^{-2} (pH = 1.94) and K_2: 5.95 x 10^{-7} (pH = 6.22).

Maleic anhydride and maleic acid are not persistent in the environment and are not expected to bioaccumulate in food webs. In the presence of water, maleic anhydride rapidly hydrolyzes to form maleic acid. The half-life of the hydrolysis of maleic anhydride to maleic acid in water at 25^{o}C has been determined to be approximately 22 seconds. The half-life of maleic anhydride in air is estimated to be 4.2 to 18.6 hours (the estimated rate constants range from 4.3 x 10^{-11} to 4.9 x 10^{-17} cm^3 $molecule^{-1}$ sec^{-1}), due primarily to direct reactions with photochemically generated hydroxyl radicals. For maleic acid, the half-life in air is estimated to be 1.346 and 1.205 days for the cis- and trans-

isomers, respectively.

Maleic anhydride and maleic acid are readily biodegraded under aerobic conditions in sewage sludge, and are expected to biodegrade in soil and water as well. Fugacity-based fate and transport modelling suggest that maleic anhydride, hydrolyzed to maleic acid in water and under humid conditions, will partition primarily to water. Level III fugacity modelling indicates water as the primary compartment for distribution (air 0.3%, water 59%, soil 40.6%, sediment 0.02%).

Acute aquatic toxicity testing indicates a low order of toxicity when the effect of pH is taken into consideration. Acute values were 96-hour LC_{50} in fish – 75 mg/Land 48-hour EC_{50} in daphnids – 330 mg/L. (in non-neutralized conditions, pH 2-3). In a study which took pH into consideration, the 24-hour daphnid EC_{50} was 88, 83, and 5600 mg/liter for non-neutralized maleic anhydride, non-neutralized maleic acid, and neutralized maleic anhydride, respectively. This supports the observation that pH may be a significant confounder in the observed aquatic toxicity of maleic anhydride/maleic acid.

The 72-hour algae NOEC of 130 mg/L (measured as maleic acid in neutralized conditions and the highest dose tested). The combination of low aquatic toxicity, low log P_{ow} and readily biodegradability suggest no significant hazard of long-term effects in the aquatic environment.

Exposure

In the United States, the capacity for maleic anhydride was 590 million pounds (267,565 metric tonnes) in 1999. Maleic anhydride is produced from the oxidation of butane using fixed-bed or fluid-bed processes. It can also be generated through the oxidation of benzene. Most of the maleic anhydride produced is used in unsaturated polyester resins, while smaller amounts are used in the production of fumaric and malic acid; lube oil additives, maleic copolymers, agricultural chemicals, and 1-4-butanediol. Maleic acid is an intermediate in the production of maleic anhydride. It is recovered in the manufacturing process to be used as a feedstock for tetrahydrofuran, fumaric acid, and 1,4-butanediol. Occupational exposure to maleic anhydride and maleic acid is likely to occur by inhalation and dermal routes in settings where maleic anhydride is produced or used. Maleic anhydride itself has no known consumer uses. Because maleic anhydride is rapidly hydrolyzed to form maleic acid in the presence of water, consumer and environmental exposures to maleic anhydride are not anticipated. Data regarding these potential exposures to maleic acid are lacking, but exposures are expected to be low outside of the workplace.

RECOMMENDATION

These chemicals are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

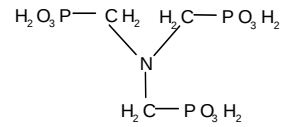
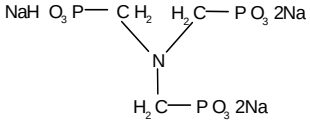
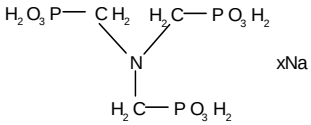
These chemicals possess properties indicating a hazard for human health (maleic anhydride is a skin/eye irritant, a skin - and possibly respiratory - sensitizer and causes minor effects at low doses in repeated-dose toxicity tests). Based on data presented by the Sponsor country, exposure is anticipated to be low to humans (controlled in occupational settings and no known exposures to consumers) and therefore these chemicals are currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by Sponsor countries.

Environment:

These chemicals are currently of low priority for further work because of their low hazard profile.

Note:
In the US maleic anhydride is listed in a proposed rule by the U.S. EPA Office of Air and Radiation, Hazardous Air Pollutants (HAPs), Title 1 Section 112.

SIDS INITIAL ASSESSMENT PROFILE

	Chemical name	CAS no.	Abbreviation
	Amino tris(methylenephosphonic acid	6419-19-8	ATMP
	Amino tris(methylenephosphonic acid), xNa Salt	20592-85-2	ATMP-xNa
	Amino tris(methylenephosphonic acid), Na Salt	none found	ATMP-Na
	Amino tris(methylenephosphonic acid), 2Na Salt	4105-01-5	ATMP-2Na
	Amino tris(methylenephosphonic acid), 3Na Salt	7611-50-9	ATMP-3Na
	Amino tris(methylenephosphonic acid), 4Na Salt	94021-23-5	ATMP-4Na
	Amino tris(methylenephosphonic acid), 5Na Salt	2235-43-0	ATMP-5Na
	Amino tris(methylenephosphonic acid), 6Na Salt	15505-05-2	ATMP-6Na
Category Name	ATMP and salts (Phosphonic Acid Compounds Group 1) Amino tris(methylenephosphonic acid) and its sodium salts		
Structural Formula	 Amino tris(methylenephosphonic acid) CAS # 6419-19-8		
	 Amino tris(methylenephosphonic acid), 5Na Salt CAS # 2235-43-0		
	 Amino tris(methylenephosphonic acid), xNa Salt CAS # 20592-85-2		

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

This category covers a phosphonic acid and various sodium salts of that acid. The different salts are prepared by neutralising the acid to a specific pH. Data are available for the acid and some salts. The substances are commercially available as aqueous solutions only and in an environmental context the speciation will be the same. In the present context the effect of the counter-ion (sodium) will not be significant. The properties of the members of the category are consistent across all end points.

The category is expressed as Phosphonic Acid Compounds Group 1 because two other groups have been identified, with close structural analogy to the present one. Group 2 is 1-Hydroxy-1,1-ethane-diphosphonic acid (CAS 2809-21-4) and its sodium and potassium salts; Group 3 is Diethylene triamine penta(methylene phosphonic acid) (CAS 15827-60-8) and its sodium salts.

Human Health

In the rat, ATMP is poorly absorbed from the gut and rapidly eliminated after oral and i.v. administration. Elimination

is primarily via the faeces following oral dosing with urine predominating after i.v. dosing. These differences demonstrate clear differences in systemic disposition of ATMP after enteral or parenteral administration. Bone is the only tissue that exhibits deposition of test substance-derived radioactivity, however this is unlikely to occur to any biologically significant extent in view of the low level of uptake reported.

ATMP is of low acute toxicity in mammals. The acute oral LD_{50} is 2910 mg/kg while the dermal LD_{50} is >6310 mg/kg. The tetrasodium salt of ATMP was of lower toxicity with an oral LD_{50} of ~8610 mg/kg and a dermal LD_{50} of >5740 mg/kg. The pentasodium salt (20592-85-2) was of lower oral toxicity (7120 mg/kg) and dermal toxicity (>6320 mg/kg).

ATMP is a moderately severe eye irritant. The tetra- and pentasodium salts of ATMP are mildly irritating. ATMP can be considered to be non-irritating to the skin. The tetra- and pentasodium salts of ATMP induced very slight skin irritation responses. ATMP is not a skin sensitizer.

Repeated exposure in the diet to 500 mg/kg bw/day of the acid for 2 years resulted in no toxicological effects of concern. The systemic NOAEL for this good quality study conducted to OECD guideline 453 is therefore considered to be >500 mg/kg bw/day. Information available on the tetrasodium salt is less robust but similarly indicates that it is of low oral toxicity following repeat exposure with a NOAEL of >600 mg active acid/kg bw/day derived from a 28 day study or >175 mg/kg bw/d derived from a 90 day study.

Neither the acid nor a sodium salt induced gene mutations in bacteria. ATMP induced gene mutations in mouse lymphoma cells but this effect was not seen when a neutralized test solution was tested up to the solubility limit and is therefore considered to be an artefact of pH. The pentasodium salt of ATMP did not induce chromosome damage either *in vitro* or *in vivo*. Both the acid and the salts are therefore considered to lack genotoxic potential. This is confirmed by a carcinogenicity study. ATMP was not carcinogenic to rats treated with dose levels up to 500 mg/kg in the diet for 24 months.

ATMP is not selectively toxic to the male or female reproductive system, with a NOAEL of 275 mg/kg bw/day for males and 310 mg/kg bw/day for females. While no reproductive toxicity data were located for the salts, physico-chemical considerations suggest these will resemble those of the parent acid. ATMP and its salts are not fetotoxic or teratogenic in the rat or mouse with a consistent NOAEL of 1000 mg/kg body weight/day in both species.

Overall the NOAEL for ATMP is > 500 mg/kg bw/day, based on a chronic toxicity study.

Environment

ATMP is a polyphosphonic acid of molecular weight 299. The phosphonic acid function is a strong acid, and it is frequently produced as a salt for reasons of ease of use. It can form stable complexes with polyvalent metal ions. As a consequence of the ionisation over typical pH ranges, it is of high water solubility ($\geq$ 500 g/l) and low octanol-water partition coefficient (Log Kow = -3.53). Its vapour pressure is very low (1.9×10^{-10} Pa (estimated)). At pH 7, ATMP in water will be almost fully ionised four times, with a majority of the molecules ionised five times.

There is a possibility that the emission of a phosphonic acid could locally decrease the pH in the aquatic environment. In the normal use of these substances, their pH, concentration and water quality have to be monitored very carefully. Therefore, a significant decrease of the pH of the receiving water is not expected. Furthermore, the substances are usually used as salts with near-neutral pH, and their effects on pH are further buffered by the presence of metal ions. Generally the changes in pH of the receiving water should stay within the natural range of the pH, and for this reason, adverse effects on the aquatic environment are not expected due to release of the phosphonic acids.

ATMP and its salts may enter the environment via normal use in water treatment applications. It is predicted and has been shown to be adsorbed by inorganic matrices (measured Koc = 11740), and therefore adsorption to sewage sludge and soil is strong. ATMP and its sodium salts are not readily or inherently biodegradable in laboratory studies carried out under standard conditions. Although these data suggest the potential for persistence, there is, however, evidence of partial degradation by abiotic processes in natural waters, and biodegradation following acclimation, or under conditions of low inorganic phosphate. In the presence of commonly found metal ions possessing redox

properties, such as iron, metal-catalysed degradation and photodegradation can be rapid, which promotes further biodegradation. ATMP is not bioaccumulative (measured BCF <25).

As complexing agents, these substances could remobilise metals in the environment; however, their high degree of adsorption to sediments suggests that this is unlikely to occur.

ATMP and its salts are of low acute toxicity to fish, acute LC_{50} values determined in short-term and prolonged-term exposure tests are all equal to or in excess of 250 mg/l. ATMP also has low chronic toxicity to fish with a 60-day NOEC of 23 mg/l having been determined in an early-life stage test ATMP and its salts are of low to moderate acute toxicity to aquatic invertebrates. The lowest reliable acute toxic concentration determined for ATMP is a 48-h EC_{50} of 94 mg/l for the marine copepod *Acartia tonsa*. A sub-lethal test with the oyster, *Crassostrea virginica*, yielded a 96-hour EC50 for effects on shell growth of 201 mg/l and a chronic test with Daphnia magna (of uncertain reliability) yielded a 28-day NOEC of >25 mg/l, suggesting that ATMP has low chronic toxicity to aquatic invertebrates.

ATMP is of low acute toxicity to the marine sediment living amphipod *Corophium volutator* (10-day LC_{50}: >5000 mg/kg dw) and to sewage sludge micro-organisms (*Pseudomonas putida* 30-min EC_0: ≥500 mg/l).

The effects of ATMP observed in tests with algae are likely to be a consequence of nutrient limitation caused by complexation and not true toxicity. Thus, a 96-hour E_bC_{50} for *Selenastrum capricornutum*[1] of 12 mg/l and a 96-hour E_rC_{50} for *Skeletonema costatum* of 80 mg/l are likely to over-estimate the true toxicity. NOECs of ≤20 mg/l (most commonly in the range 10-20 mg/l), determined in studies for which reliability could not be assessed and which might also be subject to the effects of complexation, indicate that ATMP is likely to be of low chronic toxicity to algae.

ATMP is considered to be of low toxicity to terrestrial plants (*Avena sativa* 9-day EC_{50}: >1000 mg/l), although the reliability of the study on which this conclusion is based is uncertain. ATMP is also of low acute toxicity to birds when administered via the dietary exposure route (*Anas platyrhynchos* and *Colinus virginianus* 14-day LC_{50}: >565 mg/kg bw).

[1]Now known as *Pseudokirchneriella subcapitata*

Exposure

Current worldwide production of ATMP, HEDP and DTPMP (and their salts) is estimated to be in the range of 50,000 to 100,000 metric tonnes annually. The major uses of ATMP and its salts are as an additive in water treatment, where its ability to both complex with metal ions, and to prevent crystalline scale deposition in solution and onto surfaces through adsorption, are utilised. The substances are also used in detergent and cleaning applications, and in the paper, textiles and photographic industries, and also in off-shore oil well applications.

The major route of environmental exposure is expected to be release, often via wastewater treatment plants, to rivers. Agricultural land could be exposed via spreading of sewage sludge. Oil well use would lead to direct exposure of the marine environment. In rivers, they are expected to partition predominantly to sediment.

Human exposure in manufacturing and formulating is possible, but due to the use of personal protective equipment, limited to accidental situation. Where exposure can occur, dermal exposure is the most likely route of exposure. In these cases PPE is recommended. The concentration of the substance in the product, together with PPE/engineering controls are important factors in the assessment of risk associated with the hazardous properties (mainly corrosivity/irritancy). Where concentrated solutions are handled, engineering controls and PPE are used to control exposure and reduce the risk from the corrosive/irritant properties. In downstream uses, where consumer exposure is possible, much more dilute concentrations are used, which significantly reduces or removes the likelihood of corrosivity/irritancy effects.

Consumer exposure is being assessed in more detail as part of the HERA project (HERA, in progress www.heraproject.com/).

RECOMMENDATION

The chemicals in this category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The chemicals in this category possess properties indicating a hazard for human health. Although these hazards do not warrant further work as they are related to pH effects and chelation properties, they should nevertheless be noted by chemical safety professionals and users.

Environment:

The chemicals in this category possess properties indicating a hazard for the environment. However these hazards do not warrant further work as they are related to acute toxicity, pH effects and metal chelation, which may become evident only at very high exposure levels. They should nevertheless be noted by chemical safety professionals and users.

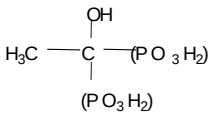
SIDS INITIAL ASSESSMENT PROFILE

Category Name	HEDP and salts (Phosphonic Acid Compounds Group 2) 1-Hydroxy-1,1-ethane-diphosphonic acid and its sodium and potassium salts

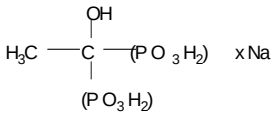
Chemical Names and CAS Numbers

Chemical name	CAS no	Abbreviation
1-Hydroxy-1,1-ethane-diphosphonic acid	2809-21-4	HEDP
1-Hydroxy-1,1-ethane-diphosphonic acid, xNa Salt	29329-71-3	HEDP-xNa
1-Hydroxy-1,1-ethane-diphosphonic acid, Na Salt	17721-68-5	HEDP-1Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 2Na Salt	7414-83-7	HEDP-2Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 3Na Salt	2666-14-0	HEDP-3Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 4Na Salt	3794-83-0	HEDP-4Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 5Na Salt	13710-39-9	HEDP-5Na
1-Hydroxy-1,1-ethane-diphosphonic acid, xK Salt	67953-76-8	HEDP-xK
1-Hydroxy-1,1-ethane-diphosphonic acid, K Salt	17721-72-1	HEDP-1K
1-Hydroxy-1,1-ethane-diphosphonic acid, 2K Salt	21089-06-5	HEDP-2K
1-Hydroxy-1,1-ethane-diphosphonic acid, 3K Salt	60376-08-1	HEDP-3K
1-Hydroxy-1,1-ethane-diphosphonic acid, 4K Salt	14860-53-8	HEDP-4K
1-Hydroxy-1,1-ethane-diphosphonic acid, 5K Salt	87977-58-0	HEDP-5K

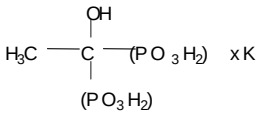
Structural Formula



1-Hydroxy-1,1-ethane-diphosphonic acid
CAS # 2809-21-4



1-Hydroxy-1,1-ethane-diphosphonic acid, xNa Salt
CAS # 29329-71-3



1-Hydroxy-1,1-ethane-diphosphonic acid, xK Salt
CAS # 67953-76-8

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

This category covers a phosphonic acid and sodium salts of that acid. The different salts are prepared by neutralising the acid to a specific pH. Data are available for the acid and some salts. The substances are commercially available as aqueous solutions only and in an environmental context the speciation will be the same. In the present context the effect of the counter-ion (sodium/potassium) will not be significant. The properties of the members of the category are consistent across all end points.

The category is expressed as Phosphonic Acid Compounds Group 2 because two other groups have been identified, with close structural analogy to the present one. Group 1 is Amino tris(methylenephosphonic acid) (6419-19-8) and its

sodium salts; Group 3 is Diethylene triamine penta(methylene phosphonic acid) (CAS 15827-60-8) and its sodium salts.

Human Health

Animal studies demonstrate that gastrointestinal absorption of 1-hydroxy-1,1-ethane-diphosphonic acid and its salts is low, with the majority of the dose excreted in the faeces. Of the material that enters the systemic circulation, a substantial amount is excreted via urine while bone is the only tissue to exhibit deposition of radioactivity (although it is noted that no adverse skeletal changes were present in sub-chronic and chronic studies suggesting this is of limited toxicological relevance). Internal body burdens are increased after injection, presumably reflecting greater systemic availability.

HEDP and its salts are of moderate acute toxicity to mammals. The rat acute oral LD_{50} of the acid is 1536-2003 mg/kg while the dermal LD_{50} is>6000 mg/kg. The mouse oral LD_{50} is 1100mg/kg. Tests on two salts indicate lower LD_{50} values. The oral LD_{50} for the disodium salt (CAS 7414-83-7) was 1340 mg/kg (rat), 3300mg/kg (mouse) and 581 mg/kg (rabbit). For the tetrasodium salt (CAS 3794-83-0) the values were 940 and 1219 mg/kg in separate studies, with dermal LD_{50} values of >2300 mg/kg. Based on these findings it could be assumed that all sodium and potassium salts will be of moderate acute toxicity, since the effect of these counter-ions will not be significant.

HEDP is considered to be a severe eye irritant/corrosive. Three salts have been tested and these have been found to be mild (CAS 3794-83-0) or moderate irritants (CAS 7414-83-7 and 29329-71-3). Since these results have been obtained on formulations, and higher doses of the pure salts could have been tested, the results obtained may underestimate the irritancy of the pure salts.

The acid and one of the salts (CAS 3794-83-0) are not skin irritants. There is evidence that CAS 29329-73-3 is an irritant when tested under occlusion for 24 hours, but is only slightly irritating when tested under semi-occlusive conditions for 4 hours. CAS 7414-83-7 has been reported to be slightly irritating, but this is a secondary reference, not available for review. HEDP is not a skin sensitiser.

Sub-chronic dietary administration of HEDP in the dog (10000 ppm, equivalent to 1746 or 1620 mg/kg bw/day for males and females respectively) resulted in minor effects associated with perturbations of iron and calcium homeostasis (possibly linked to impaired absorption of these minerals from the diet and/or complexation with the phosphonic acid). The systemic NOAEL from this study is therefore considered to be ≥1746 mg/kg bw/day. A 90 day rat study indicates an NOAEL of >1724 mg bw/kg/day since, again, the only treatment related changes appeared due to perturbations of iron and calcium uptake and homeostasis and were therefore considered to be of doubtful toxicological significance. There is a robust chronic toxicity study on a sodium salt, where indications of anaemia were induced, although these had resolved by the end of the study. A NOAEL of 24 mg bw/kg/day is assigned based on the observation of anaemia at the higher doses.

Sub-chronic toxicity studies demonstrate no adverse microscopic changes in the reproductive organs of male and female rats or dogs given HEDP and its salts at exposures equivalent to approx. 1500-1800 mg/kg bw/day. Results from a study of unknown reliability are consistent with no effect on pregnancy rate in male and female albino rats following continuous administration of up to 0.5% disodium salt in the diet, giving an approximate NOAEL of >447 mg/kg bw/day (the highest dose tested). These observations are consistent with data for phosphonic acid compounds from Group 1 and Group 3, which were not selectively toxic to the male or female reproductive system and which returned NOAELs for reproductive toxicity in the range 275-312 mg/kg bw/day. Additionally, no abnormalities in the reproductive organs were seen in a 2-year study with the sodium salt of HEDP. Using a weight of evidence approach, it is concluded that HEDP is also not likely to be selectively toxic to the reproductive system.

Similar limitations also apply to pregnancy data available for HEDP, with a developmental NOAEL of >250 mg/kg bw/day (the highest dose tested) obtained from a gavage study of unknown reliability in the rabbit. This is broadly comparable with an oral NOAEL of around >1000 mg/kg bw/day obtained in rats given structurally-related analogues from Group 1 and Group 3 during pregnancy. Since physiochemical and physiological considerations indicate that the parent acid and other Group 2 salts will exhibit broadly similar effects on fetal development, a weight of evidence approach leads to a developmental NOAEL of >250 mg/kg bw/day for HEDP and its salts.

Although the mutagenicity data available on HEDP are of limited reliability they provide some evidence for a lack of mutagenic potential. Negative responses were seen in a bacterial mutagenicity assay and a mammalian cell gene mutation assay. A salt has previously been reported to be negative in a bacterial assay and a micronucleus test, although this is secondary literature and therefore of unknown validity. Related acids (ATMP, DTPMP) have been shown to be negative in well-conducted bacterial mutagenicity assays. Conflicting results have been obtained for mammalian gene mutation assays. Positive responses in this assay in the presence of S9 are believed to be artefactual (see SIARs for ATMP and DTPMP). Therefore, despite the absence of a robust genetic toxicology test package performed to current standards, HEDP or its salts are not likely to pose a genotoxic hazard.

Overall, the subchronic toxic effects of HEDP are primarily related to its ability to chelate metal ions and affect calcium and iron homeostasis. The lowest NOAEL is >1724 mg/kg based on a 90 day rat study. There is evidence that some of the salts may have a higher toxicity, as indicated by lower oral LD_{50} values for a sodium salt and lower effect levels for haematological parameters for a sodium salt in a 2 year chronic toxicity study (NOAEL of 24 mg/kg bw/d).

Environment

HEDP is a diphosphonic acid of molecular weight 206. The phosphonic acid function is a strong acid, and it is frequently produced as a salt for reasons of ease of use. It can form stable complexes with polyvalent metal ions. As a consequence of the ionisation over typical pH ranges, it is of high water solubility (>690 g/l) and low octanol-water partition coefficient (log K_{ow} = -3.52). Its vapour pressure is very low (estimated as $1.24E^{-09}$ Pa). At pH 7, HEDP in water will be fully ionised twice and half of the molecules will be ionised three times.

There is a possibility that the emission of a phosphonic acid could locally decrease the pH in the aquatic environment. In the normal use of these substances, their pH, concentration and water quality have to be monitored very carefully. Therefore, a significant decrease of the pH of the receiving water is not expected. Furthermore, the substances are usually used as salts with near-neutral pH, and their effects on pH are further buffered by the presence of metal ions. Generally the changes in pH of the receiving water should stay within the natural range of the pH, and for this reason, adverse effects on the aquatic environment are not expected due to release of the phosphonic acids.

HEDP and its salts may enter the environment via normal use in water treatment applications. It is predicted and has been shown to be adsorbed by inorganic matrices, and therefore adsorption to sewage sludge and soil is strong. They are not readily biodegradable in laboratory studies carried out under standard conditions. Although these data suggest the potential for persistence, there is, however, evidence of partial degradation by abiotic processes in natural waters, and biodegradation following acclimation, or under conditions of low inorganic phosphate. . In the presence of commonly found metal ions possessing redox properties, such as iron and copper, metal-catalysed photodegradation can be rapid, which promotes further biodegradation. HEDP is not bioaccumulative (measured BCF in fish <2).

As complexing agents, these substances could remobilise metals in the environment; however, their high degree of adsorption to sediments suggests that this is unlikely to occur.

HEDP and its salts are of low acute toxicity to fish. Acute LC_{50}/TL_{50} values determined in short-term and prolonged-term exposure tests are equal to or greater than 180 mg/l. HEDP and its salts are of low acute toxicity to aquatic invertebrates, as supported by 9 results from 5 test species. The lowest reliable acute toxic concentration was determined for HEDP for the invertebrate *Daphnia magna*, with a 48-h EC_{50} of 167 mg/l. A sub-lethal test with the oyster, *Crassostrea virginica*, yielded a 96-hour EC_{50} for effects on shell growth of 81 mg/l and a NOEC of <52 mg/l. A NOEC of 6.72 mg/l was obtained in a 28-day reproduction test on HEDP with *Daphnia magna* but its reliability could not be verified. A second reproduction test, also of non-assignable reliability, with the sodium salt gave a NOEC of 0.1 mg/l. This result is not consistent with the general pattern of a low toxicity to aquatic invertebrates.

There are no data for the effects of HEDP on sediment-dwelling organisms. However, given the low order of acute toxicity of ATMP acid and DTPMP salts to the marine sediment living amphipod *Corophium volutator*, it is not

expected that HEDP and its salts would show significant toxicity to sediment-dwelling organisms. HEDP is of low acute toxicity to sewage sludge micro-organisms (*Pseudomonas putida* 30-min EC_0: ≥580 mg/l).

The effects of HEDP observed in tests with algae are likely to be a consequence of nutrient limitation caused by complexation and not true toxicity. Thus, a 96-hour E_rC_{50} for HEDP to *Selenastrum capricornutum*[1] of 3 mg/l is likely to over-estimate the true toxicity. A 14-day NOEC for HEDP to *S. capricornutum* of 13 mg/l, which might also be subject to the potential effects of complexation, indicates that HEDP is likely to be of low chronic toxicity to algae, atlhough there is evidence that the cultures did not remain in exponential growth during the phase of the test extending from 96 hours to 14 days.

HEDP and/or its di-sodium salt are of low acute toxicity to earthworms (*Eisenia foetida* 14-day LC_{50}: >960 mg/kg dw) and terrestrial plants (*Avena sativa* 14-day EC_{50}: >960 mg/l). HEDP is of low acute toxicity to birds when administered via the dietary exposure route (*Anas platyrhynchos* and *Colinus virginianus* 14-day LC_{50}: >284 mg/kg bw).

[1]Now known as *Pseudokirchneriella subcapitata*

Exposure

Current worldwide production of ATMP, HEDP and DTPMP (and their salts) is estimated to be in the range of 50,000 to 100,000 metric tonnes annually. The major uses of HEDP and its salts are as an additive in water treatment, where its ability to both complex with metal ions, and to prevent crystalline scale deposition in solution and onto surfaces through adsorption, are utilised. The substances are also used in detergent and cleaning applications and cosmetics (HEDP only), and in the paper, textiles and photographic industries, and also in off-shore oil well applications.

The major route of environmental exposure is expected to be release, often via wastewater treatment plants, to rivers. Agricultural land could be exposed via spreading of sewage sludge. Oil well use would lead to direct exposure of the marine environment. In rivers, they are expected to partition predominantly to sediment.

Human exposure to HEDP or its salts in manufacturing and formulating is possible, but due to the use of personal protective equipment, limited to accidental situation. Where exposure can occur, dermal exposure is the most likely route of exposure. In these cases PPE is recommended. The concentration of the substance in the product, together with PPE/engineering controls are important factors in the assessment of risk associated with the hazardous properties (mainly corrosivity/irritancy). Where concentrated solutions are handled, engineering controls and PPE are used to control exposure and reduce the risk from the corrosive/irritant properties. In downstream uses, where consumer exposure is possible, much more dilute concentrations are used, which significantly reduces or removes the likelihood of corrosivity/irritancy effects.

Consumer exposure is being assessed in more detail as part of the HERA project (HERA, in progress www.heraproject.com/).

RECOMMENDATION

Human Health: The chemicals in this category are currently of low priority for further work.

Environment: The chemicals in this category are candidates for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The chemicals in this category possess properties indicating a hazard for human health. Although these hazards do not warrant further work as they are related to pH effects and chelation properties, they should nevertheless be noted by chemical safety professionals and users.

Environment:

The substances in this category possess properties indicating a hazard for the environment. In general terms across the category, these hazards do not warrant further work as they are related to acute toxicity, pH effects and metal chelation, which may become evident only at very high exposure level. However, there are 2 unverifiable tests available for chronic *Daphnia* toxicity, of which one raises concern. A further, modern study will be conducted to clarify this. If the test indicates significant chronic toxicity to aquatic invertebrates, an exposure assessment should be conducted followed by a risk assessment.

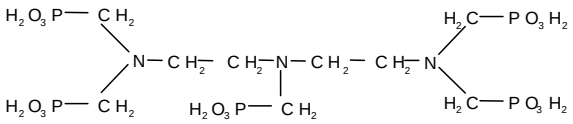
SIDS INITIAL ASSESSMENT PROFILE

Category Name	DTPMP and salts (Phosphonic Acid Compounds Group 3) Diethylene triamine penta(methylene phosphonic acid) and its sodium salts

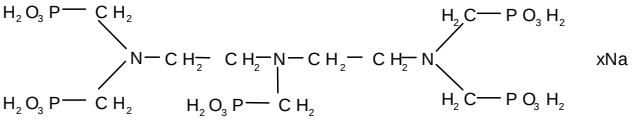
Chemical Names and CAS Numbers

Chemical name	CAS no.	Abbreviation
Diethylene triamine penta(methylene phosphonic acid)	15827-60-8	DTPMP
Diethylene triamine penta(methylene phosphonic acid), xNa Salt	22042-96-2	DTPMP-xNa
Diethylene triamine penta(methylene phosphonic acid), Na Salt	94987-76-5	DTPMP-Na
Diethylene triamine penta(methylene phosphonic acid), 2Na Salt	94987-75-4	DTPMP-2Na
Diethylene triamine penta(methylene phosphonic acid), 3Na Salt	95015-06-8	DTPMP-3Na
Diethylene triamine penta(methylene phosphonic acid), 4Na Salt	94987-77-6	DTPMP-4Na
Diethylene triamine penta(methylene phosphonic acid), 5Na Salt	61792-09-4	DTPMP-5Na
Diethylene triamine penta(methylene phosphonic acid), 6Na Salt	93841-74-8	DTPMP-6Na
Diethylene triamine penta(methylene phosphonic acid), 7Na Salt	68155-78-2	DTPMP-

Structural Formula



Diethylene triamine penta(methylenephosphonic acid)
CAS # 15827-60-8



Diethylene triamine penta(methylenephosphonic acid), xNa Salt
CAS # 22042-96-2

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

This category covers a phosphonic acid and sodium salts of that acid. The different salts are prepared by neutralising the acid to a specific pH. Data are available for the acid and some salts. The substances are commercially available as aqueous solutions only and in an environmental context the speciation will be the same. In the present context the effect of the counter-ion (sodium) will not be significant. The properties of the members of the category are consistent across all end points.

The category is expressed as Phosphonic Acid Compounds Group 3 because two other groups have been identified, with close structural analogy to the present one. Group 1 is Amino tris(methylenephosphonic acid) (6419-19-8) and its sodium salts; Group 2 is 1-Hydroxy-1,1-ethane-diphosphonic acid (CAS 2809-21-4) and its sodium and potassium salts.

Human Health

Toxicokinetic data on DTPMP and its salts are limited. The available information, together with data for phosphonic acid compounds comprising Group 1 and Group2, suggest that only minor amounts of DTPMP and its salts would enter the body after ingestion or skin contact.

The DTPMP acid and salts are of low oral and dermal toxicity. The oral rat LD_{50} is 4164 mg/kg bw and the rabbit LD_{50} is higher (>4605 mg/kg bw). The acute rat oral LD50 of the heptasodium salt lies between 5838 and 8757 mg/kg bw. The dermal LD_{50} values for the salts are >5838 mg/kg bw for the rat. For the octasodium salt, the oral LD_{50} is >3870 mg/kg bw and the dermal LD_{50} >860mg/kg bw for the rabbit. There is sufficient information from studies performed to an adequate standard, plus additional information from non-key studies, to support these values.

There is evidence that DTPMP acid is an eye irritant, although different severities were reported in the two available assays (mild and severe). While both the formulations tested contained 10% HCl, which could contribute to the irritant response, it would however appear prudent to conclude that the anhydrous acid is a severe eye irritant. Evidence from three studies on DTPMP salts indicates these are only slightly irritating to the eye.

Several studies on DTPMP acid and its salts indicate they have a low skin irritation potential. Although these studies tested formulations and therefore the limit dose for the active acid or salts was not achieved, the presence of hydrochloric acid in the formulations would be expected to exacerbate the response obtained. Therefore, in view of the very limited responses obtained, it is considered likely that the pure acid or salt, if tested to a limit dose, would be, at most, mild skin irritants.

The salt of DTPMP has been studied in a good quality 90 day feeding study conforming to OECD guidelines. Repeated exposure to 842 mg/kg bw/d (males) and 903 mg/kg bw/d (females) resulted in perturbations of iron and calcium homeostasis (in the absence of any concurrent alteration of calcium plasma levels). Changes in some blood parameters and an increase in total bone density were seen at this dose. The NOAEL for this study was therefore 92.3 mg/kg bw/day based on the mid dose female group. There are a number of further studies available on the salt, covering durations from 90 days, one year or two years. In addition to effects on iron homeostasis and haematological effects, two of these studies have reported effects on liver pathology and NOAELs down to 4 mg/kg bw/d have been assigned. As these are secondary literature, where there is insufficient information for full evaluation, the findings are not considered to outweigh the recent GLP and OECD compliant 90 day study.

Neither the acid nor the salt induces mutations in well-conducted studies in bacteria. The evidence for mutagenic potential in mammalian cells is conflicting. The acid, even when neutralized, can induce mutations at the thymidine kinase locus in mouse lymphoma L5178Y cells in the presence of S9 mix. A negative response was seen when the salt (neutralized with NaOH) was tested. The difference in outcome between the tests on the acid when neutralized with NaOH and on the salt is difficult to rationalize since the species tested should be similar for both test substances and similar dose ranges were tested. It is probable the positive response for the acid does not reflect an ability to interact with DNA due to (1) lack of structural alerts for mutagenicity, (2) lack of evidence for gene mutation potential in sub-mammalian systems and (3) lack of potential to induce gene mutations in another well-conducted assay investigating mutations at the hprt locus in CHO cells. Perturbations of pH and osmolarity are considered to be unlikely causes of the positive response due to the low concentration at which a positive response on the acid was seen (0.73 mM) and because positive responses are only seen consistently in the presence of S9. A plausible alternative explanation is the test substance interacts with S9 resulting in the formation of oxidative species. Evidence for a lack of mutagenic potential of DTPMP in vitro is supported by a negative hprt locus test and in vivo is provided by a well-conducted chromosome aberration study in rat bone marrow following gavage with doses up to 1970 mg/kg bw. Consequently DTPMP and its salt are not considered to pose a genotoxic hazard.

The reproductive NOAEL for DTPMP in the rat is 294 mg/kg bw/day for parental males and 312 mg/kg bw/day for parental females. No histopathological changes were apparent in reproductive tissue from male or female rats following gavage administration of 850-900 mg/kg bw /day of the sodium DTPMP for up to 90 days. Results from a rat reproduction study provided evidence of equivocal fetotoxicity with a NOAEL of 100 mg/kg bw/day and a NOAEL of 312 mg/kg bw/day for teratogenicity of DTPMP in the rat, however these observations were not replicated

in a developmental toxicity study on sodium DTPMP which provided a NOAEL of 1000 mg/kg bw/day for fetotoxicity and 2000 mg/kg bw/day for teratogenicity.

Environment

DTPMP is a polyphosphonic acid of molecular weight 573. The phosphonic acid function is a strong acid, and it is frequently produced as a salt for reasons of ease of use. It can form stable complexes with polyvalent metal ions. As a consequence of the ionisation over typical pH ranges, it is of high water solubility ($\geq$ 500 g/l) and low octanol-water partition coefficient (Log Kow = -3.4). Its vapour pressure is very low (1.67×10^{-10} Pa (estimated)). At pH 7, DTPMP in water will be almost fully ionised five times, with a majority of the molecules ionised six times, and some seven or eight times.

There is a possibility that the emission of a phosphonic acid could locally decrease the pH in the aquatic environment. In the normal use of these substances, their pH, concentration and water quality have to be monitored very carefully. Therefore, a significant decrease of the pH of the receiving water is not expected. Furthermore, the substances are usually used as salts with near-neutral pH, and their effects on pH are further buffered by the presence of metal ions. Generally the changes in pH of the receiving water should stay within the natural range of the pH, and for this reason, adverse effects on the aquatic environment are not expected due to release of the phosphonic acids.

DTPMP and its salts may enter the environment via normal use in water treatment applications. It is predicted and has been shown to be adsorbed by inorganic matrices, and therefore adsorption to sewage sludge and soil is strong (measured Koc = 9748). They are not readily biodegradable in laboratory studies carried out under standard conditions. Although these data suggest the potential for persistence, there is, however, evidence of partial degradation by abiotic processes in natural waters, and biodegradation following acclimation, or under conditions of low inorganic phosphate. In the presence of commonly found metal ions possessing redox properties, such as iron and copper, metal-catalysed photodegradation can be rapid, which promotes further biodegradation. DTPMP is not expected to be bioaccumulative, based on its low Log K_{ow} and read-across from the two related substances ATMP and HEDP.

As complexing agents, these substances could remobilise metals in the environment; however, their high degree of adsorption to sediments suggests that this is unlikely to occur.

DTPMP and its salts are of low acute toxicity to fish and aquatic invertebrates. The lowest reliable acute toxic concentrations determined for DTPMP are a 96-h LC_{50} for the rainbow trout, *Oncorhynchus mykiss*, that is in the range 180-252 mg/l and EC50 values determined in acute tests with aquatic invertebrates are all in excess of 150 mg/l. DTPMP is of low chronic toxicity to fish (*O. mykiss* 60-day NOEC: 25.6 mg/l). There are no chronic data for aquatic invertebrates but an acute sub-lethal test with the oyster, *Crassostrea virginica*, yielded a 96-hour EC_{50} for effects on shell growth of 155.8 mg/l and a NOEC of 55.5 mg/l.

The 2Na and 7Na salts of DTPMP are of low acute toxicity to the marine sediment living amphipod *Corophium volutator* (10-day LC_{50}: >2500 mg/kg dw). There are no reliable data describing the acute toxicity of DTPMP to sewage sludge micro-organisms.

The effects of DTPMP observed in tests with algae are likely to be a consequence of nutrient limitation caused by complexation and not true toxicity. Thus, a 95-hour E_rC_{50} for *Selenastrum capricornutum*[1] of 0.45 mg/l is likely to over-estimate the true toxicity. The true toxicity of DTPMP and its salts to algae is best represented by the 95 hour ErC50 value of >10 mg/l. This value was obtained in the only test where steps were taken to counter the effects of nutrient complexation and is therefore most likely to be indicative of true toxicity.

No data are available that describe the toxicity of DTPMP to terrestrial plants and invertebrates. DTPMP is of low acute toxicity to birds when administered via the dietary exposure route (*Anas platyrhynchos* and *Colinus virginianus* 14-day LC_{50}: >454 mg/kg bw).

[1]Now known as *Pseudokirchneriella subcapitata*

Exposure

Current worldwide production of ATMP, HEDP and DTPMP (and their salts) is estimated to be in the range of 50,000 to 100,000 metric tonnes annually. The major uses of DTPMP and its salts are as an additive in water treatment, where its ability to both complex with metal ions, and to prevent crystalline scale deposition in solution and onto surfaces through adsorption, are utilised. The substances are also used in detergent and cleaning applications, and in the paper, textiles and photographic industries, and also in off-shore oil well applications.

The major route of environmental exposure is expected to be release, often via wastewater treatment plants, to rivers. Agricultural land could be exposed via spreading of sewage sludge. Oil well use would lead to direct exposure of the marine environment. In rivers, they are expected to partition predominantly to sediment.

Human exposure in manufacturing and formulating is possible, but due to the use of personal protective equipment, limited to accidental situation. Where exposure can occur, dermal exposure is the most likely route of exposure. In these cases PPE is recommended. The concentration of the substance in the product, together with PPE/engineering controls are important factors in the assessment of risk associated with the hazardous properties (mainly corrosivity/irritancy). Where concentrated solutions are handled, engineering controls and PPE are used to control exposure and reduce the risk from the corrosive/irritant properties. In downstream uses, where consumer exposure is possible, much more dilute concentrations are used, which significantly reduces or removes the likelihood of corrosivity/irritancy effects.

Consumer exposure is being assessed in more detail as part of the HERA project (HERA, in progress www.heraproject.com/).

RECOMMENDATION

The chemicals in this category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

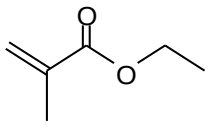
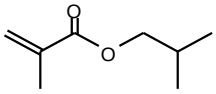
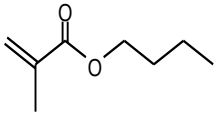
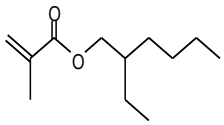
Human Health:

The chemicals in this category possess properties indicating a hazard for human health. Although these hazards do not warrant further work as they are related to pH effects and chelation properties, they should nevertheless be noted by chemical safety professionals and users.

Environment:

The substances in this category possess properties indicating a hazard for the environment. However these hazards do not warrant further work as they are related to acute toxicity, pH effects and metal chelation, which may become evident only at very high exposure level.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	97-63-2	97-86-9	97-88-1	688-84-6
Chemical Name	Ethyl Methacrylate (EMA)	Iso-Butyl Methacrylate (i-BMA)	n-Butyl Methacrylate (n-BMA)	2-Ethylhexyl Methacrylate (2-EHMA)
Structural Formula				

SUMMARY CONCLUSIONS OF THE SIAR

Category justification

The short chain (C2-C8) unsaturated linear and branched alkyl methacrylates included in this category show Structure Activity Relationship with respect to environmental toxicity, distribution and fate, and mammalian toxicity. These esters are rapidly metabolized to methacrylic acid (CAS 79-41-4) and the structurally corresponding alcohol by non-specific carboxylesterases in several tissues. Methyl methacrylate (MMA) (CAS 80-62-6), the C_1 ester, is the largest volume methacrylate ester that has been studied extensively and reviewed in the OECD HPV Chemicals Program. As such, MMA provides a robust reference chemical for this category.

Physical-chemical properties

The physico-chemical properties of MMA, EMA, i-BMA, n-BMA and 2-EHMA are as follows: boiling point: 100.5 ºC, 118.8 ºC, 155 ºC, 163 ºC and 227.6 ºC, respectively; melting point: -48ºC, <-75ºC, -35ºC, -50ºC and $\leq$ 50ºC; vapour pressure: 42, 20, 2.1, 2.1 and 0.065 hPa at 20 ºC, respectively; Log K_{ow} at 20/25 ºC: 1.38, 1.87, 2.95, 2.99 – 3.03 and 4.95 – 5.59, respectively; and water solubility: 16 g/L (20 ºC), 4.69 g/L (20 ºC), 0.47 g/L (20 ºC), 0.36 g/L (25 ºC) and 0.0016 g/L (25 ºC), respectively.

Human Health

The members of the category are of low acute toxicity by oral, dermal and inhalation routes. Any possible trend across the category would be masked by the use of limit doses in more recent guideline studies. Median oral lethal dose values (LD_{50}) are greater than 2000 mg/kg. By inhalation the median lethal concentration is likely to be in excess of 29 mg/l (circa 5000ppm). Although acute inhalation data are not available for 2-EHMA this end-point is not considered critical due to its low vapor pressure (<1 hPa @ 20 °C). These chemicals are all typically irritating to the skin of rabbits when applied under occluded conditions and upon prolonged contact. EMA is slight to moderately irritating to the eyes whereas, i-BMA, n-BMA and 2-EHMA produce, at worst, slight irritation. All four esters appear to give equivocal results in contact sensitizing studies in guinea pigs using adjuvant. Although EMA, n-BMA and i-BMA have been reported to give positive clinical challenge responses in humans, methacrylate esters have been shown to cross-react with other methacrylates esters in both animals and humans so the possibility that the inducing agent in clinical case studies may be another methacrylate ester cannot be excluded. No cross-reactivity with acrylate esters has been reported. These data conclude that the short chain methacrylate esters are weak skin sensitizers. There are no clinical case study reports linking these esters to respiratory allergy.

In a repeat oral exposure study (OECD 422) with n-BMA the NOEL in male rats was 30 mg/kg bw/day based upon reduced splenic weights and atrophy of the splenic red pulp. The NOEL in females was 300 mg/kg bw/day based upon changes in the blood and urine parameters indicative of effects on the kidneys, however, these were not confirmed histopathologically. In a similar repeated oral exposure study (OECD 422) with EHMA, the NOAEL was 100 mg/kg bw/day in male rats and 30 mg/kg bw/day in females, based on organ weight changes in kidney (absolute and relative), without confirmatory histopathology, pituitary gland (relative), and liver (relative) in males and on organ weight changes in both liver (absolute and relative) and kidney (relative only) in females.

In a subacute inhalation study in rats with n-BMA the lead effect was the development of lesions in the olfactory region of the respiratory tract. The LOEC for this effect was 952 ppm (5626 mg/m^3) and the NOEC, 310 ppm (1832 mg/m^3). No other relevant repeat dose inhalation studies are available for other members of the category; however, extensive studies have been reported on

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.

the inhalation toxicity of MMA, the reference chemical for this category. These studies consistently indicate that the lead effect is local degeneration of the olfactory tissue within the nasal cavity. For this effect a NOAEC of 25 ppm (104 mg/m^3) in a two-year inhalation study in rats was identified but only slight effects on the olfactory tissues have been observed at 100 ppm (416 mg/m^3). The mechanism of toxicity has been established as hydrolysis of the parent ester by tissue carboxylesterases to release methacrylic acid (MAA). Studies with MMA indicate that there is little or no progression of the effect from acute through to chronic exposures.

Recent inhalation studies, also in rats, have shown that EMA also produces olfactory lesions comparable to MMA following acute exposure at 200 ppm (948mg/m^3), but that alkyl-methacrylate esters larger than EMA do not elicit a toxic response at this dose level, mainly because their physicochemical characteristics prevent significant local uptake of the vapors (Jones, 2002). Based upon the available data a clear trend exists across the short-chain alkyl methacrylate category such that the NOAEC/LOAEC for olfactory nasal lesions increases with increasing ester size.

The NOAEC for olfactory lesions with EMA is, therefore, likely to be comparable to, or slightly higher than, that for MMA, i.e. 25 ppm (119 mg/m^3). In the case of i-BMA, the NOAEC is likely to be comparable to that found for n-BMA, i.e. 310 ppm (1832 mg/m^3). Considering the low vapor pressure of EHMA and that the saturated vapor concentration at equilibrium would only be 99 ppm (814 mg/m^3), it is unlikely that EHMA will cause nasal lesions under normal conditions of use. The methacrylate esters have been tested in vitro and in vivo for gene mutations, chromosome mutations and aneugenic effects over relevant dose ranges. There is no indication that the methacrylate esters in the category cause gene mutations.

Although there are no carcinogenicity studies available for any member of the category there is no relevant concern on carcinogenicity for MMA in humans and animals. Epidemiology data on increased tumor rates in MMA exposed cohorts are of limited reliability and cannot be related to MMA as the solely causal agent. On the basis of the analogy with MMA and the common, rapid metabolism and clearance of these esters from the body it is unlikely that they will represent a carcinogenic risk.

Some evidence of reproductive toxicity was demonstrated in one-generation rat reproductive toxicity studies conducted by OECD Guideline 422 with n-BMA and 2-EHMA. In the study of n-BMA, the number of corpora lutea and implantation sites was decreased at the 1000 mg/kg/day level giving a NOEL of 300 mg/kg/day. Similarly, in the study of 2-EHMA, the gestational period was prolonged and there was a decrease in the number of corpora lutea and implantation sites at the 1000 mg/kg/day level giving a NOEL of 300 mg/kg/day. In a dominant lethal study with short-term exposure to MMA, no effects on male fertility in mice were observed when animals had been exposed to up to 9000 ppm for a period of 5 days before mating.

High inhalation exposures to n-BMA and EMA in rats induced developmental toxicity characterized by reduced fetal body weight, but produced no embryolethality or teratogenicity even at concentrations producing overt maternal toxicity. Likewise, MMA does not cause developmental effects in rats even at inhalation exposure levels that produce maternal toxicity. With oral exposures, some evidence of developmental toxicity with n-BMA or EHMA was shown by the OECD Guideline 422 screening study (i.e. decreased number of neonates on Day 0 of lactation, decreases in parturition and live birth indices and total number of offspring in the 1000 mg/kg/day dose group), however, protocol limitations in this screen would suggest more weight be applied to definitive teratology studies. In studies of the metabolites of the butyl methacrylates (methacrylic acid and the corresponding alcohol), no effects on development were observed following oral exposure to rats and rabbits with isobutanol or by inhalation to iso-, or tertiary-butanol. Although n-butanol did produce increased rudimentary cervical ribs at 8000 ppm (about 50x the TWA), it occurred only in the presence of maternal toxicity. It is unlikely that exposure to butyl methacrylate esters with subsequent hydrolysis to methacrylic acid and the corresponding alcohol would produce blood levels of the alcohol high enough to result in developmental toxicity. Although no data are available on the parent ester i-BMA one would anticipate that by analogy with n-BMA, EMA, EHMA, and MMA, this chemical would not pose a developmental toxicity hazard.

A dose-related response was observed with EMA in the Morris Water Maze suggestive of potential for neurotoxicity. However, the clinical observations are more consistent with general systemic toxicity rather than a specific neurotoxic effect and the reviewing pathologists considered the reported spinal cord vacuolation to be artifact and the lesions reported in peripheral nerve and brain not to be treatment-related.

Environment

Model calculations indicate that the esters will be rapidly photolyzed in the atmosphere under the influence of atmospheric OH▪ radicals. They are stable under acidic and neutral conditions and hydrolyze rapidly at pH 9 and above. Based on Mackay Level III calculation, short-chain methacrylate esters will predominantly partition into the air, with the smaller esters below 2-EHMA will have a significant presence in the water phase. While EMA, i-BMA, and n-BMA do not have a significant presence in soil or sediments, EHMA has a potential to partition into soil sediments when released to the aquatic environment. All esters of the category are readily biodegradable. Based on the Log K_{ow} values of the short chain methacrylate esters the potential for

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.

bioaccumulation is for MMA, EMA, i-BMA and n-BMA. In a bioconcentration test with fish, 2-EHMA showed a low bioconcentration factor of 37. Elimination from the aquatic compartment is expected to be rapid, evaporation and biodegradation being the main processes involved.

The esters are of low to high toxicity to aquatic organisms as toxicity increases with increasing lipophilicity and molecular size across the category with EMA being the least toxic and 2-EHMA the most toxic. This trend was consistent between all three trophic levels studied (algae, daphnia and fish) as was the general level of toxicity. The acute fish toxicity (96h LC_{50}) ranges from 100 mg/L (EMA) to 2.78 mg/L (2-EHMA). Similarly, acute invertebrate toxicity (48h EC_{50}) ranges from >66 mg/L for EMA to 4.6 mg/L for 2-EHMA and, acute algal toxicity (72h EC_{50}) ranges from >110 mg/L for EMA to 7.68 mg/L for 2-EHMA. This general trend was also observed in the long-term and chronic aquatic tests. No chronic fish studies were available for any member of the category. Chronic aquatic invertebrate data (21-day) range from a NOEC of 18 mg/L (EMA) to 0.105 mg/L (2-EHMA). Chronic algae studies (72-hour) range from a NOEC of 110 mg/L (EMA) to 5.8 mg/L (i-BMA). All data that are considered reliable for chronic aquatic toxicity support the trend of increasing toxicity with increasing molecular weight and lipophilicity.

Exposure

EMA, i-BMA, n-BMA and 2-EHMA are used by industry to make polymers. Polymers based upon EMA are used to make automotive coatings, nail sculpturing, inks and dental products; polymers based on i-BMA/n-BMA are used the manufacture of automotive coatings, lacquers and enamels, adhesives, oil additives (lubricants), emulsions for textile, leather and paper refinishing and dental products; polymers based upon n-BMA are also used in the manufacture of toners, architectural paints, , powder coatings and floor polishes; polymers based on 2-EHMA are used in lubricants, automotive coatings, paints, printing ink, additive agents, adhesives, leather, paper, lacquer and textile industries. Estimated Global production is EMA (10 kt/y); n-BMA (100 kt/y); i-BMA (10 kt/y) and 2-EHMA (2.5 kt/y) (based upon US figures, comparable production in Europe and an estimated production of 1.7kt/y 2-EHMA in Japan). N-BMA/i-BMA may be released into the environment in fugitive and stack emissions or in wastewater during its production and use in the manufacture of resins and polymers. Estimated releases into the environment from monomer and polymer production in the EU are < 0.3 t/yr n-BMA and < 0.15 t/yr i-BMA to air; < 0.15 t/yr n-BMA and < 0.05 t/yr i-BMA to water and none to soil. For n-BMA/i-BMA processing (polymerization) limited available data indicate losses of 15 g/t monomer to air and 10 g/t monomer to water. The potential for exposure to workers occupationally involved in the production of these monomers and in the subsequent manufacture and use of polymers made from these monomers is low. These monomers are used almost exclusively in the production of polymers for use by industry or consumers. Since end-use consumer products contain only trace levels of esters (as a result of polymerization), consumer exposure to methacrylate monomers is likely to be extremely low. Small quantities of EMA, and to a lesser extent i-BMA, are used in the manufacture and repair of artificial nails. Published data on occupational exposure in nail salons indicates that inhalation exposures can occur but typical levels are relatively low and below current exposure limits. The potential for dermal exposure in this use scenario cannot be excluded. Methacrylate monomers are also used in the manufacture of polymer-based dentures and prosthetics by trained dental technicians. Levels of residual monomers in these devices are controlled under an ISO standard; hence exposure via the oral mucosa will be very low.

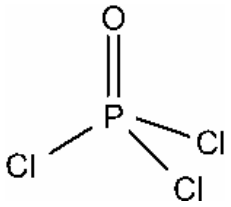
RECOMMENDATIONS AND NATURE OF FURTHER WORK RECOMMENDED

Health: These chemicals possess properties indicating a hazard for human health (skin sensitization, skin and eye irritation). Based on data presented by the Sponsor country, exposure to humans is anticipated to be low, and therefore these chemicals are currently a low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The category members possess properties indicating a hazard for the environment (acute toxicity between 1 and 100 mg/L). However, the chemicals in this category are of low priority for further work because of their rapid biodegradation and their limited potential for bioaccumulation

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	10025-87-3
Chemical Name	Phosphoryl trichloride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Phosphoryl trichloride is hydrolyzed in seconds or minutes in water or moist air. Studies on metabolism and toxicokinetics of the parent compound are not feasible. Distribution in the body is limited due to hydrolysis. Phosphoryl trichloride is a toxicant acting at the portal-of-entry. It is unlikely to reach organs distant from the portal of entry. Therefore, systemic toxicity not related to the effects of irritation is not expected by any route. The products of hydrolysis, hydrochloric acid and phosphoric acid, also act at the portal of entry.

The acute toxicity of phosphoryl trichloride following inhalation is high. The 4-h-LC_{50} of phosphoryl trichloride is 48.4 ppm (308 mg/m³) to 11.1 ppm (71 mg/m³) for rats and 52.5 ppm (335 mg/m³) for guinea pigs. Clinical signs included severe respiratory tract irritation, nasal discharge and eye irritation. The oral LD_{50} was determined as 36 to 380 mg/kg bw for rats showing a very steep dose/mortality relation in individual studies. After dermal exposure the LD_{50} was > 250 mg/kg in rabbits. Signs of toxicity were decreased locomotor activity, necrosis and eschar.

Phosphoryl trichloride reacts with water, forming hydrochloric acid and phosphoric acid. Due to this hydrolytic reaction, phosphoryl trichloride is corrosive to the skin, eyes and respiratory tract. Studies with phosphoryl trichloride concerning sensitising properties are not available. The hydrolysis product hydrochloric acid gave no indication for a sensitising potential in humans and experimental animals. Data on phosphoric acid, the second hydrolysis product, are not available, but no specific effects are expected due to its structure.

From a 4 months inhalation study with phosphoryl trichloride in rats, a NOAEC could not be derived, since weight loss, respiratory irritation and increased kidney weights were still observed at the lowest exposure level of 0.48 mg/m^3 (=LOAEC). The evaluation of this study is limited as methodology and results were published in little detail. Most findings were confined to the site of first contact and can be explained by the irritating/corrosive properties of the compound and its degradation products. The LOAEC found in a 90-day study with hydrochloric acid was 15 mg/m³. The excess phosphate produced by hydrolysis of phosphoryl trichloride may play a role in the development of effects on kidney, bone and calcium levels in animals. Also by other routes (oral, dermal) phosphoryl trichloride is expected to produce effects at the site of first contact (irritation, corrosion). The long term effects observed in humans (chronic bronchitis, angina, sleeping disorders) are considered as sequelae of the irritation in the lungs which after prolonged periods may lead to an impairment of lung function.

Phosphoryl trichloride as well as the hydrolysis product hydrochloric acid did not show mutagenic activity in a bacterial mutagenicity assay. As phosphoryl trichloride decomposes to hydrochloric and phosphoric acid in aqueous media the resulting acidity of the hydrolysis products may cause unspecific effects of low pH in in-vitro tests. The

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.

change in pH may induce chromosomal aberrations and other DNA damage. Specific effects of phosphoryl trichloride are not expected, due to the rapid hydrolysis. In vivo, the hydrolysis products, phosphoric and hydrochloric acid, will be neutralized immediately in the physiologic medium at low concentrations. The reduced pH levels could lead to chromosomal changes and DNA damage at the portal-of-entry of phosphoryl trichloride. However, it is unlikely that systemic changes in pH would occur after exposure to phosphoryl trichloride, that are sufficient in magnitude to induce this effect in distant tissues or organs. Due to the corrosive nature of phosphoryl trichloride the performance of studies in animals with doses inducing corrosive effects is not warranted.

No carcinogenicity studies with phosphoryl trichloride were identified. The hydrolysis product hydrochloric acid gave no indications for an increased tumor incidence after life-time exposure in laboratory animals. Data on phosphoric acid, the second hydrolysis product, are not available, but no specific effects are expected. At low concentrations the hydrolysis products, phosphoric and hydrochloric acid, will be neutralised immediately in the physiologic medium at the portal of entry. Nevertheless prolonged irritation could give rise to a constant stimulus to local cell proliferation.

Studies with phosphoryl trichloride concerning effects on fertility and development were not available and there were also no data on fertility effects for the hydrolysis products phosphoric acid and hydrochloric acid. Because phosphoryl trichloride as well as its hydrolysis products is a toxicant acting at the portal-of-entry, and because it is unlikely to reach the reproductive organs or the embryo/fetus, toxicity to reproduction or developmental toxicity in mammals are not likely to occur following exposure to phosphoryl trichloride by any route. Studies with PCl_3 did not show respective effects. The other product of hydrolysis and subsequent partial neutralisation of phophorus trichloride, mono sodium phosphite, gave also no indication of a carcinogenic potential after long term oral exposure.

Environment

Phosphoryl trichloride is a moisture/water sensitive fluid with a melting point of 1.3 °C, a boiling point of 105.1 °C, and a density of 1.675 g/cm³ at 20 °C. The vapour pressure of the substance is 53.3 hPa at 27.3 °C. The log K_{ow}, the water solubility and several other parameters cannot be determined due to hydrolysis. Phosphoryl trichloride hydrolyzes completely in water within less than 10 s at 20 °C (via the hydrolysation intermediate phosphorodichloric acid), forming phosphoric acid and hydrochloric acid. Any emission into water, air, or the terrestrial compartment would be affected by humidity and also results in the formation of the hydrolysis products. Hydrochloric acid dissociates readily in water causing a pH shift which determines the impact of phosphoryl trichloride on aquatic life. The tolerance of water organisms towards pH is diverse. Recommended pH values for test species listed in OECD guidelines are between 6 and 9.

Phosphoric acid is of medium acidity (pK_a = 2.1) and partly dissociates in water causing a pH shift. Phosphoric acid and phosphates may affect aquatic life due to their fertilizing effect. Several aquatic toxicity tests have been undertaken in non-buffered solution. The observed toxicity effects in these studies can be attributed to the acidity of the degradation products and are not used for the hazard assessment. Acute toxicity of phosphoryl trichloride to fish was evaluated by using fish tests with phosphorus trichloride and phosphorus pentachloride. Toxicity of phosphorus trichloride (buffered) on *Danio rerio* (tested according to the German guideline proposal "Lethal effects on *Brachydanio rerio*") yielded a 96 h-LC_0 (nominal concentration) ≥ 1000 mg/l.

Tests with invertebrates were done with phosphoryl trichloride and phosphorus trichloride, for proving the validity of the evaluation approach. With *Daphnia magna* an EC_{50} (48 h) of > 100 mg/l in buffered solution was determined for both substances (92/69/EEC, method C.2). Algal toxicity was determined with phosphoryl trichloride and phosphorus trichloride. In a growth inhibition test with *Desmodesmus subspicatus* (92/69/EEC, method C.3) in buffered solution no effect was observed at 100 mg/l (nominal).

There is no result available on chronic toxicity. With activated sludge a 3 h-EC_{50} of 9450 mg/l (nominal) and an EC_0 of 3520 mg/l (nominal) were measured according to the ISO 8192 (pH not reported) for phosphorus trichloride.
There are test results available for acute testing from three trophic levels (all in buffered media). Using the lowest acute test result (> 100 mg/l) and an assessment factor of 1000 (EU Technical Guidance Document), a $PNEC_{aqua}$ > 0.1 mg/l is obtained.

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.

Exposure

The global production capacity of phosphoryl trichloride was estimated to be 0.2 million tonnes for about 15 producers in 2002. Approximately 0.15 million tonnes/year of the manufacturing capacity are in the OECD countries and 0.05 million tonnes/year in non-member countries.
Phosphoryl trichloride is a basic chemical which is used industrially as an intermediate. Because of its reactivity phosphoryl trichloride has a large number of applications as an intermediate in chemical processes (percentages reported for the USA 2001):

- Plastics and elastomers additives (55 %)
- Functional fluids, e.g. phosphate ester hydraulic fluids (22 %)
- Pesticides (7 %)
- Lubricant oil additives (4 %)
- Surfactants and sequesterants (2 %)
- Miscellaneous (10 %)

At one company in the Sponsor country phosphoryl trichloride is manufactured and processed in closed systems.
The exhausts from manufacturing and processing (including filling) of phosphoryl trichloride are connected to air washing units. Thus, at this company, during production and processing virtually no phosphoryl trichloride is emitted into the atmosphere. Due to water-free production, processing, and rapid hydrolysis phosphoryl trichloride is not detectable in the wastewater. In this company, the exposure of workers is well below the maximum admissible concentration of phosphoryl trichloride in the workplace air (MAK) of 1.3 mg/m^3 (0.2 ppm). The exposure of workers to the hydrolysis product hydrochloric acid is also well below the MAK value of 8 mg/m^3 (5 ppm) for hydrogen chloride. Immunoglobulines against phosphoryl trichloride have not been detected.

No direct use is known. Phosphoryl trichloride is not listed in the Norwegian and Swiss product registers. In the Finnish, and Swedish product registers, in total, there are about a dozen industrial preparations, all with a non-dispersive use in closed systems. Entries in the Danish Product Register are confidential. An exposure of consumers to phosphoryl trichloride is unlikely to occur.

The use of phosphoryl trichloride as a solvent in cryoscopy respectively as an anhydrous solvent in general is limited to some scientific laboratories. Phosphoryl trichloride can be converted by multistage -chemical synthesis to nerve gases. Therefore the production and export of phosphoryl trichloride is stringently controlled under the International Chemical Weapons Convention.

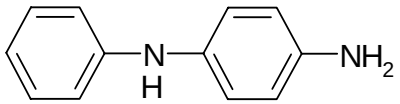
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (acute toxicity, corrosiveness). Based on data presented by the Sponsor country (relating to production by one producer which accounts for 5 – 25 % of global production and relating to the use pattern of several OECD countries), exposure is limited to the technically feasible extent in occupational settings in the sponsor country. There is no exposure of consumers. No recommendation for further testing within the context of the SIDS program is therefore warranted. Although there are no valid data regarding reproductive effects, due to the fast hydrolysis it is unlikely that POCl3 could reach organs and tissues distant from the site of first contact, therefore, and due to the corrosive properties, studies in animals are not warranted. The chemical is currently of low priority for further work.

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	101-54-2
Chemical Name	4-Aminodiphenylamine (4-ADPA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

4-Aminodiphenylamine (4-ADPA) can be taken up into the body by the oral and dermal routes of exposure as evidenced by the results of animal studies. In rats the substance and/or its metabolites are eliminated mainly with the feces, but can also be detected in the urine. An indirect evidence of dermal absorption in humans is provided by the detection of 4-ADPA in the urine of one worker after a single dermal contact with the substance. 4-ADPA can bind to hemoglobin and proteins.

Methemoglobinemia was observed in cats after single oral administration. In rats, the oral LD_{50} value was determined as 720 mg/kg bw. Clinical signs of toxicity included ataxia, nasal, oral and ocular discharge, difficult breathing, and hypoactivity. The acute dermal toxicity of 4-ADPA was very low with an LD_{50} value of greater than 5,000 mg/kg bw in rabbits. The only clinical signs noted in some animals were nasal and ocular discharge and single occurrences of red and/or swollen eyes.

4-ADPA was not irritating to the skin of rabbits (OECD TG 404). Transient irritant effects were observed after instillation of 4-ADPA into the eyes of rabbits (OECD TG 405). 4-ADPA is a skin sensitizer in guinea pigs. Skin sensitizations have been reported also in humans. In the majority of human case reports, however, there was evidence that the sensitizing effects observed were due to cross-reactivity with antibodies to structural analogues of 4-ADPA such as p-phenylenediamine.

The NOAEL in a rat 90-day feeding study with male rats was 1,000 ppm (approximately 100 mg/kg bw/day). In this study slight anemia and changes in liver enzyme levels were seen at approximately 250 mg/kg bw/day (2,500 ppm). At 5,000 ppm (approximately 435-500 mg/kg bw/day) pathological changes in the liver were found at the histological examination, and at 7,500 ppm (approximately 555-750 mg/kg bw/day) histopathological changes were found in the testes (degeneration of seminiferous tubules). The NOAEL in a rat carcinogenicity study with dietary exposure over 78 weeks was 1,200 ppm (approximately 60-120 mg/kg bw/day; highest dose tested).

4-ADPA did not induce gene mutations in standard bacterial and mammalian cell tests (Ames, HPRT) with and without metabolic activation. The substance was, however, genotoxic in the mouse lymphoma test, and also demonstrated the potential to induce chromosomal aberrations *in vitro*. 4-ADPA did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro* and *ex vivo*. A bone marrow micronucleus test in male mice was negative. Although some systemic toxicity was observed in the high dose animals, there was no evidence that an adequate exposure of the target tissue was achieved. Based on the weight-of-evidence, and taking into account structure-activity relationship information, an in vivo genotoxic activity of 4-ADPA cannot be excluded.

Early feeding studies in rats and mice revealed no evidence of carcinogenicity but they were not adequate to judge the carcinogenic potential of 4-ADPA, mainly because of the shortened period of administration of the test substance, i.e. only 78 weeks in rats, and 41-48 weeks in mice, respectively.

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.

There was no fertility study available. In a 90-day feeding study on male rats, degeneration of seminiferous tubules in the testes, accompanied by marginal changes in enzyme activities (LDH and hyaluronidase) were found at a severely toxic dose level (about 7,500 ppm = 555-750 mg/kg bw/day). The NOAEL for testicular toxicity was determined as 5,000 ppm (approximately 435-500 mg/kg bw/day). In early NTP carcinogenicity studies with rats and mice no histological changes in the reproductive organs of both sexes were observed up to and including the highest doses tested (corresponding to approximately 60-120 mg/kg bw/day for the rat. Due to severe limitations in the study no reliable dose could be derived for the mice).

Developmental toxicity (significantly increased resorptions, reduced fetal weight and increased fetal anomalies) was observed in two reliable gavage studies on CD rats, exposed from gestational day 6 to 15 to doses (vehicle: corn oil) that caused clear maternal toxicity (≥ 100 mg/kg bw/day), as evidenced by significantly decreased weight gain and food consumption. The maternal and developmental NOAELs were identified at 50 mg/kg bw/day.

Environment

4-ADPA is a brown to purple crystalline solid substance with a melting point of 72.1 to 74.6 °C. According to the flask method the substance is soluble in water to a value of 504 mg/l at 20 °C. pKa-values of 4.4 (pKa1) and 0.72 (pKa2) are reported. The vapor pressure was experimentally determined to be 7.6×10^{-5} Pa at 20 °C. A log K_{ow} value of 1.82 was calculated. The flash point of the substance is 193 °C. From the water solubility and vapor pressure, a Henry´s Law Constant of 2.8×10^{-5} Pa m^3 mol^{-1} at 20 °C is calculated indicating a low potential for volatilization from surface waters. According to Mackay fugacity model level I the main target compartment for 4-ADPA is water (99 %).

In air, the substance is indirectly photodegraded with a calculated $t_{1/2}$ = 1.9 h and will also undergo direct photolysis. In water, indirect photodegradation was shown to occur in the presence of a photosensitizer. In anaerobic buffer solutions with acid till neutral pH, the half life period of 4-ADPA is in the range of months. At higher pH the abiotic degradation was faster, however, a half-life could not be derived. Under aerobic conditions and in presence of nutrient medium containing traces of heavy metals, stability of the substance is clearly reduced. A half-life of 2.5 d can be estimated for 20 °C.

4-ADPA is not readily biodegradable. In a Zahn-Wellens test with industrial sludge 100 % DOC elimination was observed within 7 days. The calculated log K_{ow} value (log K_{ow} = 1.82) and a calculated BCF of 7 indicate that there is a low potential for bioaccumulation in aquatic organisms. The calculated K_{oc} (K_{oc} = 95) suggests that 4-ADPA has a low sorption potential. However, as it cannot be excluded that significant adsorption to sewage sludge was observed in the Zahn Wellens test, a higher adsorption than predicted from the log Kow could be expected also in the soil compartment. Using EPIWIN a Koc value of 3000 can be estimated.

Concerning the toxicity of 4-ADPA towards aquatic species experimental results of tests with fish, *Daphnia*, and algae are available. In the acute studies no analytical monitoring of the test substance concentration was performed. Therefore, the half-life of 2.5 d was used to derive effective concentrations from the nominal values.

In an acute fish test (*Danio rerio*) a 96 h LC_{50} of 1.9 mg/l (nominal, 1.1 mg/l effective) was observed. According to a standard procedure equivalent to OECD Guideline 202 an EC_{50} (48 h) of 0.37 (nominal, 0.28 mg/l effective) was reported for *Daphnia magna*. The toxicity of 4-ADPA to algae was studied in a test according to DIN 38412, part 9, without analytical monitoring. *Desmodesmus subspicatus* showed 72 h EC_{50} values (nominal) on growth rate of 4.8 mg/l 4-ADPA (3.2 mg/l effective). and on biomass of 2.4 mg/l (1.6 mg/l effective). In this test a nominal 72 h EC_{10} value of 1.8 mg/l (1.2 mg/l effective) was obtained which is considered as a NOEC.
The inhibitory effect of 4-ADPA to nitrification was studied with microorganisms of non-adapted sludge in both a semi-continuous and continuous culture system. An EC_{50} of nominal 30 mg/l 4-ADPA (26 mg/l effective) was determined.

A chronic test was performed with *Daphnia magna* during 21 days for immobilisation and reproduction in semi-

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.

static system with analytical monitoring by GC/MSD. Nominal EC_{50} values for immobilisation of 0.52 mg/l (0.34 mg/l effective) and of 0.1 mg/l (0.07 mg/l effective) for reproduction rate were observed. The nominal NOEC for reproduction was 0.04 mg/l (lowest tested concentration). The effective NOEC for reproduction is estimated to </= 0.01 mg/l.

It has to be considered that the toxicity observed in the reported studies was caused both by the 4-ADPA as well as by the degradation products due to the instability of the test substance.

From the lowest acute effect value of 0.28 mg/l a PNEC of 0.28 ug/l can be derived using an assessment factor of 1000, as no definitive NOEC can be derived from the chronic *Daphnia* study.

Tests on terrestrial species are not available.

Exposure

The global manufacturing capacity of 4-ADPA was about 140,000 tons in 1995. 4-ADPA is nearly exclusively used as an intermediate for the manufacturing of antiozonants (ca. 20 producers) for the rubber industry. Further uses are as a dye intermediate and as component for hair dyes.

The manufacturing of dyes is assumed to be equivalent to 200 - 300 t/a of 4-ADPA, less than 0.5 % of the 4-ADPA manufactured. In Germany the production of these textile dyes has been discontinued in 1990. The use of 4-ADPA in hair dyes is currently allowed in the EU. 4-ADPA is not used as an ingredient in hair dyeing products manufactured by the major suppliers in Europe, but 4-ADPA containing products are offered by other companies via the Internet. Consumers may also be exposed to 4-ADPA through contact with rubber products containing 4-ADPA as residue. According to the SPIN database 4-ADPA was present in 9 consumer preparations in Sweden in 2002.

Releases of 4-ADPA into the environment may occur during manufacturing and processing, in the rubber industry from the use of antiozonants containing 4-ADPA as residue, from the utilization of rubber products and from hair dyeing and other direct uses of the substance.

At the only manufacturing and processing site in the Sponsor country nearly no 4-ADPA was emitted into the environment in 2002. The effluent concentrations were below the detection limit of 10 µg/l. No information is available from other sites.

Losses of 4-ADPA from rubber articles into the environment, including tyre abrasion, evaporation from rubber surfaces, and losses from landfilled rubber wastes, is estimated to be 4 t/a in Germany.

Workplace air sampling of precursors and auxiliaries, which are thought to be indicators of any exposure, suggest that the exposure of workers to airborne 4-ADPA is negligible in these manufacturing and processing workplaces. Biological monitoring for 4-ADPA in workers show that urinary 4-ADPA levels and blood levels of 4-ADPA adducts with hemoglobin are below the detection limits.

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

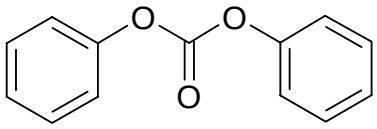
Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health. Based on data presented by the Sponsor country, exposure is controlled in occupational settings. Consumers may be exposed to 4-ADPA through the use of hair dye products and rubber products. It is therefore recommended that countries perform an exposure assessment, and, if then indicated, a risk assessment.

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: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment. Releases of 4-ADPA into the environment may occur during manufacturing and processing, in the rubber industry from the use of antiozonants containing 4-ADPA as residue, from the utilization of rubber products and from hair dyeing and other direct uses of the substance (cf. information from product registers). Therefore, an exposure assessment and, if then indicated an environmental risk assessment is recommended. This should also include further investigations on the identities and properties of degradation products.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	102-09-0
Chemical Name	Diphenyl carbonate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute dermal toxicity of diphenyl carbonate is relatively low with LD_{50} values exceeding 2000 mg/kg bw in rats and rabbits (no clinical signs noted). The acute oral LD_{50} in rats was 1500 mg/kg bw, with clonic convulsions as main clinical sign appearing at doses near to or exceeding the LD_{50} value. There are no acute inhalation studies available.

Diphenyl carbonate was not irritating to the skin and eye of rabbits (OECD TG 404, 405). Diphenyl carbonate showed no skin sensitisation potential in a Buehler patch test on 10 guinea pigs, limited by the small number of treated animals.

Repeated oral dosing of rats with diphenyl carbonate over 11 weeks (males) or 18 weeks (females) led to increases in liver weight and to hepatocellular hypertrophy and histopathological changes in the adrenals in males at a dietary concentration of 5000 ppm (about 427 mg/kg bw/day), and in females of 1500 ppm (about 219 mg/kg bw/day). At 1500 ppm, females exhibited also morphological changes in the ovaries (increased number and mononuclear infiltration of corpora lutea, granulated luteal cells, hypertrophic ovarian interstitial cells). The NOAEL in males was 1500 ppm (about 132 mg/kg bw/day) and in females about 50 mg/kg bw/day.

Diphenyl carbonate showed no mutagenic properties in bacterial and mammalian cell gene mutation assays performed according to current guidelines. In the *in vitro* chromosome aberration assay diphenyl carbonate led to increased frequencies of structural chromosomal aberrations in V79 cells both in the absence and in the presence of metabolic activation. This positive result could not be confirmed *in vivo* by two mouse bone marrow micronucleus assays performed according to current guidelines and with evidence of target cell exposure. An *in vivo/in vitro* UDS assay on rat liver, also performed according to current guidelines with oral doses up to the MTD, gave negative results. It is concluded that the genotoxic properties observed *in vitro* are not expressed *in vivo.*

In repeated dose toxicity studies on rats, diphenyl carbonate led to increased organ weights and morphological alterations in adrenals and ovaries. These effects did not influence reproductive performance in a one-generation dietary study on rats (OECD TG 415/416; NOAEL for fertility: 15 000 ppm = about 1561/2432 mg/kg bw/day for males/females; highest tested dose).

In a developmental toxicity study on rats according to OECD TG 414, daily gavage administration of 750 mg diphenyl carbonate/kg bw/day to pregnant rats on gestation days 6 to 19, led to severe maternal toxicity (mortality, convulsions, piloerection, body weight loss). Fetuses of this dose group showed reduced body weights and increased incidences of unspecific malformations (mainly dysplastic forelimb bones). The NOAEL for maternal toxicity and developmental toxicity of diphenyl carbonate in rats was 50 mg/kg bw/day. At 200 mg/kg bw/day slight maternal toxicity occurred and a retarding effect on fetal skeletal ossification of toes and cervical vertebral bodies could not be

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.

completely excluded.

Environment

Diphenyl carbonate is a white solid (flakes) with a melting point of 78.8 °C, and a boiling point of 302 °C. The density of the solid is 1.272 g/cm^3 at 14 °C. The vapour pressure is 0.014 Pa at 20 °C. The log K_{ow} is 3.21 - 3.28. The solubility of the substance in water is ca. 13 mg/l at 20 °C. The flash point is 168 °C.

Diphenyl carbonate hydrolyses under environmental conditions forming phenol and carbon dioxide. A study on the abiotic degradation of diphenyl carbonate in water predicted that the test substance has a $t_{1/2}$ of 39.9 h at pH 7 and 25 °C.

According to a Mackay Level I calculation the favourite target compartment of the substance is water with 72.2 % (soil 11 %, sediment 11 % and air 6 %). Henry's law constants of 8.59 Pa × m^3 mol^{-1} (calculated according to the Bond method) and 0.23 Pa × m^3 mol^{-1} respectively (derived from water solubility and vapour pressure) indicate that the compound has a slight to moderate potential for volatilization from surface waters. These results should only be considered of theoretical interest since the calculation programs are adequate for substances which show stability in water. The calculated half-life of diphenyl carbonate in air due to indirect photodegradation is $t_{1/2}$ = 4.0 days. Due to the low absorption in the UV-B range, no direct photodegradation is expected.

Diphenyl carbonate is not readily biodegradable but biodegraded by adapted microorganisms. After 28 days 37 % of the test substance had been degraded in a closed bottle test (Directive 92/69/EEC, C.4-E). With adapted domestic sewage, more than 99 % of the test substance had been degraded after 20 days in another closed bottle test (OECD TG 301 D).

According to the bioconcentration factor BCF = 66.9, calculated from the octanol-water partition coefficient the substance has a low potential to bioaccumulate in aquatic organisms. With a calculated K_{oc} value of 3926, diphenyl carbonate could be regarded as a substance with high geoaccumulation properties. However, due to hydrolysis geoaccumulation is not expected.

For fish (*Danio rerio)* the acute toxicity (LC_{50}, 96 h) of diphenyl carbonate (Directive 92/69/EEC, C.1) was 3.9 mg/l (effective concentration; nominal concentration: 10.0 mg/l). The acute toxicity (EC_{50}, 48 h) of diphenyl carbonate to the invertebrate *Daphnia magna* (Directive 92/69/EEC, C.2) was 6.5 mg/l (effective; nominal: 14.2 mg/l). Concerning the algal toxicity (Directive 92/69/EEC, C.3), for *Desmodesmus subspicatus* a 72 h-E_rC_{50} of 0.9 mg/l (effective; nominal: 2.4 mg/l) for the growth rate and a 72 h-E_bC_{50} 0.5 mg/l (effective; nominal: 1.4 mg/l) for the integral of biomass were determined. The corresponding 72 h-NOEC obtained from growth rate and biomass were 0.22 mg/l and 0.11 mg/l, respectively (effective; nominal 0.63 mg/l and 0.31 mg/l, respectively). The corresponding 72 h-LOEC obtained from growth rate and biomass were 0.44 mg/l and 0.22 mg/l, respectively (effective; nominal 1.25 mg/l and 0.63 mg/l, respectively).

Based on the lowest effect concentration observed for the algae a Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000. Using the effective 72 h-E_rC_{50} of 0.9 mg/l (growth rate) found for the algae species *Desmodesmus subspicatus* a $PNEC_{aqua}$ of 0.9 µg/l was determined.

Exposure

Phosgenation of phenol is the most important method for producing diphenyl carbonate. In 2002, the world wide production capacity of diphenyl carbonate is estimated to be 254 000 metric tonnes (Western Europe 141 000, Japan 61 000, Far East (excl. Japan) 52 000) by about 10 producers. The total manufacturing capacity of the sponsor company amounts to 10 000 - 50 000 tonnes/a in 2002 in Belgium (no production in the Sponsor country).

Diphenyl carbonate is a chemical intermediate mainly used for the synthesis of aromatic polycarbonates. It is also

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.

used for the synthesis of aliphatic polycarbonates and some aliphatic mono-isocyanates. Diphenyl carbonate is listed in the Danish, Finnish, Norwegian, and Swedish product registers as a product with industrial applications. No consumer applications are listed. Based on this data no exposure of the environment due to releases from consumer products occurs.

At the Sponsor company, diphenyl carbonate is manufactured and processed in closed systems. The exhausts from manufacturing and processing of diphenyl carbonate are connected to absorbing units, thermal exhaust purification plants and air washing units, thus virtually no emissions of diphenyl carbonate occurred into the atmosphere.

Due to the water-free processing processes emissions into wastewater may occur only in the case of cleaning procedures. The wastewater of the production plant is treated with activated carbon and subsequently in a biological wastewater treatment plant. For the biological wastewater treatment plant an effluent concentration of < 2 µg/l is calculated. Using the local dilution factor of 554, this results in a local PEC of <0.0036 µg/l. Emissions of diphenyl carbonate from polycarbonate resins were 0.14 - 4.94 mg/m^3 exhaust stream during experimental extrusion.

There are no environmental monitoring data available for diphenyl carbonate.

Occupational exposure at production and processing sites of the Sponsor company is controlled and the concentration of diphenyl carbonate is currently below the detection limit of 0.003 mg/m^3 (time weighted average). Based on data presented by the Sponsor company, consumer exposure to diphenyl carbonate via the environment is anticipated to be low.

Diphenyl carbonate is used for the manufacturing of food contact material. Based on a very low migration from the food contact material into food, and based on the toxicological data, the European Scientific Committee on Food classified diphenyl carbonate in “List 3”, i.e. substances for which an ADI or TDI could not be established, but where the present use could be accepted. In the EU, the use is restricted to a maximum limit of 0.05 mg/kg of food.

No consumer preparations containing diphenyl carbonate are listed in the Nordic product registers.

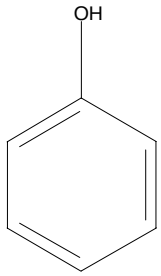
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

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

Environment: The chemical 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 approximately 4 % to 20 % 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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-95-2
Chemical Name	Phenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Phenol is well absorbed via gastrointestinal and respiratory tract and the dermal route in animals and man. Concerning the oral route a high absorption was measured in rats, sheep and pigs with 90, 85, and 84% of the orally administered phenol dose of 25 mg/kg bw after 8 h. Volunteers exposed to phenol concentrations of 6-20 mg/m3 via inhalation absorbed 60 to 88% of the substance. After dermal application of phenol to rats about 80% of the applied dose was absorbed. Distribution of phenol in body tissues occurs rapidly. Phenol is metabolized to sulfate and glucuronide conjugates. Excretion via urine is the main elimination pathway of phenol metabolites in man and animals for the different exposure routes. The ratio of sulfate/glucuronide conjugates excreted in urine is dose-dependent with a capacity-limited sulfatation at high dosages in rats and mice. Cats showed a poor glucuronidation of phenol, only conjugation with sulfate occurred. Small amounts of conjugated hydroquinone were only detected in the metabolic profiles for man and rats. Metabolism predominantly occurs in liver, gut and kidneys.

Phenol shows acute toxicity by the oral, dermal and inhalation route of application. Oral LD50 values of 340 mg/kg bw are reported on rats, of about 300 mg/kg bw on mice, and of less than 620 mg/kg bw on rabbits. A dermal LD50 value of 660-707 mg/kg bw was determined for female rats. LC50 values are not available, however, rats are reported to tolerate phenol concentrations as high as 900 mg/m3 for 8 hours, resulting in ocular and nasal irritation, loss of co-ordination, tremors, and prostration.

Acute oral toxicity of phenol in humans leading to death is reported for doses as low as 140-290 mg/kg bw. Absorption from spilling phenolic solutions on the skin of humans seems to be very rapid, and death resulted from collapse within 30 minutes to several hours. Death has resulted from absorption of phenol through a skin area of 64 inch^2, too. Signs and symptoms of acute toxicity of phenol in experimental animals and humans are similar regardless of the route of administration.

Eye irritation in rabbits caused by a 5% aqueous phenolic solution was irreversible after an observation period of 7 days. Thus, local irritation caused by phenolic solutions cannot be assessed properly. Initial skin contact of humans with phenol produces a white wrinkled discoloration with no experience of pain due to the local anaesthetic properties of phenol. Phenol causes severe chemical burns, occasionally skin necrosis is seen with diluted solutions (1%).

Phenol did not cause any signs of skin sensitization in tests with guinea pigs (modified Buehler Test) and mice

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.

(Mouse Ear Swelling Assay), and there is no evidence of allergic contact dermatitis in humans.

A 28-day administration of phenol in the drinking water (4.7, 19.5 and 95.2 mg/l) induced anaemia in CD-1 mice at concentrations of 19.5 mg/l (6.2 mg/kg bw/d). Furthermore, it was shown to induce T- and B-cell suppressive effects (reduced lymphocyte proliferation response to mitogens, antibody levels and T-cell dependent humoral immunity) in mice at low dosages (6.2 mg/kg bw and above). A significantly dose-dependent reduction of erythrocyte numbers by 32% was already seen at the lowest dose of 4.7 mg/l (1.8 mg/kg bw/d, LOAEL). Rats exposed to phenol containing drinking water did not show any alteration of the T-cell dependent humoral response up to 5000 ppm (301 mg/kg bw/d).

In the 103-weeks cancer NIH studies (1980), F344 rats and B6C3F1 mice were administered drinking water containing 2500 or 5000 ppm phenol (equivalent to an assumed phenol uptake of 200 and 450 mg/kg bw/d for rats and 281 and 375 mg/kg bw/d for mice) for 103 weeks. Treated animals showed reduced body weights (rats at high dose, mice at both doses) and reduced water consumption (both species and sexes at both doses). No other relevant toxic effect was seen related to non-neoplastic lesions. Because the reduction of body weight gain was attributed to the reduced water consumption, the NOAEL from this study is 450 mg/kg bw/d for rat and 375 mg/kg bw/d for the mouse, respectively. Haematology parameters were not examined in these studies.

In a study on potential neurotoxicity of phenol male and female Sprague-Dawley rats were treated for 13 weeks via drinking water with phenol concentrations of 200, 1000 or 5000 ppm, respectively, corresponding to an average intake of 18, 83 and 308 mg/kg bw/d for males and 0, 25, 107 and 360 mg/kg bw/d for females. The Functional Observation Battery evaluation did not reveal any findings of neurotoxicological significance following qualitative or quantitative measurements throughout treatment or following recovery except a significant decrease in body temperature noted for males in the 1000 and 5000 ppm groups at the week 13. The motor activity test indicated a significant reduction in total group mean activity counts at the week 4 and 8 for the 5000 ppm females and for females of the 1000 and 5000 ppm group at week 17 during recovery. At week 13 total mean activity counts were significantly higher in 1000 and 5000 ppm females. Thus, the NOAEL for neurotoxicity on rats was 200 ppm (18 mg/kg bw/d for males, 25 mg/kg bw/d for females). Dysfunctions of the nervous system including tremor, convulsions, loss of co-ordination, paralysis, reduced motor and spontaneous activity, and reduced body temperature have been reported in other studies.

Specific effects of phenol on the respiratory tract were investigated in a 14 day-inhalation study in F344 rats with a study design similar to OECD TG 412 (nose-only exposure for 10 exposures, 5 d/week, 6 hours/d). No adverse effects were seen at phenol concentrations up to 25 ppm in the respiratory tract or in any other organ system (local and systemic NOAEC of 96 mg/m3). This value is used in the risk characterisation as NOAEC for local effects after inhalation.

Prolonged dermal exposure of rabbits to phenol induced epidermal hyperkeratosis and ulceration. As dermal NOAEL for systemic effects the dose of 1.18% (130 mg/kg bw/d) was derived from the 18-day rabbit study, whereas the NOAEL for local effects was 2.37% (260 mg/kg bw/d).

Other limited repeated dose studies reported unscheduled deaths after inhalation (100 - 200 mg/m3, hamster), dermal exposure (783 mg/kg bw/d, rabbit) or gavage (120 mg/kg bw/d, rat) to phenol, but no treatment-related mortalities have been seen after long-term exposure of phenol within the drinking water at dosages up to 450 mg/kg bw/d in rats and 375 mg/kg bw/d in mice. In some studies, mortalities were associated with growth retardation or respiratory distress. Liver damage has also been observed in rats repeatedly exposed to phenol by inhalation and the oral route (enlarged liver, elevated levels of liver enzymes and liver cell degeneration). Necrosis of renal tubules and papillary hemorrhage have been reported in rats after repeated oral administration.

Limited data are available on chronic effects of phenol in humans from oral, dermal or inhalation exposure indicating reduced spontaneous activity, muscle weakness, pain and disordered cognitive capacities. In phenol-exposed workers (mean exposure duration 13.5 ± 6.55 years) elevated activities for serum transaminases (especially ALAT) and increased clotting time were observed at a time weighted average concentration of 21 mg/m3 indicating hepatotoxicity after chronic inhalation (LOAEC for systemic effects).

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.

Phenol did not induce gene mutations in the vast majority of bacterial tests similar to OECD TG 471. In mammalian cell cultures positive effects were found for chromosomal aberrations, micronuclei, and gene mutations (hprt locus, Na+/K+ locus) in mouse lymphoma assays and in several indicator tests (SCE, UDS, DNA strand breaks and DNA adducts). A test for induction of aneuploidy was negative. In vivo, negative results were found in rodents for chromosomal aberrations, DNA strand breaks and DNA adducts. In vivo micronucleus tests showed negative and weakly positive results. The frequency of micronuclei is extremely low even in doses which correspond to the LD50. The induction of micronuclei at high doses may be based on an indirect mode-of-action (hypothermia). Drosophila tests were negative.

In 103-weeks cancer studies on F344 rats and B6C3F1mice with oral administration (drinking water, 2500 and 5000 ppm, ≈ 200 and 450 mg/kg bw/d for rats and 281 and 375 mg/kg bw/d for mice, respectively) phenol was not carcinogenic for both species and sexes. A medium-term study in a transgenic mouse model did not give any indication on treatment-related proliferative responses. Phenol was shown to act as a promoter in a skin cancer bioassays in mice. A weak carcinogenic effect was observed after long-term skin application of a 10% solution of phenol in benzene (without initiation), but was considered less relevant because the test solution was strongly irritative and it contained the carcinogen benzene. Some concern which may be derived from weakly positive in vivo mutagenicity data and from the phenol metabolite hydroquinone suspected as a carcinogen is considered to be of minor significance, as the long term studies revealed no relevant indication for carcinogenicity.

There are no epidemiologic data revealing an association of phenol exposure to increased tumor rates in humans. No firm conclusion could be drawn from a case-control study on respiratory cancer of workers exposed to phenol.

Phenol was investigated for impairment of reproductive performance and fertility in a two-generation (drinking water) reproductive toxicity study in rats according to OPPTS 870.3700 resp. OECD TG 416. No adverse effects on reproductive capability and fertility were revealed for either sex across two generations up to and including the highest dosages tested (5000 ppm, according to 300 (males) and 320 (females) mg/kg bw/d). At this dose reduced water intake, decreased body weight and body weight gain including organ weight impairment were observed in animals of the P0 and F1 generation. No effects on sperm parameters or on estrous cyclicity were revealed. No substance specific developmental toxicity was revealed for phenol in studies on mice and rats with oral (gavage) administration. From the overall assessment of all available data a NOAEL/developmental toxicity of 93 mg/kg bw/d is derived which is based on the observations upon offspring performance and development in the rat two-generation study.

Environment

Phenol is a solid with a boiling point of about 182 °C and a melting point of about 41 °C. Its density is 1.132 g/cm3 at 25 °C. It has a water solubility of 84 g/l at 20 °C, a vapor pressure of 0.2 hPa (at 20 °C) and a measured log Kow of 1.47. With a Henry's law constant of 0.022 Pa.m3.mol-1 phenol is only slightly volatile from aqueous solutions.

Based on the results of standard biodegradation tests, phenol is readily biodegradable (OECD 301C: 85 % after 14 d). From available investigations on the biodegradation of phenol in surface waters a rate constant of 0.05 d^{-1} was determined. In soils phenol is biodegraded with an experimentally determined rate constant of 0.1 d^{-1}.
Hydrolysis under environmental conditions is not expected due to the chemical structure of phenol.

In the atmosphere phenol reacts with photochemically formed OH radicals with an estimated half-life of 14 hours. Products of this degradation are catechol and ring cleavage products. In addition, degradation through NO3 radicals may also play an important role with a half-life of approx. 44 min. A half-life of 42 min is calculated for the degradation of phenol in the atmosphere considering both processes.

According to a fugacity model (Mackay level I) the hydrosphere is identified as target compartment for phenol (98.8 %). Based on the measured log Kow of 1.47, the Koc value is calculated to 82.8 l/kg. This value indicates a low potential for geoaccumulation. From the available studies on bioaccumulation it can be stated that phenol has a

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.

low bioaccumulation potential (*Brachydanio rerio*: BCF = 17.5).

Short- and long-term tests are available for fish, invertebrates and algae. The lowest effects values from the short-term tests are: *Ocorhynchus mykiss*: 96h-LC_{50} = 5.02 mg/l; *Ceriodaphnia dubia*: 48h-LC_{50} = 3.1 mg/l, *Selenastrum capricornutum*: 96h-ErC_{50} = 61.1 mg/l, *Skeletonema costatum*: 120h-EC_{50} = 49.6 mg/l, 120h-NOEC = 13 mg/l. In long-term tests with fish the lowest valid effect value was found for *Cirrhina mrigala*: 60d-NOEC = 77 µg/l (survival and growth). In a 16d test with *Daphnia magna* an EC_{10} of 0.46 mg/l was found for gowth reduction as test endpoint. The PNECaqua is derived from the lowest available NOEC using an assessment factor of 10, resulting in a PNEC of 7.7 µg/l. In a nitrification inhibition test with *Nitrosomonas* a 24h-EC_{50} of 21 mg/l was found.

For the terrestrial compartment short-term tests with plants and earthworms are available. The following results were obtained: *Lactuca sativa*: 14d-EC_{50} = 79 - 168 mg/kg dw; *Eisenia fetida*: 14d-LC_{50} = 401 mg/kg dw.

Exposure

The total amount of phenol produced in the EU is about 1,820,000 t/a. In addition, a quantity of about 113,000 t/a is imported into the EU annually. 290,000 t/a are exported to non-EU countries. The quantity used in the EU is therefore approx. 1,643,000 t/a. Data about global production volumes are not available.

Phenol is mainly used as an intermediate in organic synthesis. Phenol essentially serves as a raw material for the production of Bisphenol A, phenol resins, alkylphenols, caprolactam, salicylic acid, nitrophenols, diphenyl ethers, halogen phenols and other chemicals. A small, non-quantifiable part serves as a component in cosmetics and medical preparations.

According to information from the Nordic product register phenol is contained in a large number of products. The following product types are described: intermediate, adhesive, binder, impregnating agent, paints, lacquers and varnishes, solvents, flooring, hardeners and insulating materials. The Swedish product register (2000) gives the information that there are 5 consumer products that contain phenol. 3 products have a phenol content of max. 0.1 %, 2 products (hardeners for adhesives) have a phenol content of 1 – 5 %. It is not clear from the product registers which quantity of the substance is used as an intermediate in the manufacture of products such as phenol resins and binders and how much remain unchanged in the final product.

Phenol is released from a number of man-made sources. The primary sources of environmental phenol are automobile exhaust (direct emission and photochemical degradation of benzene), human and animal metabolism and different combustion processes. From industrial sources, it enters the environment from production and processing operations. Releases also occur due to the waste water from cooking plants and low-temperature carbonisation plants using hard coal and brown coal, from refineries, from pulp manufacture and landfill leachate. Phenol may enter the soil as a result of the spreading of sewage sludge and liquid manure from livestock farming.

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. Due to the use pattern of the substance, member countries are invited to perform an exposure assessment, and if necessary a risk assessment for human health.

Note: A risk assessment performed in the European Union in the context of the EU Existing Substances Regulation reveals concern for several toxicological endpoints. Regarding systemic repeated dose toxicity and possible irritation, risk reduction measures are considered to be necessary for dermal exposure of consumers via cosmetics (soap, shampoo as well as cleaners). Concern is expressed for repeated inhalation exposure due to application of floor waxes. For workers additional risk reduction measures are necessary for inhalative and dermal exposure in several scenarios. Concern is expressed for corrosivity following skin contact and contact to the eyes, acute toxicity, and

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.

systemic toxicity following repeated dermal exposure. Special emphasis should be given by risk managers to all dermal exposure scenarios, because it is known, that sensation of pain due to local exposure to phenol may be diminished possibly leading to less awareness and thus higher degrees of local damage.

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

Note: A risk assessment for phenol was prepared in the EU in the context of the EU Regulation 793/93. No concern was identified for the environmental compartments from production and use of phenol. A concern for industrial wastewater treatment plants was identified for 8 out of 32 sites. For all these sites the wwtp concentration is based on default values and could possibly be lowered by site-specific and traceable exposure data. However, it was not possible to get this information with reasonable effort and time expenditure anda risk reduction strategy is therefore currently under development in the EU. In addition, some unintentional releases of phenol were identified in the risk assessment that may result in a risk to the aquatic compartment. However, based on the insufficient data basis, no clear conclusion could be drawn. This applies to:

- direct discharges of phenol as a product of human metabolism without purification of the municipal waste water in a biological treatment plant.
- the coking, gasification and liquefaction of coal, refineries and pulp manufacture.
- exposure to the aquatic and terrestrial environment from landfills without landfill leachate collecting system
- the terrestrial compartment as a result of the spreading of liquid manure from livestock farming

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-48-8
Chemical Name	Thiodiglycol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No data are available on the absorption of thiodiglycol from the gastrointestinal tract, or after dermal or inhalation exposure. In rats ca. 90 % of i.p. injected thiodiglycol is metabolized and excreted via urine within 24 hours after application. The major metabolite detected in urine is thiodiglycol sulphoxide. Only small amounts (0.5-1%) of the administered dose were excreted unchanged within 8 days.

The acute oral LD_{50} value in rats was >9900 mg/kg bw, with depression of the central nervous system as the main clinical sign at doses near to or exceeding the LD_{50} value. The inhalation of the saturated vapour for 8 h resulted in no mortality. Thiodiglycol is not irritating to the skin and slightly irritating to the eyes and mucous membranes. No sensitizing potential was detected in two guinea pig maximization tests following current guidelines.

In a study performed according to OECD guideline 407 (1981), repeated exposure of rats by gavage to 1000 mg/kg bw/day for 28 days resulted in no effects of toxicological relevance. In a 90-day gavage study (comparable to the current OECD guideline 408; 0, 50, 500, 5000 mg/kg bw/day), effects on body and kidney weight (without a histopathological effect) as well as altered parameters of the urine analysis were observed in males and females at 5000 mg/kg bw/day. A dose level of 500 mg/kg bw/day is considered as NOAEL.

With or without addition of a metabolic activation system, thiodiglycol did not induce mutations in bacteria (OECD guideline 471) and in the mouse lymphoma assay (OECD guideline 476). At high dose levels resulting in cytotoxic effects thiodiglycol induced chromosomal aberrations *in vitro*, both in the presence and the absence of a metabolic activation system (study design comparable with OECD guideline 473). No clastogenic activity was detected in the mouse bone marrow micronucleus assay at oral doses up to and including 2000 mg/kg bw (OECD guideline 474). It is therefore concluded that the clastogenic effects seen *in vitro* are not expressed *in vivo*.

There are no fertility studies available. In a 90 day gavage study (see above) no effect was observed on the gonads of male and female rats dosed up to and including 5000 mg/kg bw/day. In two gavage studies (OECD guideline 414) on the prenatal developmental toxicity in Wistar rats, the NOAEL for maternal and developmental toxicity was 400 mg/kg bw/day. Borderline effects concerning a certain type of skeletal variations (dumbbell ossification of thoracic vertebral bodies) were observed at oral doses of 1000 mg/kg bw/day which resulted also in marginal maternal toxicity.

No data are available on carcinogenicity.

Environment

Thiodiglycol is an organic liquid of unpleasant odour with a melting point of -10 °C and a relative density of 1.1824 at 20 °C. It is miscible with water at 20 °C (pH 5 - 9 at 100 g/l) and the vapour pressure at this temperature is

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.

< 0.101 hPa. A Henry's law constant of $1.87 \cdot 10^{-4}$ Pa · m³/mol at 25 °C can be calculated. The partition coefficient log K_{OW} is – 0.75 as measured at 25 °C.

According to the distribution model *Mackay*, Level I, the target compartment for thiodiglycol is the hydrosphere with 99.95 %. The substance has a low potential for bio- or geoaccumulation. As shown in a guideline study according to OECD 301 A thiodiglycol can be regarded as readily biodegradable (90 - 100 % after 21 days). Hydrolysis or photodegradation in water do not occur. For indirect photodegradation in air due reaction with OH radicals a half-life of 13.8 hours is calculated.
The aquatic effects data base meets the requirements of the SIDS package. Aquatic effects data are as follows:

fish (*Leuciscus idus):* LC_{50} (96 h) > 10 000 mg/l;
crustacea: (*Daphnia magna)* EC_{50} (48 h) > 500 mg/l;
algae (*Desmodesmus subspicatus*): ErC_{50} (72 h) > 500 mg/l.

These values indicate that thiodiglycol is of low toxicity to aquatic organisms. For microorganisms (activated sludge) an EC_{20} (30 min) of > 1000 mg/l was determined. Applying an assessment factor of 1000 to the lowest available acute effect value according to the EU Technical Guidance Document, a $PNEC_{aqua}$ of ≥ 0.5 mg/l is derived.

Exposure

Thiodiglycol is produced by ATOFINA SA (France) and BASF AG (Germany), further producers in the EU are not known. The production volume in the EU in the year 2003 was 1000 to 5000 tonnes. Imported volumes are not known. Both companies export minor amounts to Asia and the Pacific as well as to the USA. Further producers of thiodiglycol are known in China (4), Japan (1), Mexico (1), and USA (1) but no data on production volumes are available. Thiodiglycol is used as a chemical intermediate, as a solvent in colouring processes in the textile industry, as a solvent in preparations for colouring paper and as a softener in special caoutchoucs. Thiodiglycol is a component of different products listed in European product registers; the substance is used in the manufacture of pulp, paper products, paints, pigments, dyestuffs, varnishes, coatings and inks. Some of them are available to consumers. The chemical may be also used as antioxidant in cosmetics.

Releases of thiodiglycol into the environment may occur from production and processing, from its use as solvent in industrial applications and from use of products containing this substance. However, no detailed exposure information is available. A source of exposure might also be given by the hydrolysis of the chemical warfare agent sulfur mustard (see below) to thiodiglycol.

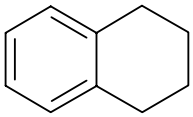
Thiodiglycol can be converted by chemical synthesis to mustard gas. Therefore the production and export of thiodiglycol is stringently controlled under the International Chemical Weapons Convention.

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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	119-64-2
Chemical Name	1,2,3,4-Tetrahydronaphthalene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,2,3,4-Tetrahydronaphthalene is rapidly absorbed when ingested or inhaled. The chemical is metabolized by hydroxylation at the non-aromatic portion of the molecule. The metabolites are excreted mainly as glucuronides with the urine, but elimination with the feces was also observed. Dark green colored urine, which is observed as a typical symptom in humans, indicates metabolization to a pigment.

The acute toxicity of 1,2,3,4-tetrahydronaphthalene was found to be relatively low with an oral LD_{50} of 2860 mg/kg bw (male rats), a dermal LD_{50} of 16,800 mg/kg bw (male rabbits) and no mortalities within 8 hours inhalation of a saturated atmosphere (ca. 1300 mg/m^3; male rats. In humans, the chemical is known to produce headache, nausea, vomiting, green-gray urine, and restlessness at high concentrations.

1,2,3,4-Tetrahydronaphthalene was a moderate irritant to the skin (OECD TG 404), but not to the eye (OECD TG 405). High exposure from the gas phase may cause irritation of mucous membranes and profuse lacrimation in humans. 1,2,3,4-Tetrahydronaphthalene was not sensitizing in a guinea pig maximization test (OECD TG 406, 1981).

In 13-week inhalation studies on rats and mice (performed within the U.S. National Toxicology Program and currently available only as abstracts plus key tables), no mortalities, no clinical abnormalities, and no gross pathological findings were observed at exposure concentrations up to and including 660 mg/m^3. In mice, transitional epithelial eosinophilic granules were observed in the urinary bladder of all exposed groups (dose-related), the toxicological significance of this finding is however unclear. In female mice, uterus atrophy was found at 82.4 mg/m^3, and atrophy of the ovary at 330 mg/m^3. In rats, a NOAEL could also not be established due to increased liver weight down to the lowest tested concentration (41.2 mg/m^3). The NOAEL for nasal lesions in rats was 82.4 mg/m^3 in males and 41.2 mg/m^3 in females, and 164.8 mg/m^3 in mice.

In a 28 day toxicity study in rats with gavage application of up to 150 mg 1,2,3,4-tetrahydronaphthalene/kg bw/day, no mortalities occurred in any group. Squatting position and closed eyes were observed in all treated groups. There was a transient decrease in absolute body weights of all treated males. Results of hematology were indicative of a hemolytic anemia in males and females of the high dose group, which was still present, though to a lesser degree, at the end of the recovery period. As a secondary reaction to the anemia, the reticulocyte counts for high dose females were increased and the extramedullary hematopoesis in the spleen of both high dose genders was enhanced. Based on the adverse effects on blood and spleen (significant at 150 mg/kg bw/day, but already beginning at 50 mg/kg bw/day), the NOAEL in this study was at 15 mg/kg bw/day.

1,2,3,4-Tetrahydronaphthalene was not genotoxic in bacterial systems *in vitro* (Ames test). In a Mouse Lymphoma test, results were negative and equivocal, without and with metabolic activation, respectively. *In vivo*, no mutagenic

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.

activity was detectable in two micronucleus assays on mice according to OECD TG 474 using the oral and inhalation routes of administration.

No specific studies have been performed on the toxicity of 1,2,3,4-tetrahydronaphthalene to reproduction. There were no indications of an adverse effect on vaginal cytology, sperm and on reproductive organs from the 13-week inhalation study on rats. In mice, no effects on vaginal cytology and sperm were noted in the 13-week inhalation study, but uterus atrophy and atrophy of the ovary were found in the absence of systemic toxicity (*cf.* repeated dose section). Therefore, an effect of the chemical on reproduction cannot fully be excluded.

1,2,3,4-tetrahydronaphthalene did not show any developmental effects in a gavage study with rats performed in accordance with OECD TG 414 (2001) up to and including the highest tested dose level of 135 mg/kg bw/day. The NOAEL for maternal toxicity was 45 mg/kg bw/day, effects at 135 mg/kg bw/day were reduced food consumption and reduced body weight gain. The NOAEL for developmental toxicity was 135 mg/kg bw/day.

Environment

1,2,3,4-Tetrahydronaphthalene has a melting point of -35.8° C, a boiling point of 207.57° C at 1013 hPa, a water solubility of 45 mg/l and a vapor pressure of 0.34 hPa at 20 °C. The measured log K_{ow} is 3.78 (23 °C).

According to Mackay Level I model calculation, the main target compartment for 1,2,3,4-tetrahydronaphthalene will be the atmosphere (94.7 %), followed by water (2.7 %). The experimental Henry's law constant of 138 Pa m^3/mol indicates high volatility from surface waters. With a calculated K_{oc} of 1837 l/kg, the sorption potential to soil or sediment organic matter is expected to be high.

In the atmosphere, 1,2,3,4-tetrahydronaphthalene is removed by reaction with hydroxyl radicals with a calculated half-life of 11.2 hours based on an experimental rate constant. In water, it is not expected to hydrolyze under environmental conditions. Photolytic degradation in surface waters is an additional removal process of unclear significance with a half-life at least above 34 hours. 1,2,3,4-Tetrahydronaphthalene is not readily biodegradable by every inoculum, but is degraded well by several rare microorganisms. Anaerobic degradation was also observed. Calculated bioconcentration factors between 162 and 326 indicate a bioaccumulation potential of 1,2,3,4-tetrahydronaphthalene.

The lowest valid acute test results of aquatic testing determined for fish, invertebrates, and algae were as follows:

Danio rerio: 96-h-LC_{50} = 3.2 mg/l
Daphnia magna: 48-h-EC_{50} = 9.5 mg/l
Daphnia pulex: 48-h-EC_{50} = 2.4 mg/l
Desmodesmus subspicatus: 72-h-E_rC_{50} = 11.0 mg/l; 72-h E_bC_{50} = 7.0 mg/l
Long term aquatic toxicity data are available for one trophic level:
Desmodesmus subspicatus: 72-h E_rC_{10} = 5.3 mg/l; 72-h E_bC_{10} = 3.8 mg/l

From the lowest among the acute values, an aquatic PNEC of 2.4 µg/l is calculated using an assessment factor of 1000 according to the EU Technical Guidance Document.

Exposure

1,2,3,4-Tetrahydronaphthalene is produced in the Czech Republic, Germany, Japan, and the United States of America with production capacities of < 1000, 9000, < 1000, and 12,000 t/year, respectively. Production rates are known or assumed to be well below capacities. The annual quantity on the market is estimated to be below 10,000 t/a. Use as an intermediate and as an industrial solvent are the only applications of 1,2,3,4-tetrahydronaphthalene with significant quantities. Direct use and use as an intermediate are of approximately equal importance. Beside 1-naphthol, from which Carbaryl® is made, the most important substance made from 1,2,3,4-tetrahydro-

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.

naphthalene is decahydronaphthalene. 1,2,3,4-Tetrahydronaphthalene is used as a solvent in a wide variety of applications including viscosity adjustment. In European product registers products are listed for both professional and consumer use that contain 1,2,3,4-tetrahydronaphthalene in concentrations up to 50 % (higher for two professional use products).

1,2,3,4-Tetrahydronaphthalene also occurs in fossil materials such as coal and petroleum and their downstream products, and it is formed in various plants as well as in combustion processes.

Releases of synthetic 1,2,3,4-tetrahydronaphthalene into the environment may occur during production, solvent use, formulation, and use of formulations as well as from its use as a starting material for organic syntheses. Release from production in the Sponsor country is negligible because a closed system is used, there is no water involved in the process, and solid waste is incinerated. Releases into the terrestrial compartment may occur from the use of 1,2,3,4-tetrahydronaphthalene as solvent in herbicides. Further data for anthropogenic 1,2,3,4-tetrahydronaphthalene are not available.

Release of fossil 1,2,3,4-tetrahydronaphthalene may occur when fossil materials are stored in open containers, burnt incompletely, spilt, or disposed of improperly. Naturally formed 1,2,3,4-tetrahydronaphthalene already occurs in the environment.

The order of magnitude of background concentrations is approximately 10 – 30 ng/l in surface waters, based on monitoring data from around 1990.

The most probable human exposure to 1,2,3,4-tetrahydronaphthalene is through dermal contact or inhalation during manufacture or use. In the Sponsor country, exposure is controlled in occupational settings.
Consumers may be exposed to 1,2,3,4-tetrahydronaphthalene used as solvents in paints, varnishes, lacquers, waxes, shoe polishes, and in petroleum products (gasoline, motor oils).

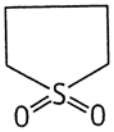
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (irritant to skin and mucous membranes, repeated dose toxicity, potential effect on reproduction). Based on data presented by the Sponsor country, adequate risk management measures are being applied for occupational settings. A high potential for consumer exposure exists as a result of the use as solvent in e.g. paints, waxes, and polishes. It is therefore recommended to perform an exposure assessment and, if then indicated, a risk assessment. It is further noted that the chemical is currently being tested in a 2 year inhalation carcinogenicity study on mice and rats under the US National Toxicology Program.

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment. Based on data presented by one company in the Sponsor country, exposure from production is low. However, environmental exposure may result from the use of 1,2,3,4-tetrahydronaphthalene as solvent and from the formulation and use of products containing the substance. Therefore, an exposure assessment and, if then indicated, an environmental risk assessment is recommended.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	126-33-0
Chemical Name	Tetrahydrothiophene 1,1-dioxide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In rats dosed intravenously at 500 mg/kg, 28%, 36% and 37% of the dose was excreted unchanged between days 0-2, 0-4 and 0-7, respectively. At 1000 mg/kg, 50% and 67.2% of the dose was excreted unchanged between days 0-2 and 0-4, respectively. The observation that the proportion of the dose recovered increased with dosage suggests that the metabolic pathway is saturable. In rabbits, dogs and squirrel monkeys given a single iv injection, this chemical was rapidly distributed throughout the body and was slowly removed from plasma with a half-life of 3.5-5 hours. One major metabolite with 85% of the urinary radioactivity was found in male rats injected intraperitoneally with this chemical. In a follow up study, the metabolite was identified as 3-hydroxysulfolane in the urine of rabbits injected intraperitoneally with this chemical.

LD_{50} values by gavage [OECD TG 401] were 2006 mg/kg (males) and 2130 mg/kg (females) in rats. Dermal LD_{50} in male and female rats was greater than 2000 mg/kg [84/449/EEC, B3]. Inhalation LC_{50} in male and female rats(four hours) was greater than 12,000 mg/m^3. Acute behavioural studies in rats indicated that hypothermia contributed to the behavioural effect of an interperitoneal injection of 800 mg/kg of sulfolane. Rabbits became hyperthermic, at 28°C, upon subcutaneous injection of 600 mg/kg sulfolane.

The chemical is not irritating to guinea pig and rabbit skin or to rabbit eyes. The chemical was not sensitising (0/20) in a guinea pig maximisation test [84/449/EEC, B6].

In a 28 day repeat dose toxicity study [Japanese TG] conducted under GLP, male and female rats were dosed by gavage with this chemical at 0, 60, 200 and 700 mg/kg/day. At 700 mg/kg some females showed transient reduction in locomotor activity during the early administration period. Bodyweight gain and food consumption at this dose were decreased in both males and females. Blood chemistry revealed increases in cholinesterase activity and total bilirubin levels in males and GPT in females and decreases of chloride levels in males and glucose levels in females. Histopathological examination in males dosed at 700 and 200 mg/kg/day revealed increases of hyaline droplets and eosinophilic bodies in the renal tubules which was accompanied by an increase in relative kidney weight. There was a decrease of splenic weight in females at 700 mg/kg/day, but no histological abnormalities were detected. No changes considered to be attributable to sulfolane were observed on urinary and haematological examinations at any dose. Kidney lesions tended to recover and the other changes related to the chemical disappeared after a 14 day recovery period. The NOAEL was 60 mg/kg/day for male rats and 200 mg/kg/day for female rats.

The chemical was not mutagenic in bacteria [OECD TG 471 and 472] and did not induce chromosome aberrations in mammalian cells in vitro [OECD TG 473] either with or without metabolic activation.

In a reproduction/developmental toxicity screening test [OECD 421]) rats were dosed at 0, 60, 200, or 700 mg/kg/day

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.

by gavage for 41 to 50 days from 14 days prior to mating to day 3 of lactation. Some mortality occured in the high-dose group. There was a decrease in body weight gain and food consumption of males and females during the pre-mating period, at 700 mg/kg. The number of oestrus cycles was decreased in the 700 mg/kg group. Four dams lost all their pups during the lactation period in the 700 mg/kg group. Birth index, live index, number of pups on days 1 and 4 of lactation, viability index and body weights of pups of both sexes on days 0 and 4 of lactation decreased, and the number of still births increased in the 700 mg/kg group. Birth index and the number of pups on day 0 and 4 of lactation decreased in the 200 mg/kg group. The NOAEL for reproductive and developmental toxicity was 60 mg/kg/day. There were no treatment-related findings in the external appearance, general conditions and necropsy findings in offspring.

Environment

The chemical has a log Pow of –0.77, a vapour pressure of 0.0083 hPa at 20°C and a water solubility of greater than 100 g/l. Fugacity model Mackay level III calculations suggest that the chemical will distribute almost completely to water if released to the aquatic compartment and equally to soil and water if released into air or soil separately or simultaneously to all three compartments.. The chemical is not readily biodegradable (10% after 14 days), and is hydrolytically stable (t1/2 greater than 1 year at pH 4, 7 and 9, 25°C). It can be biodegraded after acclimatisation of activated sludge and by a variety of bacterial cultures, and may be substantially biodegradable. Inorganic sulphate has been identified as the final degradation product of sulfolane metabolism. The chemical has been shown to have low potential for bioaccumulation. Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 9.7 h (calculated using AOPWIN rate constant, 1.328×10^{-11} cm^3/molecule/sec).

In an acute fish toxicity study [OECD TG 203, *Oryzias latipes*] a 96-hLC_{50} > 100 mg/l was reported. In *Daphnia magna* [OECD TG 202], an acute toxicity value of 48h EC_{50} = 852 mg/l was reported. The results in algae [OECD 201] were an E_rC_{50} (72h) >1000 mg/l,E_bC50 = 500mg/ l and a $NOEC_r$ (72 h) = 556 mg/l, $NOEC_b$ = 171 mg/l. The chronic toxicity to *Daphnia magna* [OECD 211] was a NOEC (21d, reproduction) of 25 mg/l and an LC_{50} (21d, parental) > 100 mg/l.

In a study to determine plant toxicity [Environment Canada protocol, lettuce (*Lactuca sativa*), carrot (*Daucus carota*), alfalfa (*Medicago sativa*) and timothy (*Phleum pratense*)] it was determined that plants were generally most sensitive to sulfolane in till and least sensitive in loam. A five day seed germination/root elongation test conducted using lettuce (*Lactuca sativa*) reported NOEC values of 290 mg/kg (root elongation) and 570 mg/kg (seed germination) for lettuce grown in fine-textured soil.

Exposure

Production of the chemical during 2003 was 1100 t/year in Japan. Global production in 2003 was approximately 13,300 t/year. Geographically, production was divided between sites in the Americas (35-45%), Asia (20-30%) and Europe/Africa (35-45%).

The major use of Sulfolane is as a solvent for extraction of aromatic hydrocarbons from oil refinery streams and acid gas purification. These uses account for approximately 80% of production. A number of minor uses (accounting for 20% of production) include fractionation of wood tars, tall oil and other fatty acids, electronic applications, textile manufacturing and finishing, as a plasticizer and as a solvent in pharmaceutical manufacturing. Other uses mentioned in the literature include solvent for jet printing inks, a component of hydraulic fluid, a curing agent for epoxy resins and medicinal application (although this latter application is thought to exist in the patent literature only).

Monitoring studies performed in the vicinity of gas processing facilities in Canada have shown that environmental release of sulfolane during its use in these facilities is possible. Sulfolane was detected in soil, bedrock and shallow till aquifers, wetlands and creeks near these facilities. It was also detected in wetland vegetation.

There is low potential for exposure to workers during production of the chemical. It is manufactured in a closed

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.

system and transferred directly from the reactors into storage tanks. There is potential exposure to workers during drum filling. This operation is performed on 16 days per year for 7 hours each day. The concentration of sulfolane close to the drums has been measured at 0.2 ppm. There is potential exposure to workers at user sites. Since the predominant use of sulfolane is as a solvent in commercial extraction processes there is little potential for direct consumer exposure, however there is a potential for indirect human exposure via drinking water and food crops in areas surrounding processing plants.

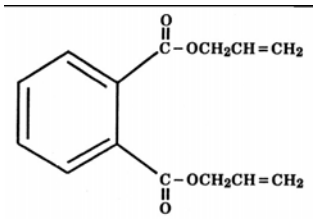
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (reproductive and developmental toxicity). Based on data presented by the Sponsor country worker exposure in sites manufacturing the chemical is controlled. No information is available for occupational exposure in industries using the chemical nor for indirect human exposure via drinking water and food crops in areas surrounding processing plants. It is therefore recommended that member countries perform an exposure assessment for industrial users and indirect human exposure, and if then indicated, risk assessments be performed.

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	131-17-9
Chemical Name	Diallyl phthalate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Excretion, distribution and pharmacokinetic studies have been performed with rats and mice using ^{14}C-diallyl phthalate (DAP). In the excretion and distribution studies, ^{14}C-DAP was administered by gavage and $^{14}CO_2$, volatile metabolites, urine and faeces were collected for 24 hours. In rats, 25 – 30% of the DAP was excreted as CO_2, and 50 – 70% appeared in urine within 24 hours. In mice, 6 – 12% of the DAP was excreted as CO_2, and 80 – 90 % was excreted in the urine within 24 hours. Tissue distribution and pharmacokinetic studies were conducted in rats and mice dosed via the tail vein with ^{14}C-DAP. The DAP was found to clear rapidly from the blood of rats and mice, with a half-life of approximately 2 minutes in both species. No DAP was found in blood, liver, kidney, muscle, skin or small intestine 30 minutes after intravenous administration of DAP in both species. Monoallyl phthalate (MAP), allyl alcohol (AA), 3-hydroxypropylmercapturic acid (HPMA), and an unidentified polar metabolite were found in the urine of rats and mice dosed with ^{14}C-DAP. The polar metabolite was present in the urine of rats after administration of DAP or AA, indicating that this compound is a metabolite of AA.

DAP was more hepatotoxic to rats than to mice. The same species difference was observed in toxicity for AA. Because DAP was metabolized to AA, it was postulated that the differential hepatotoxicity of DAP was related to the toxicity of AA. AA is a potent periportal hepatotoxicant, and because mice produced more HPMA as a by-product of phase II metabolism than rats, it was postulated that the differential hepatotoxicity of DAP was related to the extent of glutathion conjugation with AA or acrolein (the active metabolite of AA). Oral LD_{50} values [NTP] were 891 mg/kg bw (males) and 656 mg/kg bw (females) in rats, and 1070 mg/kg bw (males) and 1690 mg/kg bw (females) in mice. Oral LD_{50} in dogs was ca. 800 mg/kg bw (combined). Dermal LD_{50} (rabbit) was 3300 mg/kg bw. Inhalation LC_{50} in rats (one hour) was 8300 mg/m^3 (combined), 10310 mg/m^3 (males) and 5200 mg/m^3 (females) [FIFRA Guidelines, 43FR 37336].

DAP is not irritating to rabbit skin [16 CFR 1500.41] or eyes [FSHA 16 CFR 1500]. DAP was sensitising in a local lymph node assay in mice [OECD TG 429].

In a repeated dose toxicity study [NTP], male and female rats (10 animals/sex/group) were dosed by gavage with DAP at 0, 25, 50, 100, 200 and 400 mg/kg bw/day on 5 days/week for a total of 13 weeks. Eight male rats that received 400 mg/kg bw/day either died during the study or were killed when found in moribund condition. Body weight gain for male rats at 400 mg/kg bw/day appeared to be depressed relative to that of the vehicle controls. Clinical signs in both sexes were observed at 400 mg/kg bw/day and less frequently at 200 mg/kg bw/day, but not at lower doses. The clinical signs consisted of diarrhoea, rough hair coat or alopecia around the head, hunched posture

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.

and general emaciation. At necropsy, gross abnormalities of the liver were observed in all eight 400 mg/kg bw/day male rats that died early and three of these male rats also exhibited multifocal renal cortical tubular necrosis. The lungs in many of these male rats appeared darkened or bright red. Liver lesions were observed in the two surviving males and in most females at 400 mg/kg bw/day, and in 5/10 males at 200 mg/kg bw/day. The severity appeared to be dose related and greater in males than in females. Histopathological examination indicated that the liver was the primary target organ. Periportal lesions of hepatic lobules, necrosis, fibrosis, bile duct hyperplasia, and hepatocellular hyperplasia occurred in males and females at 200 and 400 mg/kg bw/day. Necrosis, fibrosis and biliary hyperplasia were not observed at doses lower than 200 mg/kg bw/day in both sexes, but hepatocellular alterations in the periportal region were observed with decreasing frequency and severity at doses as low as 50 mg/kg bw/day in males and 100 mg/kg bw/day in females. The NOAEL for females was 50 mg/kg bw/day. The NOAEL and the LOAEL for males were not determined because no histopathological examination at 25 mg/kg bw/day in the liver was performed.

DAP was weakly mutagenic in two strains of bacteria (WP2 with metabolic activation and TA 1535 without metabolic activation) [OECD TG 471 and 472]. Clear positive responses were observed in mouse lymphoma cells, both with and without metabolic activation *in vitro*. It also induced chromosomal aberrations in Chinese hamster cultured cells with and without metabolic activation [OECD TG 473] and an increase in sister chromatid exchanges and micronucleus formation with metabolic activation. DAP was not genotoxic *in vivo* in mouse micronucleus test [OECD TG 474]. It did induce a small number of chromosome aberrations in mice [OECD TG 475] although the biological significance of these data is not clear. Based on these data, DAP is considered to be genotoxic *in vitro*, however these findings were not clearly manifested when tested in good quality *in vivo* studies.

For carcinogenic potential of DAP, based on the NTP results in mice and rats, the observed evidence of lymphoma (mice) and mononuclear cell leukemia (rat) in aged animals is considered to be equivocal evidence of carcinogenicity.

In an oral study in rats by OECD reproduction/developmental toxicity screening test [OECD TG 421], rats (10 animals/sex/group) were dosed by gavage at 0, 16.7, 50 and 150 mg/kg bw/day from 14 days prior to mating to day 4 of lactation. At 150 mg/kg/day there were 3 mortalities, which were associated with possible dystocia. Effects on newborns and live newborns were not evaluated in these female rats. Histopathological changes in the liver of parental animals were observed at this dose. There were no treatment-related effects on the fertility of male or female rats. No treatment-related histopathological changes were found in the reproductive organs of parental animals. There were no treatment-related effects on offspring viability, growth and development from conception to early lactation. No morphological abnormalities were seen in offspring of rats given this chemical pre- and postnatally. The NOAELs for general toxicity in parent animals and for reproductive toxicity were 50 mg/kg bw/day.

Environment

DAP has a log Pow of 3.23 at 20°C, a vapour pressure of 0.000213 hPa at 25°C and a water solubility of 148 mg/L. Fugacity model Mackay level III calculations suggest that the majority of DAP would distribute to water if released into the water compartment, mainly to soil if released to the air or soil compartments. DAP is readily biodegradable (76 – 92% based on BOD, 28 days) [OECD TG 301C], and is hydrolytically stable at pH 4 and 7 ($t_{1/2}$ greater than 1 year). At pH 9 the half-life is 217 hours. The hydrolysis products are phthalic acid and AA. The estimated BCF is 61.25 and hence the potential for bioaccumulation is low. Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 2.3 hours.

In acute fish toxicity studies [OECD TG 203, 96 hours] LC_{50} values of 0.23 mg/L (measured, *Oncorhynchus mykiss*) and 0.44 mg/L (measured, *Orizias latipes*) were reported. In *Daphnia magna* [OECD TG 202], acute toxicity values of 48-h EC_{50} of 5.5 mg/L (measured) and 16.2 mg/L (measured) were reported. The results in algae [DIN 38412 L9 Part 9, *Scenesdesmus subspicatus* and OECD TG 201, *Selenastrum capricornutum*] were E_rC_{50} (72 hours) of 5.5 mg/L (nominal) and 14.9 mg/L (measured), respectively. The corresponding value for biomass was 15.1 mg/L (measured). The chronic toxicity values to *Daphnia magna* [OECD 211] were NOEC (21d, reproduction) of 1.16 mg/L (measured) and 3.2 mg/L (nominal). NOEC (72 hours) values from growth rate and biomass in algae were both 2.4 mg/L (measured) [OECD TG 201, *Selenastrum capricornutum*].

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.

Exposure

Production of DAP during 2002 is estimated at 4400 tonnes worldwide. Annual production at the two manufacturing sites in Japan is estimated at 3900 tonnes. There are a wide variety of uses for this chemical, where DAP is covalently bound into a polymer matrix DAP is used in the production of polyvinyl chloride (PVC), unsaturated polyesters (UP), or polyDAP as a crosslinking agent, a dye carrier, an insulating agent, an agent for improving flowability and viscosity of compound mixtures (during chemical processing), or an agent which gives hardness to articles for goods such as ship bodies (sheet moulded compound, SMC), coil bobbins, window frames, UV curable inks, hot stamping foils, grindstones, impregnated paper-decorated particle boards for wall materials or furniture and so on.

The exposure of DAP may occur mainly according to the following three scenarios:
Occupational exposure: Limited exposure to workers through inhalation and dermal routes during operations at production and user sites is expected. A survey of occupational exposure in a Japanese factory producing DAP and polyDAP found that workers were exposed to DAP at concentrations of $\leq$0.11 mg/m^3 during manufacture of DAP itself and 0.02 – 0.96 mg/m^3 during manufacture of the polymer.

Consumer exposure: Based on the following information, exposure to consumer through inhalation and dermal routes is anticipated to be low. In studies performed in the residential indoor air environment, DAP was detected in the range of 0 – 134.5 ng/m^3, depending on the study. DAP is an intermediate and is used as a reactive plasticizer, which is covalently bound into the polymer matrix of products. One such application is the manufacture of decorative boards. A study performed to measure the amount of DAP emitted from decorative boards manufactured using DAP found that the amount was generally below the limit of detection of 0.05 µg/m^3 [JIS A1901: 2003].

Environmental exposure: Limited emission to the environment is expectedvia waste water at production and user sites, and evaporative emissions associated with its use in building and household materials, etc., and disposal of consumer products. No DAP was detected in either the sediment (Limit of detection 0.02 µg/g in dry sediment) or hydrosphere(Limit of detection 0.2 µg/L) of 27 monitoring points in Japan in 1985. Monitoring of wastewater from DAP manufacturing plant in Matsuyama, Japan found that levels of DAP were in the range of 0.003 – 0.005 mg/L. Sampling was conducted in the surface water of the settling pond, just downstream from the aerating facilities and leading to the outfall facing the bay in Seto Inland Sea in Matsuyama-shi, Ehime Prefecture. The annual estimated emission from the plant is considered to be 5.3 kg/year. Based on these monitoring surveys, use patterns and a nature of ready biodegradability it can be concluded that the environmental concentration of the substance is anticipated to be low in the Sponsor country.

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

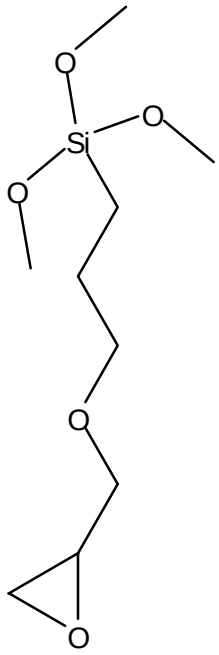
Human Health: The chemical is a candidate for further work.The chemical possesses properties (sensitization, mutagenicity, liver and kidney toxicity, equivocal carcinogenicity and reproductive toxicity) indicating a hazard for human health. Based on data presented by the Sponsor country, worker exposure in sites manufacturing DAP and PolyDAP is controlled. No information is available for occupational exposure in industries using DAP or PolyDAP. It is therefore recommended that member countries perform an exposure assessment for workers and if then indicated, risk assessments.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties (acute toxicity) indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by two producers which accounts for approx. 89 % of global production and relating to the use pattern in one OECD country), exposure to the environment is anticipated to be low. Therefore, this chemical is currently of low priority for further work. Countries may wish to investigate any exposure scenarios that were not presented by the Sponsor country.

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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2530-83-8
Chemical Name	Trimethoxy [3-(oxiranylmethoxy)propyl] silane (TMSPGE)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The chemical, trimethoxy[3-(oxiranylmethoxy)propyl]-silane (TMSPGE) rapidly hydrolyzes at environmental pH levels and in acidic conditions. An abiotic hydrolysis study showed that hydrolysis products of the test substance underwent continuous, condensation reactions to produce higher molecular weight cyclic and linear siloxanes; about 73 percent of the area of the chromatogram showed molecular weight peaks greater than 1000 after one hour. Substances with molecular weights of greater than 1000 are generally considered to have a very limited biological availability.

If TMSPGE is slowly released into a water environment such that the concentration of the resulting epoxy-functional silanetriol hydrolysis product is not high enough to result in polymerization, the product will exist largely as a silanetriol monomer. The monomer is known to be water soluble because of the hydroxy groups on the silicon. However, as noted below, water solubility and the partition coefficient of the parent compound cannot be easily measured and only estimates are provided.

Human Health

TMSPGE is subject to rapid hydrolysis, and the observed toxicity is expected to be due primarily to methanol and

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.

silanetriols. TMSPGE has been tested for acute toxicity by the oral, dermal, and inhalation routes of exposure. Reported acute oral LD_{50}s in rats range from 7010 to 16900 mg/kg bw and > 5 ml/kg bw to 22.6 ml/kg bw. The dermal LD_{50}s are 6800 mg/kg bw and 4.0 ml/kg bw. The 4-hour inhalation LC_{50} was greater than 2.7 mg/L in one study and greater than 5.3 mg/L in another study. TMSPGE is mildly irritating to the skin and eyes and is not a known skin sensitizer in humans or in animals.

Following inhalation exposures of rats to target aerosol concentrations of 0, 75, 225 and 750 mg/m3 (actual concentrations were 0, 77, 226, 707 mg/m^3 (males) and 0, 73, 226, 734 mg/m^3 (females)), TMSGPE in 9 repeated exposures administered over two weeks, 6 animals in the high dose group died or were sacrificed from three to five days after initiation of the study. These animals had signs of inanition but no acute tissue toxicity. At both the mid and high doses, rats exhibited some clinical signs including a dose-related decrease in body weight. Under the conditions of this study, the No Observed Adverse Effect Concentration is 225 mg/m3. Repeated exposure of rats by gavage to TMSPGE doses of 40, 400 and 1000 mg/kg bw/day for 5 days/week for 4 weeks resulted in no test substance-related organ weights effects or gross or microscopic pathological changes. Under the conditions of this study, the NOAEL for the test substance was found to be 1000 mg/kg bw/day.

TMSPGE did not induce chromosomal damage in mouse bone marrow cells by gavage at doses of 500, 1670 and 5000 mg/kg bw/day, or when administered by intraperitoneal (i.p.) injection at 1600 mg/kg bw/day. However, chromosomal damage was induced in mouse bone marrow cells when administered by i.p. in water at doses of 500, 1000 and 2000 mg/kg bw/day. TMSPGE induced gene mutations in bacteria. TMSPGE induced gene mutations in mouse lymphoma L1578Y TK cells but did not induce forward mutations in CHO cells. TMSPGE induced SCE in vitro. There are no in vivo gene mutation data. TMSPGE was not considered tumorigenic when applied to the clipped skin of mice (25 µl dose of 25% TMSPGE in acetone) three times per week for approximately 78 weeks. Note that there was only one dose level, and this dose was relatively low.

In a one-generation reproduction toxicity study in rats, no reproductive effects were observed at any of the doses tested (250, 500, or 1000 mg/kg bw/day). At 1000 mg/kg bw/day, treatment with TMSPGE resulted in the following signs in parental animals: discomfort after dosing (noted for females from early/mid gestation onwards), decreased body weight gain (males), increased mean relative liver and kidney weights (noted for males and females), and histopathological effects on livers and kidneys (males). Based on these data, a NOAEL for parental animals was established at 500 mg/kg bw/day. A NOAEL for reproductive effects was established at 1000 mg/kg bw/day. Three developmental studies have been conducted using TMSPGE. In a rabbit study, the maternal NOAEL was 200 mg/kg bw/day and the developmental NOAEL was 400 mg/kg bw/day (the highest dose tested). In a rat study, the NOAELs for both maternal and developmental toxicity were also at the highest dose tested (1000 mg/kg bw/day). In another rat study, developmental effects were observed at the maternally-toxic dose of 3000 mg/kg bw/day (again, the highest dose tested).

Environment

The melting point of TMSPGE is < -70°C, the boiling point is 290°C at 1013 hPa, and the vapor pressure is 0.003 hPa at 20°C. Because TMSPGE is hydrolytically unstable, the water solubility was not measured. Estimated values for water solubility (1x 10^{+6} mg/L) and partition coefficient (log K_{ow} = -0.9), may also not be accurate because of the chemical's rapid hydrolysis. From photodegradation modeling, the half-life in the atmosphere due to reaction with photochemically-induced OH radicals is estimated to be 5.8 hours. However, the overall half-life may be even shorter, as concurrent hydrolysis will also occur.

The measured hydrolysis half-life for TMSPGE at 25ºC ranges from 3 minutes to 6.5 hours over the pH range of 5 to 9. At pH 7 and 25 °C, the half-life of the parent compound is 6.5 hours and the conversion of TMSPGE to methanol and 3-glycidoxypropylsilanetriol is expected to reach 99.9% in ≤ 2.8 days. The epoxy group slowly reacts (over a period of months) to form diols in water. The Si-C bond will not undergo hydrolysis. The transient silanol groups will condense with other silanols to yield an epoxy-functional silicone resin (oligomer resin). The measured (and calculated) hydrolysis half-lives demonstrate that TMSPGE is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions.

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.

The EQC Level III model was used to evaluate the fate, transport and distribution of TMSPGE between environmental matrices. 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 TMSPGE: Air = 0.6%; Soil = 92.5%; Water = 6.9 %; Sediment = 0.00 %. However, TMSPGE is unlikely to be found in the environment, as this material is hydrolytically unstable. The environmental fate, transport, and distribution of 3-glycidoxypropylsilanetriol were evaluated to provide a more realistic assessment of TMSPGE. 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 3-glycidoxypropylsilanetriol: Air = 0.0%; Soil = 60.9%; Water = 39 %; Sediment = 0.1 %. Biodegradation studies suggest that about 37 % of TMSPGE is degraded after 28 days. TMSPGE is not readily biodegradable. Bioaccumulation of the parent compound is not anticipated since the material is hydrolytically unstable. In addition, the silanetriol has a low Log K_{ow} (-2.61, estimated) and is also not expected to bioaccumulate.

A static test using juvenile rainbow trout (*Oncorhynchus mykiss*) resulted in a 96-hour LC50 of 237 mg/L and in a semi-static test, the LC50 was 55 mg/L in carp (*Cyprinus carpio).* In aquatic invertebrates, the reported 48-hr EC50s for (*Daphnia magna*) were 473 and 710 mg/L. In algae, (*Selenastrum capricornutum*) the 72-hr EC_b50 was 250 mg/L and the 72-hr EC_r50 was 350 mg/L. The 96-hr EC50 for biomass is 260 mg/L. The 72-hour $EC_b50$for *Scenedesmus subspicatus* exposed to TMSPGE was 255 mg/L; the 72-hr EC_r50 was >420 mg/L. In a 21-day daphnia reproduction test, the NOEC was 100 mg/L. Since TMSPGE is subject to hydrolysis, which may occur during preparation of the dosing solutions and/or during testing, the observed toxicity is likely due to the hydrolysis products methanol and silanetriols.

Exposure

Greater than 90% of all uses of TMSPGE are as an intermediate for industrial applications. TMSPGE is used as an additive for adhesion promotion and as a cross-linking agent in adhesives, sealants, encapsulants and coatings and as coupling agents in composites. TMSPGE is generally used at <2% in all of these applications (a level of 1 to 2 % is commonly recommended as a "starting-point" in many applications) and is usually not used at concentrations higher than 6 percent. One sealant product with a higher percentage (10-30 percent) TMSPGE was identified outside the Sponsor Country. In 2002, the annual production volume of TMSPGE in the U.S. was 1702 tonnes.

The physical and chemical properties of TMSPGE minimize the potential for exposure to this substance during its manufacture. In addition, necessary engineering controls during production include proper ventilation, containment, safety equipment and actual hardware designed to minimize exposure through splashing or to the air. More than 50 air samples, collected during production and handling at ambient temperature in production plants, have shown no detectable TMSPGE. The detection limit ranged from 0.05 to 1 ppm, depending upon the volume of air sampled.

Transfer of this material is in closed pipes rather than in open systems to minimize loss of this material (hydrolysis) although some customers do transfer the material in open systems. TMSPGE is transported from the production site as the parent silane to processors/formulators. Although there is no consumer use of the pure substance, it will be found as a minor component (<0.1% as free un-reacted TMSPGE) in caulks. The reactive nature of this material results in the destruction of the parent material in moisture-containing environments, thus limiting public or environmental exposure to the free un-reacted material. TMSPGE will hydrolyze in a spill situation; the rapid hydrolysis means that the parent silane is unlikely to be found in the environment. Once reacted in an application, there is a very low potential for release outside of spills because the glycidoxy- and/or trimethoxysilyl-groups react with the application and no longer exist as free un-reacted TMSPGE.
As noted earlier, TMSPGE hydrolyzes with a half-life of approximately 3 minutes to about 6.5 hours, depending on the aqueous solution temperature, pH and concentration of buffer. Polymerization reduces the potential for exposure to the parent compound and the silanetriol monomer.

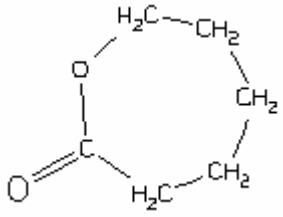
This document may only be reproduced integrally. The conclusions and recommendations (and their rationale) in this document are intended to be mutually supportive, and should be understood and interpreted together.

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

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (aquatic toxicity) and a hazard for human health (several positive genetic mutation results *in vitro* and mixed results in several chromosomal aberration studies conducted *in vivo*). Based on exposure 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 the Sponsor Country as well as Europe and Japan), under normal manufacturing, formulation, industrial and consumer use, this chemical is a low priority for further work. Countries may wish to investigate any exposure scenarios that were not presented by the Sponsor Country.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	502-44-3
Chemical Name	ε-Caprolactone
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

After absorption of ε-caprolactone, the substance will be hydrolyzed rapidly in stomach and blood resulting in the formation of 6-hydroxyhexanoic acid. This hydrolysis product is water soluble and expected to be distributed throughout the body and excreted rapidly, principally through the urine.

ε-Caprolactone exhibits low acute toxicity by all potentially relevant routes of exposure. The acute oral LD_{50} for rats was 4290 mg/kg, while the acute dermal LD_{50} in rabbits was 6400 mg/kg body weight. The primary symptoms following a single high exposure are skin erythema (dermal) as well as apathy and effects on motor coordination and respiration (oral). ε-Caprolactone is considered not-irritating to skin and irritating to eyes.

In a 9-day inhalation study in which ε-caprolactone was administered at a concentration of 45 ppm (213 mg/m^3), no treatment-related effects were found. Therefore the 45 ppm level can be considered a NOAEL. A 90-day inhalation study with ε-caprolactone at concentrations of 15 ppm (71 mg/m^3) and 45 ppm (213 mg/m^3) resulted in perinasal and periocular encrustation and eyelid swelling in the males of the 45 ppm group. As no other treatment related effects were found, this level is considered the lowest observed adverse effect level (LOAEL). The 15 ppm level is considered the NOAEL. ε-Caprolactone given by drinking water to rats at levels of 500, 2000 and 5000 ppm in a 14-day study did not result in any treatment-related clinical signs of toxicity, clinical pathology findings, organ weight changes, necropsy observations or histopathological findings. ε-Caprolactone affected food and water consumption (low palatability) as well as body weight gain at the level of 5000 ppm only. The NOAEL was 2000 ppm, which is equivalent with a dose 152 and 184 mg/kg bw for males and females, respectively.

Bacterial and mammalian *in vitro* mutagenicity tests gave in general negative results. *In vivo*, ε-caprolactone was negative in the mouse micronucleus assay.

No studies are available with regard to reproduction and developmental toxicity of ε-caprolactone. However, a well conducted 90-day inhalation repeated dose study showed no macroscopic and histopathological changes on reproductive organs and also other systemic effects were not found during this study. The lack of systemic effects can be explained by the rapid hydrolysis in stomach and blood, resulting in the formation of 6-hydroxyhexanoic acid. Analogues of 6-hydroxyhexanoic acid show no evidence of reproductive or developmental toxicity. For this reason there is no indication for a reprotoxic concern. This is supported by the toxicological profile of structurally similar lactones, where also no organ specific toxicity was observed in long term studies (with up to 2-year 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.

Environment

ε-Caprolactone is a colourless liquid with a melting point of -1.3 °C and a boiling point of 237 °C. The substance is miscible with water in all proportions and the calculated log Kow (octanol-water partition coefficient) is 0.68. The vapour pressure of ε-caprolactone is 0.81 Pa.

Based on the Mackay model (level III) ε-caprolactone is expected to partition almost exclusively to the aquatic compartment (> 99.9 %). In water ε-caprolactone is hydrolysed to 6-hydroxyhexanoic acid. At 20 degrees Celsius the half-life at pH values of 4, 7 and 9 was 16, 53 and 2.2 days, respectively. 6-Hydroxyhexanoic acid (CAS 1191-25-9) is not listed on the European Inventory of Existing Commercial Substances (EINECS). Ecotoxicity data of this hydrolysis product were not found. However, based on structural comparison the ecotoxicological properties of this substance are expected to be similar to hexanoic acid and adipic acid. ε-Caprolactone is readily biodegradable according to an OECD 301 B guideline study. It is anticipated that ε-caprolactone will not bioaccumulate based on its low octanol-water partition coefficient and rapid degradation in the environment.

Aquatic ecotoxicity tests, which were done according to GLP and standard guidelines, are available for 4 different species encompassing the 3 trophic levels and microorganisms. A 72 hour toxicity test with algae (*Scenedesmus subspicatus*) revealed an EC_{50} and NOEC value of 1217 and 256 mg/l, respectively (based on biomass). Based on the specific growth rate (μ), the EC_{50} (72 h) was calculated to be 2616 mg/l. Water fleas (*Daphnia magna*) appeared to be more sensitive than algae. An acute test with an exposure period of 48 hours resulted in EC_{50} and NOEC values of 204 and 124 mg/l, respectively. For guppy (*Poecilia reticulata*) a steep concentration-response relatonship was observed. A toxicity test with a duration of 96 hours with this fish species revealed an LC_{50} and NOEC value of 295 and 250 mg/l, respectively. However for bacteria (*Pseudomonas putida*) a large difference between the EC_{50} (1260 mg/l) and NOEC (32 mg/l) was found. During this test the bacteria were exposed for 16 hours. Neither chronic aquatic toxicity tests nor terrestrial toxicity tests are available for ε-caprolactone.

Exposure

In 2003, the estimated world-wide production of ε-caprolactone was 40,000 – 60,000 tonnes. In recent years the world-wide production was growing slowly (<5 % per year). The production occurs at four sites located in the USA (two sites), Japan and the United Kingdom.

About 50 % of the quantity produced is used on site for the production of polymers (polycaprolactones). The remaining 50 % is sold to customers (downstream users). The total number of downstream users is less than 1000. ε-Caprolactone is used by downstream users to modify resins and polymers in order to enhance the performance of the end-products. The majority is used for the modification of acrylic resins and polyesters, but it is also used for modification of epoxy resins and polyurethanes. A small quantity of ε-caprolactone (< 1 %) is used as reactive diluent and as a solvent (e.g. for vinyl resins).

During production and processing, inhalation of vapours and direct skin contact are potentially relevant exposure scenarios. However, inhalation exposures to vapours of ε-caprolactone at ambient temperature are likely to be limited due to its low volatility. Based on the information available to the consortium members, ε-caprolactone is not used in consumer products.

Releases into the environment may occur during production and processing of ε-caprolactone. A release of ε-caprolactone to the environment could potentially also occur via use and disposal of polycaprolactone because polycaprolactone may be (bio)degraded to ε-caprolactone, 6-hydroxyhexanoic acid and oligomers.

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.

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

Human Health: The chemical possesses properties indicating a hazard for human health (eye irritation). This hazard does not warrant further work as it relates to reversible effects. This 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 potential.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	513-35-9
Chemical Name	2-Methyl-2-butene (2M2B)
Structural Formula	CH3 | CH3-C=CH-CH3

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No toxicokinetic studies have been conducted with 2-methyl-2-butene (2M2B). Mice are likely to be more sensitive to 2M2B compared to rats, consistent with data on the metabolism of other olefins. The oral LD_{50} of 2M2B is in the range of 1000 to 1700 mg/kg (1.6-2.5 mL/kg). Survivors showed reversible signs of intoxication. The dermal LD_{50} is >2 g/kg. The 4-hour LC_{50} is 61,000 ppm (174,500 mg/m^3). Inhalation of 2M2B can produce central nervous system depression, anesthesia and/or asphyxiation that are reversible following cessation of exposures. 2M2B is a mild skin irritant but does not produce eye irritation. 2M2B is not a skin sensitizer.

In a combined repeat dose/reproductive/developmental study (OECD 422), rats were exposed (whole body) via inhalation to 580, 2,000, and 7,000 ppm (1,660; 5,720; and 20,000 mg/m^3) 2M2B. For the repeated dose phase of the study the exposures were for 6 hr/day, 7 days/week for 28 days. There was a slightly lower bodyweight gain at 7,000 ppm, slightly longer clotting times at 2,000 ppm (prothrombin time for females) and 7,000 ppm (prothrombin times for both sexes and activated partial thromboplastin times for males). Cholesterol levels were increased among the females exposed to 7,000 ppm but in the absence of any further effects in the clinical chemistry parameters or the males this finding is of uncertain significance. Pathological changes were noted among the high-dose females in the liver, as evidenced by increased organ weight and minimal centrilobular hepatocyte hypertrophy. There was also a decreased incidence of extramedullary hematopoiesis in the spleen in the high dose animals and an increase in goblet cell hyperplasia in the nasal passages of the high dose males. In addition, a slight increase in severity of myocardial inflammatory heart lesions and in cortical/medullary tubular basophilia in the kidneys was observed in the high- and intermediate-dose males. Although some general systemic effects were observed in this study, these effects were slight and were most apparent in those animals exposed to the highest dose, 7,000 ppm, and to a lesser extent to those exposed to 2,000 ppm. Based on these observations, the No Observed Effect Level (NOEL) in this study was 580 ppm (1,660 mg/m^3).

2M2B is not mutagenic *in vitro*. It did not induce gene mutations in reverse mutation assays conducted in *Salmonella typhimurium* and *Escherichia coli* either in the presence or absence of metabolic activation. 2M2B did not produce revertant colonies in a gene conversion assay conducted in *Saccharomyces cerevisiae* and it did not induce chromosome damage in cultured rat liver cells.

2M2B was mutagenic at high exposure concentrations ($\geq$ 3,207 ppm ($\geq$ 9,199 mg/m^3)) when tested *in vivo* for its ability to induce micronuclei in bone marrow polychromatic erythrocytes in both mice and rats. However, the incidence was not considered statistically significant at 1,000 ppm (2,869 mg/m^3).

In the combined repeat dose/reproductive/developmental study (OECD 422), rats exposed to concentrations up to 7,000 ppm, 6 hr/day, 7days/week for two weeks prior to breeding, during breeding and through day 19 of gestation. No evidence of reproductive or developmental toxicity was seen. The estrus cycle was unaffected by exposure, and mating performance, fertility indices, and gestation length were similar in all groups. There were no adverse effects

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.

upon survival or growth of the offspring *in utero* or up to day 4 of lactation. Thus, the No Observed Effect Level (NOEL) for reproductive and developmental toxicity is 7,000 ppm (20,000 mg/m^3) (highest dose tested).

Environment

2M2B is a flammable liquid with a measured vapour pressure of 623.9 hPa (25 °C), water solubility of 193 mg/l (25 °C), log K_{ow} of 2.67boiling point of 38.5 °C, and density of 0.662 g/cm^3 (25 °C).

In the air, 2M2B has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals and ozone with calculated degradation half-lives ranging from approximately 1 to 4 and 0.6 hours, respectively, depending on hydroxyl radical and ozone concentrations. Aqueous photolysis and hydrolysis will not contribute to the transformation of 2M2B in aquatic environments because it is either poorly or not susceptible to these reactions.

The photochemical ozone creation potential index for 2M2B has been reported to range from 77.1 to 84.2. Because of the relatively short half-life of 2M2B in the atmosphere and the low environmental concentrations typically found, its contribution to potential global warming can be considered minor. The ozone depletion potential of this substance is negligible as indicated by its net ability to form ozone in the atmosphere.

Results of Mackay Level I distribution modeling show that 2M2B will partition primarily to the air compartment (99.97%), with a negligible amount partitioning to water (0.02%) and soil (0.01%). Level III modeling indicates that at steady state, water is the dominant medium on a percentage basis. Level III modeling may not be representative of ultimate disposition of 2M2B because default emission data used in the model (1000 kg/h) is not a representative rate of chemical discharge. However, concentrations in water are most likely very low because 2M2B is quite volatile, and any volatilised substance will be quickly degraded in the atmosphere. When released primarily to the air compartment, the primary mode of removal would be via photodegradation based on the volatility of 2M2B. In spite of its water solubility, wet deposition of 2M2B is not likely to play a significant role in its atmospheric fate because of rapid photodegradation. Volatilisation to the air will contribute to the rapid loss of 2M2B from aqueous and terrestrial habitats.

2M2B is not readily biodegradable. Bioaccumulation of 2M2B is unlikely based on a low potential to bioconcentrate based on a BCF of 22.7. 2M2B is not expected to sorb significantly to organic matter in soil, sediment, and wastewater solids based on a log K_{oc} of 1.83.

Acute aquatic toxicity values for fish and invertebrates are 5.0 (96hr-LC50) and 3.8 (48hr-EC50) mg/L, respectively. For algae, the 96-hr EC_{50} values are 10.1 mg/L and 13.2 mg/L for biomass and growth rate, respectively, while the NOEC values are 3.61 mg/L and 7.22 mg/L for biomass and growth rate, respectively.

Measured chronic aquatic toxicity values for fish and invertebrates are not available. However, QSAR (Quantitative Structure-Activity Relationship) data include a fish 30-day chronic value of 1.75 mg/L and a 16-day daphnid chronic value of 0.94 mg/L.

Although there are no experimental terrestrial toxicity data available, a 14-day LC_{50} value of 268.3 mg/kg soil has been calculated for an earthworm.

Exposure

Production of 2M2B in the United States is between 5,000 and 23,000 metric tonnes annually. 2M2B is largely used as a chemical intermediate, primarily in the production of isoprene and hydrocarbon resins. It is also used as an intermediate in the production of tertiary pentyl alcohol and is a constituent of gasoline, typically at levels below 1%. 2M2B is a component of natural gas and crude oil. Although 2M2B has been identified in natural environments, this has traditionally been associated with losses from petrogenic sources resulting from off gassing or venting.

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.

Anthropogenic sources of 2M2B can result from combustion of fossil fuels and losses from gas plants and refineries.

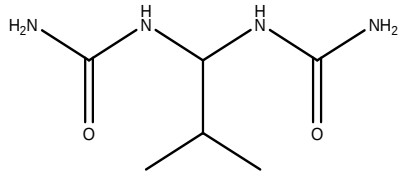
Exposure to 2M2B may occur at workplaces where it is manufactured. Based on physical properties, inhalation and dermal contact would be the primary workplace routes of exposure. One company reports there are 228 workers potentially exposed to 2M2B during production at 6 sites in 5 countries (2 in the US, 3 in Europe, 1 in Asia-Pacific). Since 2M2B production occurs in closed systems, significant worker exposure would occur only during equipment maintenance or under upset conditions. An exposure assessment indicated that 2 of 228 workers (1%) were likely to be exposed to concentrations of 2M2B between 1 and 5 ppm. Slightly less than 10% (22/228) would be exposed to concentrations between 0.1 to 1 ppm, and approximately 90% of workers would have negligible exposures (below the limit of detection, or < 0.1 ppm).Inhalation of 2M2B by consumers can occur and is the primary route of exposure at gas stations where gasoline-containing 2M2B is sold. Average 2M2B air concentrations at gas stations were reported as 0.11 ppm (0.3 mg/m^3) (air) based on data for six stations from three United States cities between October to November 1990. Mean 2M2B exposure levels for gas station attendants, transport drivers, and outside operators were reported as 1.986, 0.740, and 0.446 mg/m^3, respectively. Fueling at gas stations may result in air-borne concentrations of 1 to 3.5% in the vapor phase from those formulations containing 2M2B.

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

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (mutagenic at high concentrations) and the environment (acute fish, aquatic invertebrates, and algae). Based on exposure 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), under normal manufacturing, formulation, industrial and consumer use, this chemical is a low priority for further work. Countries may wish to investigate any exposure scenarios that were not presented by the sponsor country.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6104-30-9
Chemical Name	Urea, N,N''-(2-methylpropylidene)bis- (IBDU)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Urea, N,N''-(2-methylpropylidene)bis- (IBDU) had a low acute toxicity by the oral route. The only clinical signs noted after oral exposure to rats were tachypnoea and piloerection (LD50, rat, oral: > 10 000 mg/kg bw, IBDU purity. 90 - 96 %). There are no valid acute studies available using the inhalation or dermal routes of exposure.

No eye or skin irritation studies of IBDU according to the current standard are available. Nevertheless the available studies with rabbits are considered of sufficient and good quality to allow the evaluation of these endpoints. IBDU (0.5 g) as a 50 % aqueous suspension was not irritating to the skin of rabbits under semi-occlusive conditions for 20 hours and 0.05 ml IBDU was slightly irritating to the eyes of rabbits.

After repeated oral administration over 4 weeks by gavage to rats in a screening study following OECD TG 422 (1996), the “No Observed Effect Levels” (NOAELs) were 300 mg/kg bw/day for females (reduced body weight gain during pregnancy and lactation at 1000 mg/kg bw/day), and 1000 mg/kg bw/day for males (highest tested dose level).

IBDU was tested negative in a standard and pre-incubation Ames test performed with *Salmonella typhimurium* TA1535, TA1537, TA98 and TA100 according OECD TG 471 (1983) both with and without metabolic activation (rat liver S-9 mix) up to 5000 µg/plate. In vivo, IBDU did not induce micronuclei in male mice treated up to the highest guideline recommended dose (2000 mg/kg bw) in a study performed in accordance with OECD TG 474. Although the ratio between polychromatic and normochromatic erythrocytes was not changed thus lacking to show that the test substance has reached the bone marrow, there is evidence for systemic availability from the above mentioned repeated dose toxicity study in rats where kidney effects were observed in males at 300 mg/kg bw/day.

In a reproductive/developmental toxicity screening test (OECD TG 422), and in a modern one-generation study, IBDU had no effects on the reproductive function of rats (NOAEL: 1200 mg/kg bw/day; highest dose tested). The NOAEL for general toxicity was 300 mg/kg bw/day (reduced body weight gain in females during pregnancy and lactation at 1000 mg/kg bw/day). No developmental effects were seen in a study performed in accordance with OECD TG 414 on Wistar rats (NOAEL developmental toxicity: 1000 mg/kg bw/day; NOAEL maternal toxicity: 300 mg/kg bw/day), and in the above mentioned screening test in rats according to OECD TG 422 (NOAEL developmental toxicity: 1000 mg/kg bw/day and NOAEL maternal toxicity: 300 mg/kg bw/day).

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

IBDU is a solid substance which melts at 205 °C under decomposition. The water solubility is in the range between 0.3 and 3.0 g/l at 20 °C. Henry's law constant was calculated as $4.11*10^{-13}$ Pa*m^3/mol from which a vapour pressure of $4.7*10^{-12}$ can be derived. According to a fugacity model (Mackay level I), the main target compartment for IBDU is water (almost 100 %), with negligible amounts in the other compartments. The Henry Constant indicates a negligible volatility from water. In air the substance is indirectly photodegraded by hydroxyl radicals (0.5×10^6 OH/cm^3 as a 24 h average) with a calculated half-life for photo-oxidation of 8.2 hours.

IBDU is potentially susceptible to hydrolysis because of its structure. The calculated half-life for hydrolysis, however, is more than one year. Adsorption to solid phase is not expected based on a calculated log K_{oc} of 1.4.

The substance is readily biodegradable as shown in a test according to OECD TG 301C with non-adapted inoculum. At a test substance concentration of 100 mg/l, a biodegradation of 78 % was found within 28 days (72 % within 7 days, and 78 % within 14 days). In soil, IBDU is hydrolyzed to urea and isobutyraldehyde. These two substances are at least inherently biodegradable and have a low acute toxicity (urea: > 100 and isobutyraldehyde: > 10 mg/l). Urea is decomposed by urease into NH_3 and CO_2 (ammonification) and NH_3 then protonated into the ammonium ion. The latter volatilizes or is oxidized via nitrite into nitrate (nitrification). The measured log K_{ow} of - 0.903 for IBDU (at room temperature) does not indicate a significant potential for bioaccumulation.

Short-term tests with fish, invertebrates and algae were available for IBDU. The effect values from the short term tests are: *Salmo gairdneri*: 96h-LC_{50} > 1000 mg/l, *Daphnia magna*: 48h-EC_{50} = 500 mg/l, *Scenedesmus subspicatus*: 72h-E_rC_{50} > 500 mg/l. Applying an assessment factor of 1000 according to the EU Technical Guidance Document, a $PNEC_{aqua}$ of 500 µg/l is derived from the 48h-EC_{50} for *Daphnia magna*.
The 14d-LC_{50} for *Eisenia fetida* was 648 mg/kg soil.

Exposure

In 2003, the worldwide production volume for IBDU was between 30 000 and 50 000 metric tons. Since there is only one producer in each region (Germany, Canada, Japan), no production volumes can be provided for the regions for confidentiality reasons.

The main use of IBDU is as a slow nitrogen release fertilizer for horticulture and turfgrasses. It is marketed worldwide, mainly in the form of granules for professional and consumer use (wide dispersive use). The main route for occupational and consumer exposure is skin contact.

Emissions of IBDU to the environment may occur during manufacture, processing and use of products containing the substance. In the sponsor country, emissions from a production plant amount to about 2 tons/year (as TOC) and 8 tons/year (as NH_4-N). Approximately 488 kg/year are emitted into the air. From the use as fertilizer, an exposure of the terrestrial compartment takes place.

Occupational exposure may occur during production, processing and use of IBDU containing products. No workplace exposure information is available with regard to the manufacturing and processing sites. Exposure of the general public through the environment is not considered as significant as the substance is biodegradable and has no bioaccumulation potential.

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

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	64-17-5
Chemical Name	Ethanol
Structural Formula	CH_3-CH_2-OH

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The assessment of the substance is focused on its use as industrial chemical. Ethanol consumption in alcoholic beverages is out of the scope of this report.

Ethanol is readily absorbed by the oral and inhalation routes and subsequently, metabolized and excreted in humans. At exposures relevant to occupational and consumer exposure during manufacture and use of ethanol containing products, the alcohol dehydrogenase metabolic route in the liver dominates and does not become saturated. This mechanism follows first order kinetics. The first step of the metabolic path is the rate-determining step; concentrations of the intermediate metabolite acetaldehyde are very low. Ethanol is not accumulated in the body. Dermal uptake of ethanol is very low.

Ethanol has a low order of acute toxicity by all routes of exposure. Lowest robust reported values are an inhalation LC_{50} of >60,000ppm (114,000 mg/m^3), 1 hour, mouse), and an oral LD_{50} of 8300mg/kg.bw (mouse). Ethanol is a moderate eye irritant but is neither a skin irritant nor a sensitizer.

For repeat dose effects, the lowest reported NOAEL is approximately 2400 mg/kg bw/day from a dietary study with rats. At higher doses, male rats showed minor changes to organ weights and haematology/biochemistry; female rats showed minor biochemistry changes and increased length of oestrus cycle along with liver nodules; adverse liver effects were observed at concentrations of 3600mg/kg.bw/day and above

The balance of evidence is that ethanol is not genotoxic. Negative results from a number of bacterial mutation assays appear to be reliable. Of the mammalian cell mutation assays a weak mutagenic effect in mouse lymphoma cells occurred only at very high ethanol concentrations. *In vivo* tests for chromosome aberrations in both rats and Chinese hamsters have given negative results. There is very little evidence to suggest that ethanol is genotoxic in somatic cells and it may have a very limited capacity to induce genetic changes *in vivo* but under very specific circumstances and at very high doses achievable in humans only by deliberate oral ingestion.

Evidence of the carcinogenicity of ethanol is confined to epidemiological studies assessing the impact of alcoholic beverage consumption. These do not indicate any such hazard exists from potential exposure to ethanol in the work place or from the use of ethanol in consumer products.

No fertility or developmental effects were seen at inhalation exposures up to 16000 ppm (30,400 mg/m^3). The lowest reported NOAEL for fertility by the oral route was 2000 mg/kg bw in rats, equivalent to a blood alcohol concentration of 1320 mg/l, although this was based on a significant increase in the number of small pups rather than a direct effect on fertility; such direct effects are not seen until much higher doses. Many studies exist examining the developmental end point for ethanol. However, most use very high doses and few are individually robust enough to allow a NOAEL to be established. However, the collective weight of evidence is that the NOAEL for developmental effects in animals

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.

is high, typically >=6400mg/kg bw, compared to maternally toxic effects at 3600 mg/kg bw. The potential for reproductive and developmental toxicity exists in humans from deliberate over-consumption of ethanol. Blood ethanol concentrations resulting from ethanol exposure by any other route are unlikely to produce reproductive or developmental effects.

Environment

The available physicochemical data are adequate to describe the properties of ethanol. The melting point for ethanol is -114^{o}C, the boiling point is 78.3 ^{o}C and the log K_{ow} is –0.31. Ethanol has a measured vapour pressure of 57.3 hPa at 20°C. Ethanol has a specific gravity (density) of 0.7864 and a flashpoint of 14 ^{o}C. It is fully water miscible at ambient temperatures. Henry's Law constant is 0.000252.

Ethanol is stable to hydrolysis but is readily biodegradable (74% after 5 days) and is not likely to bioaccumulate (calculated logBCF=0.5). Ethanol is not persistent in the environment. Fugacity-based modelling shows that ethanol released into the environment will become distributed mainly into air and water. Relative distributions between compartments based on an emission pattern of 1000:100:10 were 57 % in air, 34 % in water, and 9 % in soil. These predictions are supported by the limited data available on prevailing concentrations, which shows that ethanol has been detected in outdoor air and in river water. The total tropospheric half life of ethanol is estimated to be 10-36 hours, with degradation due to hydroxyl, NOx and SOx radical-mediated photooxidation. As a volatile organic compound in the atmosphere, ethanol is a potential contributor to tropospheric ozone formation under certain conditions, however its photochemical ozone creation potential is considered to be moderate to low (40-45 relative to ethylene as 100).

The aquatic toxicity data in fish, invertebrates, and algae indicate a low order of acute toxicity with LC_{50}/EC_{50} values greater than 1000 mg/l. The most sensitive species were algae *Chlorella vulgaris* with a 96hr EC_{50} of 1000 mg/l and the invertebrate *Artemia Salina* with a 24hr LC_{50} of 1833 mg/l. Valid chronic toxicity data are available for two trophic levels. The lowest reported NOEC for invertebrates is 9.6 mg/l (10 day reproduction) whilst for plants it is 280mg/l (7 day study).

Exposure

Worldwide ethanol production was 25,000 kt in 2001. European production is 1,700 kt. Ethanol is manufactured either by fermentation of biomass or by the hydration of ethylene in a continuous, closed process; release from production facilities is low.

Ethanol use falls into four main categories: use as a solvent, in manufacture of chemicals, as a fuel additive and for potable drink manufacture. Solvent use is mainly in paint and ink manufacture and in pharmaceutical production. Ethanol is widely used in consumer products, mainly cosmetics, but also detergents, winter deicing and cleaning products, including detergents.

There is limited published data on exposure of workers to ethanol but what is available indicates that the vast majority of exposures are well below current occupational exposure limits (OELs). However, some scenarios were identified in one of the sponsor countries with the potential for high inhalation exposure (eg pharmaceutical manufacture). Personal protective equipment should be used in these situations to reduce actual exposure There is no data on consumer exposure from the use of products containing ethanol, but it is likely that the dominant source of consumer exposure to ethanol is through natural sources in foodstuffs and the consumption of alcoholic beverages.

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.

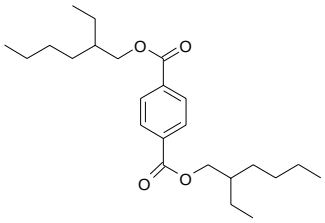
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The assessment of the substance is focused on its use as industrial chemical. Ethanol possesses properties that indicate a hazard for human health but these are manifest only at doses associated with consumption of alcoholic beverages. In the context of an industrial chemical, these hazards do not warrant further work as they are not likely to result from the manufacture and use of ethanol and ethanol containing products.

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6422-86-2
Chemical Name	Di(2-ethylhexyl)terephthalate (DEHT)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Di(2-ethylhexyl)terephthalate (DEHT) has been shown in both *in vitro* and *in vivo* studies to have the potential to undergo complete hydrolysis to yield terephthalic acid and 2-ethylhexanol (2-EH), which are rapidly eliminated. Results of these metabolism studies also indicate DEHT was not well absorbed within the gastrointestinal tract, with 36% of it recovered in the feces still intact. In addition, a study to assess dermal absorption rate indicated that DEHT has a very low potential to penetrate the skin (0.103 $\mu g/cm^2/hr$), which further limits systemic exposure potential.

The acute oral LD_{50} values are in excess of 3,200 mg/kg in mice and 5,000 mg/kg in rats. The acute dermal LD_{50} value is in excess of 19,670 mg/kg bw in guinea pigs, and skin and eye irritation studies in animals and/or humans indicate that DEHT has only a slight potential to induce irritation. In studies with some limitations, no skin sensitization was observed in humans or animals.

In one repeated dose study, rats were fed diets containing up to 2.5% (approx. 2,000 mg/kg bw/day) DEHT for 21 days, while in the other they received up to 1% DEHT in the diet for 90 days (approx. 561 mg/kg bw/day for males and 617 mg/kg bw/day for females). The NOELs in both studies were 0.5 % (approximately 500 mg/kg bw/day in the 21 day study and 277 – 309 mg/kg bw/day in the 90 day study). The only effect noted at 1.0 % in the 90 day study was increased relative liver weight. In the 21-day study, administration of 1.0 % was associated with increased relative liver weight in females but was without effect in males. Peroxisome proliferation in the liver was not noted in animals treated with either of these dosing regimens.

DEHT has been shown to be negative in both mutagenicity and chromosomal aberration assays with and without metabolic activation. No carcinogenicity data are available.

The reproductive toxicity of DEHT has been assessed through a two-generation study in rats following OECD Test Guideline 416. The NOAEL for reproductive toxicity was 1.0% in the diet (500-700 mg/kg bw/day for males and 800-1000 mg/kg bw/day for females; highest dose tested), and the NOAEL for parental and offspring toxicity based on reduced body weight gains was 0.3% (150-200 mg/kg bw/day for males and 250-300 mg/kg bw/day for females). Mean maternal body weights and body weight gains were reduced for F0 and F1 females in the 1.0% group throughout pregnancy and decreased mean terminal body weights were noted in F1 males and females given 0.6% or 1.0% test material. The results of this study, in conjunction with the 90-day study described above which also showed no effect of DEHT on histology of reproductive organs indicate that DEHT has a low potential to induce reproductive toxicity.

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.

Developmental toxicity was evaluated in a dietary study following OECD Test Guideline 414. The NOEL for maternal toxicity was 0.6% (458 mg/kg/day) and the NOEL for developmental toxicity was 1.0% (747 mg/kg/day; highest dose tested). The ability of DEHT to induce anti-androgenic like effects in male offspring was assessed by giving pregnant rats 750 mg/kg DEHT by gavage on gestation day 14 until postnatal day (PND) 3. No changes indicative of a feminization effect were induced in male pups. Results of a uterotrophic assay in which immature females were given up to 2000 mg/kg/day DEHT by gavage on PND 19-21 also indicate that DEHT does not possesses estrogenic activity.

Environment

DEHT is a high boiling liquid (boiling point 383°C at 1015 hPa) with a very low vapour pressure (estimated to be 2.85 E-5 hPa at 25°C by EPIWIN). It has a melting point of -48°C, a water solubility of 0.0004 mg/l and an EPIWIN-estimated octanol/water partition coefficient of 8.39. The atmospheric photodegradation half-life is 0.487 days (5.84 daylight hours). Based on its molecular structure, DEHT is not anticipated to undergo rapid hydrolysis in the presence of water. Level III fugacity modeling assuming equal distribution indicates 0.743% to air, and 7.26% to water with greater percentages in the soil and sediment compartments (28% and 64%, respectively). These results are supported by a Koc value of 1.62 E+5. While the vapour pressure of DEHT is very low, the Henry's Law Constant is relatively high (1.02 E-5 atm-m^3/mol) due to the substance's offsetting low aqueous solubility. A biodegradation study failed to show that the material was "readily biodegradable" under the method and conditions of the test, but did show 40.2% conversion to CO2 in 28 days indicating that the material is ultimately biodegradable. Results of an activated sludge respiration inhibition test indicate that DEHT is not toxic to wastewater microbes. Studies assessing acute and chronic toxicity to fish (Fathead minnow and Rainbow trout) and invertebrates (*Daphnia magna*, Planorbid snail, Eastern oyster), and acute affects on algal (*Selenastrum capricornutum*) growth showed no effects at water concentrations that were often significantly greater than its limit of solubility in distilled, deionized water that is free of particulate matter (0.0004 mg/L). Terrestrial plant growth in three species was not affected by DEHT exposure. An OECD sediment-water chironomid toxicity test using spiked sediments indicated that the EC50 was greater than the highest concentration recommended by the method (1000 mg/kg nominal, 950 mg/kg measured) and the NOEC was 180 mg/kg. A bioconcentration study in oysters indicated that the material has a medium to low potential to bioconcentrate (BCF = 393). However, due to its propensity to be eliminated by higher trophic organisms, it is not expected to bioaccumulate.

Exposure

A single U.S. manufacturer produces DEHT using a continuous reactor, distillation column and storage tanks. Annual production is about 25-50 thousand metric tons. Occupational exposure is limited by the closed process, and also because the substance is a high boiling liquid of limited volatility. The primary use of DEHT is as a plasticizer whereby it is bound in a polymer matrix, limiting consumer exposure. Some consumer exposure may occur based on a minor use in coated fabrics, but the application is on the exterior of the fabric, away from direct dermal contact, and the DEHT is bound up in the polymer. Concentrations of DEHT in the environment in air or water have not been reported, but there is limited potential for release into the environment. Environmental releases during manufacture and processing are limited by the use of enclosed processes and by in-plant treatment of any waste streams through biodegradative waste treatment or incineration. DEHT is released slowly into the environment from various uses of PVC, such as in PVC waterstops, gaskets, weather stripping, shoe soles, pond linings and wire coatings. Any DEHT that may enter the environment will have a strong tendency to be adsorbed onto solid matter such as soil and sediment.

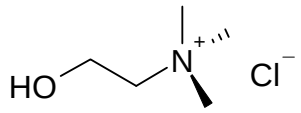
This document may only be reproduced integrally. The conclusions and recommendations (and their rationale) in this document are intended to be mutually supportive, and should be understood and interpreted together.

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

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	67-48-1
Chemical Name	Choline chloride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

In some circumstances, available data for other choline salts (e.g. choline magnesium salicylate) have been evaluated in Human Health to assist the weight of evidence approach for choline chloride. Due consideration was given to potential toxicity exerted by byproducts e.g. in parenteral exposure.

Human Health

Choline is a dietary component and found in foods as free choline and as esterified forms such as phosphocholine, glycerophosphocholine, sphingomyeline, and phosphatidylcholine. It functions as a precursor for acetylcholine, phospholipids, and the methyl donor betaine and is important for the structural integrity of cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, and lipid and cholesterol transport and metabolism.

Dietary choline is absorbed from the lumen of the small intestine. Additionally to dietary supply choline can be made available by enzymatic cleavage in the pancreas from other nutritional sources (e.g. phosphatidylcholine). Before choline can be absorbed from the gut, some is metabolised by bacteria to form betaine and methylamines. Fasting plasma choline concentrations vary from 9 to 20 µmol/L.

The critical adverse effect from high intake of choline is hypotension, with corroborative evidence on cholinergic side effects (e.g., sweating and diarrhoea) and fishy body odour. After inadequate dietary intake decreased choline stores and liver damage (as assessed by elevated alanine aminotransferase) may develop.

Animal studies with choline chloride show a low acute toxicity after oral uptake (with a range of LD50s of 3150 – ≥5000 mg/kg bw determined in different studies). . No acute toxicity attributable to choline was observed in humans following oral doses of ≥3000 mg choline magnesium trisalicylate/day.

In rabbits, choline chloride may lead to a slight irritation of the skin and eye. No data on sensitization in animals are available. The skin sensitisation potential of choline chloride is regarded as negligible in humans.

In a limited, specialised, repeated dose study designed to investigate the impact of choline on the liver tumour promoting activity of phenobarbital and DDT in DEN-initiated animals, rats were dosed with approximately 500mg/kg bw/day over 72 weeks via feed, with a post-observation period of 30 weeks. No significant effects were observed relative to controls with respect to survival rates, body weights and relative liver weights. Only limited

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.

pathological investigations were carried out at autopsy (gross examination with histological investigation of only the liver and any tissues showing gross abnormalities). No adverse effects were observed. Therefore the NOAEL for this study was ≥500mg/kg bw/day. The tolerable upper intake level for human adults was set at 3.5 g/day corresponding to approx. 58 mg/kg bw/day (USA's Standing Committee on the Scientific Evaluation of Dietary Reference Intakes).

Choline chloride does not show a mutagenic, clastogenic or DNA damaging potential when tested *in vitro*; furthermore it has no structural alerts. There is therefore no indication of a genotoxic potential *in vivo*.

No developmental toxic effects were observed in mice after oral doses of 1250 mg/kg bw/day on gestation days 1 to 18. Doses above the levels recommended currently (4160 mg/kg bw/day and higher) and associated with maternal toxicity, did produce developmental toxic effects, but these were secondary to the maternal toxicity at the excessive doses used. The compound does not produce any significant developmental toxicity in the mouse.

Thus evidence from animal studies and from human exposure indicates that choline chloride has low toxicity, is not mutagenic and has no developmental toxicity. This is not unexpected in view of its presence in the diet and its production in metabolic processes in the body; it fulfils key roles in nerve transmission, cell membrane integrity, and lipid metabolism. Only limited animal data are available on effects on fertility, but the normal exposure of humans to appreciable amounts of choline chloride both from the diet and formed from normal metabolic processes, would argue against it having any significant adverse effects on fertility. This is supported by the fact that it has been widely used as an animal feed additive for decades with no apparent adverse effects being noted on fertility.

Environment

Choline chloride is a white crystalline solid but is marketed as an aqueous solution (70 – 75 % w/w in water) which is a colorless liquid with an amine-like odor. It has a measured water solubility of ca. 650 g/L (calculated water solubility: 1,000,000 mg/L) and a calculated vapor pressure of $6.57*10^{-10}$ hPa at 25°C. A Henry's Law Constant of $2.06*^{10-}11$ Pa*m³/mole at 25 °C could be calculated. Distribution modeling using Mackay Level I indicates water (100 %) to be the main target compartment. The amount in the other compartments is with < 0.0001 % negligible. Choline chloride is readily biodegradable according to OECD-criteria (MITI-I Test; BOD measurements) reaching 93 % degradation within 14 days. Due to the chemical structure hydrolysis can be excluded. In the atmosphere choline chloride will be rapidly degraded according to a half life time ($t_{½}$) of about 6.9 hours for hydroxyl-radicals based on a 12 hours day. Due to the measured and calculated $\log K_{ow}$ of –3.77 and –5.16 both at 25°C, respectively, and a calculated $\log K_{oc}$ of 0.37 a bio- or geoaccumulation is not to be expected.

The aquatic toxicity has been determined for freshwater and saltwater species according to several GLP and non-GLP test guidelines. For the freshwater fish species *O. latipes* a LC_{50} (96h) of > 100 mg/L and for the saltwater fish species *L. limanda* a LC_{50}(96h) of > 1,000 mg/L could be determined, respectively. The acute toxicity (EC_{50}) for the invertebrate species *D. magna* was found to be 349 mg/L after 48 h of exposure, In a 21d Daphnia reproduction test, a 21d NOEC (reproduction) of 30.2 mg/l was obtained. For the freshwater algae *Pseudokirchneriella subcapitata* an Er(b)C_{50} (72h) of > 1,000 mg/L could be determined.

Exposure

The world production of choline chloride in the year 2002 was in the range of10,000 to 50,000 tons.

At the European production sites choline chloride is produced under pressure and room temperature by reaction of trimethylammonium chloride with ethylene oxide in closed systems. Exposure may occur during manufacture, transportation and industrial use. The likely primary routes of human exposure to choline chloride are skin contact and inhalation at the work place. Worker exposure is limited by enclosed systems, industrial hygiene controls and personal protective measures are adequate.

Choline chloride has a widespread use as a food additive for animal husbandry since the early 1930s. For this

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.

application area almost 100% of the produced choline chloride is either premixed as solid and then directly mixed with animal feed or marketed as a fluid compound to the customers and directly released into special installed mixing apparatus. A very small amount of the choline chloride production is used for formulations in the field of plant growth regulators. In general the following formulations are used for commercial applications: Bulk, in solution (up to 70%), on vegetable carriers, on amorphous silica carriers.

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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	67-56-1
Chemical Name	Methanol
Structural Formula	CH_3OH

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Toxicokinetics, Metabolism, and Distribution: Methanol is readily absorbed by inhalation, ingestion and dermal contact and distributes rapidly throughout the body. Metabolism in humans, rodents, and monkeys contributes up to 98 percent of the clearance, with more than 90 percent of the administered dose exhaled as carbon dioxide. Renal and pulmonary excretion contributes only about 2 – 3 percent. The metabolism and toxicokinetics of methanol varies by species and dose. In humans, the half-life is approximately 2.5 – 3 hours at doses lower than 100 mg/kg bw. At higher doses, the half life can be 24 hours or more.

The mammalian metabolism of methanol occurs mainly in the liver, where methanol is initially converted to formaldehyde, which is in turn converted to formate. Formate is converted to carbon dioxide and water. In humans and monkeys, the conversion to formaldehyde is mediated by alcohol dehydrogenase. In rodents, the first reaction occurs mainly via a catalase-peroxidase pathway which is rate-limiting. Methanol in turn accumulates in the blood at high doses. In primates, the last reaction step, conversion of formate to carbon dioxide by the formyl-tetrahydrofolate synthetase, is rate-limiting, leading to a disproportionate increase of formate in the blood and sensitive target tissues (such as CNS and the retina).

In humans, when exposed via inhalation up to an air concentration of 0.065 mg/L, no increase of blood methanol is expected. Up to 0.26 mg/L (single or repeated exposure), the methanol blood level is likely to increase 2 to 4-fold above the endogenous methanol concentration in humans, but still remains significantly below 10 mg/L. Air concentrations up to 1.6 mg/L resulted in similar blood methanol among rats, monkeys, and humans. However, above 1.6 mg/L, a steep exponential increase occurs in rats, a smaller exponential increase occurs in monkeys, and humans exhibit a linear relationship between air concentrations and blood methanol levels.

Baseline levels of formate in blood are about 3 to 19 mg/L (0.07 – 0.4 mM) in humans. Toxic blood formate concentrations are reported to be 220 mg/L and higher ($\geq$5 mM formate). Inhalation of about 1.20 mg methanol/L for 2.5 hours contributed only insignificantly to the internal formate pool in monkeys (in the µM-range); this also held true for folate-deficient conditions. Also after repeated inhalation of 2.6 mg/L (2000 ml/m^3) for 6 hrs/day, 5 days/week, for 1 or 2 weeks, monkeys showed no discernible increase in formate concentration in blood [estimated body burden 200 to 300 mg/(kg bw$*$d)], whereas formate accumulation has been observed in primates at methanol doses greater than 500 mg/kg bw given as a bolus. The critical methanol dose that saturates the folate pathway in humans is estimated to be ≥200 mg/kg bw. Based on data produced in monkeys, metabolic saturation in humans is also less likely to happen during inhalation if the amount is divided over a prolonged time and not incorporated as a bolus.

Acute Toxicity: Formate is considered to be the ultimate toxicant in acute methanol intoxication in humans. Acidosis and ophthalmologic changes are typical primary effects. However, these effects do not occur in rodents or rabbits., which are able to remove formate more efficiently. In these animals, CNS depression is usually the cause of defects and finally death.

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.

A blood level of 500 mg methanol/L in acutely poisoned patients generally is regarded as requiring hemodialysis. This blood concentration can transiently be achieved in an adult person (70 kg) by ingestion of 0.4 ml methanol/kg (approximately 0.32 mg/kg). Generally, in humans, transient central nervous system (CNS) effects appear above blood methanol levels of 200 mg/L and serious ocular symptoms appear above 500 mg/L.

The minimal acute methanol dose to humans that can result in death is considered to be 300 to 1000 mg/kg by ingestion, and fatalities have occurred in untreated patients with initial methanol blood levels in the range of 1500-2000 mg/L. However, such high blood methanol levels able to cause death are not .likely to be achieved through inhalation exposure. For example, 2.6 or 6.5 mg/L resulted in methanol blood levels that barely exceed 100 and 200 mg/L, respectively, after an 8-hour working shift. Exposure to 0.26 mg methanol/L for 4 hours was without significant physiologic effects in human volunteers.

In rats, LC_{50} values have been calculated to be 83.2 and 128.8 mg/L after 4 hours. In cats, the LC_{50} was 85.4 mg/L after four hours. In monkeys, air concentrations of 52 mg/L after 1-4 hours and 13 mg/L after 18 hours led to an unspecified level of mortality. Dermal LD_{50}s in rabbits range from 15800 to 20000 mg/kg bw. In rats, the dermal LD_{50} is greater than 45,000 mg/kg bw. In monkeys, four daily dermal doses of 400 mg/kg bw eventually resulted in death. Oral LD_{50}s in rats range from < 790 to 13,000 mg/kg bw; in mice, the values range from 7,300 to 10,000 mg/kg bw; in rabbits, the LD_{50} was approximately 14,200 to 14,400 mg/kg bw; and in monkeys, the values range from 7000 to 9000 mg/kg. Although most of the references for these values provided only limited details, the values are consistent within species and route of exposure.

Irritation/Sensitisation: Methanol exhibited no skin irritation in one study in which the chemical was administered under occluded conditions as a 100 percent concentration. Limited information from another study showed moderate irritation with 500 mg. Available studies show that methanol is a slight eye irritant with doses of 0.05 to 0.1 mL. Some reversibility of effects was observed. High concentration of methanol vapours may be irritating to mucous membranes. A guinea pig maximization assay gave no evidence of contact sensitisation after induction and challenge doses of 50 percent.

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

In another whole body inhalation study in monkeys exposed up to 20 days for 21 hours per day, coma and lethality were observed at concentrations $\geq$ 9.1 mg/(L$*$d). In the brain, necrosis of the basal ganglia and cerebral edema were observed at 6.5 mg/(L$*$d) and at 3.9 mg/(L$*$d), hyperplasia and fibrosis around myelin sheaths of the basal ganglia as well as a slight to moderate increase in astroglia cells were observed. The optic nerve showed atrophy at >3.9 mg/(L$*$d), along with reduction in myelin fibers. In the liver, fibrosis was observed at 6.5 mg/(L$*$d) and mild fatty degeneration was observed at 3.9 mg/(L$*$d). In the kidney, partly vacuolated hyaline degeneration was observed at 6.5 mg/(L$*$d).

In rats exposed to methanol up to 6.5 mg/L for 6 hours per day, five days per week for 28 days, no adverse effects were observed except local nasal irritation and increased relative spleen weights, which were observed only at the middle dose. The estimated blood level of methanol was about 250 mg/L under this condition.

In a whole body inhalation study in mice exposed for 12 months to concentrations of 0.013, 0.13, and 1.3 mg/L 20 hours per day, slight changes in clinical signs, body and organ weights, and some changes in histopathology were observed. In rats exposed in the same manner, slight changes in body weight and organ weights were observed at the highest dose. The NOEL is 0.13 mg/L. In rats, gavage doses of 100, 500, and 2,500 mg/(kg bw$*$d) for 90 days

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.

resulted in increased liver enzymes and reduced brain weights at the highest dose resulting in a NOAEL of 500 mg/(kg bw*d).

Mutagenicity: Numerous *in vitro* assays (including seven Ames assays, four micronucleus/cytogenetic assays, a mammalian gene mutation assay, a yeast gene mutation assay, a mouse lymphoma test, three cell transformation assays, and a DNA damage and repair assay) were conducted on methanol. The majority of these assays are negative, with the exception of positive results in the mouse lymphoma test and a mitotic recombination assay in Aspergillus, and ambiguous results in an Ames assay for strain TA102 and in the DNA damage and repair assay. Only limited details were available for the mouse lymphoma test. Of the eleven *in vivo* assays (all micronucleus and cytogenicity assays plus a *Drosophila* SLRL assay), all are negative except one cytogenetic assay, which was positive for aneuploidy, sister chromatid exchange, and micronuclei. Limited information was available regarding this positive result. Thus, although most studies indicate that methanol does not have the potential to be mutagenic, not all studies lead to that conclusion.

Carcinogenicity: Methanol was tested in two long-term whole body inhalation studies (24 months in rats and 18 months in mice for 20 and 19 hours per day, respectively). There was no evidence of a carcinogenic potential in rats and mice exposed to air concentrations of up to 1.3 mg/L.

Reproductive/Developmental Toxicity: ***Monkeys.*** In monkeys, parents were exposed via inhalation prior to and during breeding as well as during pregnancy to doses of 0.26, 0.78, and 2.34 mg/L. A late wasting syndrome was observed at the highest dose in 2 out of 7 female descendants, associated with signs of severe malnutrition and gastroenteritis noted at autopsy. Mild neurobehavioral effects in offspring and some vaginal bleeding in mothers were observed at all concentrations. However, due to the normal variance in and the low number of animals, along with pre-term delivery of several mothers, the observed findings are difficult to interpret.

Rats. Several inhalation studies in rats resulted in a variety of effects in offspring due to prenatal and/or postnatal dosing. In a 2-generation whole body inhalation reproductive study in which rats were exposed for 19-20 hours/day, decreased brain weights in the first and second generation offspring (F1, F2) resulted in a NOAEL of 0.13 mg/L. In a developmental study in which rats were exposed by whole body inhalation on gestation days 1 to 19 at the two lowest doses and days 7 to 15 at the highest dose for 7 hours/day, malformations and fetal weight changes resulted in a NOAEL of 6.5 mg/(L*d) (the lowest dose tested). A second whole-body inhalation developmental study in which rats were exposed on gestation days 7 to 17 for 23 hours/day, malformations, increased fetal resorptions, and decreased numbers of live fetuses were observed, resulting in a NOAEL of 1.3 mg/(L*d).

Mice. In a study of reproductive effects, there was an insignificant increase in morphological anomalies in spermatozoa in male mice at 1000 mg/(kg bw*d) after oral dosing for five weeks. A developmental whole body inhalation study in mice exposed on gestation days 6 to 15 for 7 hrs/day resulted in developmental effects including increased exencephaly and cleft palate, fully resorbed fetuses, decreased numbers of live pups, and decreased body weights; this study resulted in a NOAEL of 1.3 mg/(L*d). Oral studies in mice resulted in various malformations at 4000 mg/(kg bw*d) (the LOAEL) and higher; no NOAELs could be established from these studies.

Humans. No epidemiological studies in humans have been located to demonstrate that there is a link between methanol exposure and an increased incidence of fetal malformations or developmental impairment.

Rodent data on reproductive and developmental toxicity are relevant for humans despite the known differences in methanol metabolism between rodents and humans. Rodents are adequate models for human exposure to methanol at levels where formate does not accumulate. However, blood methanol concentrations associated with serious teratogenic effects and reproductive toxicity observed in the rodent studies are in the range of 1000 – 2000 mg methanol/L blood, associated with formate accumulation in humans, which is likely to result in metabolic acidosis and visual and clinical effects in humans. In humans, generally, transient central nervous system (CNS) effects appear above blood methanol levels of 200 mg/L, ocular symptoms appear above 500 mg/L, and fatalities have often occurred in untreated patients with initial methanol levels in the range of 1500-2000 mg/L. Other effects (e.g., subtle, not yet definitive neurological effects observed in primates) may be exhibited at lower inhalation concentrations and lower methanol blood levels.

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

Methanol is a colorless, clear, highly flammable liquid with a mild alcoholic odor. Physicochemical property values for methanol are: melting point –97.8 ^{0}C, boiling point 65 ^{0}C, density 0.79 g/m^3, vapor pressure 128 hPa, and log Kow –0.74. Methanol is miscible with water at 20 °C. It does not undergo hydrolysis. A value of 0.461 Pa m³/mol for the Henry's Law constant indicates that volatilization is not a significant removal process from the aquatic compartment.

Air is the main target compartment, based on a fugacity model calculation (Mackay Level III) with about 73 % of environmental methanol distributing to air and 16 % to water. Methanol is degraded in the atmosphere by photochemical, hydroxyl-radical dependent reactions. The estimated elimination half-life is calculated to be about 17-18 days with a rate constant of 0.93 x 10^{-2} cm^3/molecule-sec. Methanol is readily biodegradable. Bioaccumulation in fish is expected to be low.

In several 96-hour studies in fish in which methanol concentrations were measured during the tests, LC50s ranged from 15,400 to 29,400 mg/L. In *Daphnia magna*, 24-hour and 48-hour EC50s were > 10,000 mg/L (highest dose tested). In one 24-hour study, the actual EC50 value reported in Daphnia magna was 21,400 mg/L. In aquatic plants, an EC50 for growth inhibition of *Chlorella pyrenoidosa* was calculated to be 28,440 mg/L over 10-14 days. No information on analytical monitoring was available for the invertebrate and plant studies.
The low toxicity of methanol for aquatic organisms is confirmed by QSAR calculations, resulting in acute toxicity values for fish, daphnids and algae well above 1000 mg/L.

Exposure

The world-production volume of methanol is approximately 30 million tonnes annually in 2000, about 11 million tonnes used in countries participating in NAFTA (North American Free Trade Agreement) and about 3.3 million tonnes in Western Europe, of which 70% is being used for the manufacture of formaldehyde, MTBE and acetic acid. Several additional compounds are synthesized from methanol.

Methanol occurs naturally in humans, animals and plants. The general population is exposed to methanol mainly through consumption of food and beverages and through use of consumer products such as paints, sealers and adhesives that contain methanol as a solvent. Worldwide, air concentrations of methanol have been measured at ranges from 1.05 to 13.1 x 10^{-5} mg/L.

Releases into the environment may occur from both natural and man-made sources. It is however released predominantly from production and use in industrial processes. According to the U.S. Toxics Release Inventory, about 89,225 tonnes of methanol were released on- and offsite for facilities in all industries in the U.S. in 2000. The largest emitter was the pulp and paper industry. About 90 percent of the emissions were to the air and about 1.7 percent was released to surface water.

The most important routes of potential exposure are inhalation and dermal exposure at the workplace.
A mean background body burden of 0.5 mg methanol/kg bw has been estimated based on baseline blood levels and elimination kinetics of methanol.

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.

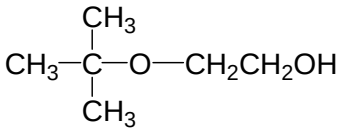
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: This chemical is a candidate for further work. Methanol exhibits potential hazardous properties for human health (neurological effects, CNS depression, ocular effects, reproductive and developmental effects, and other organ toxicity). Rapid metabolism and excretion is noted depending on the dose. In the US (the Integrated Risk Information System), further work is being performed regarding the use and refinement of pharmacokinetic models for extrapolating animal data to humans.

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7580-85-0
Chemical Name	Ethanol, 2-tert-butoxy-
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics.

In an acute oral toxicity study [OECD TG 401, now deleted] with ethanol, 2-tert-butoxy- (ETB), Crj:CD (SD) IGS rats (five animals/sex/dose) were given ETB by gavage at 0, 500, 1000, or 2000mg/kg bw. No deaths occurred in any groups. Anemia and chromaturia at 500 mg/kg bw and higher, abnormal gait at 1000 mg/kg bw, and adoption of a prone position, decreased locomotor activity and irregular respiration at 2000 mg/kg bw were observed. No abnormalities were observed in body weights or necropsy findings. The oral LD_{50} values were more than 2000 mg/kg bw for both sexes. In an acute oral toxicity study of ETB in male ddY mice (four animals/dose), the LD_{50} was 1328 mg/kg bw.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], Crj:CD (SD) IGS rats (12 animals/sex/dose) were given ETB by gavage at 0, 4, 20, or 100 mg/kg bw/day. Males were dosed for 37 days from day 14 before mating and females were dosed for 42-47 days from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. There were no deaths in any groups. Reddish urine was apparent in all animals at 100 mg/kg bw/day. No effects of ETB on body weight, food consumption, or urinalysis were observed. In the hematological examination, decreases in erythrocyte count, hemoglobin, hematocrit, mean corpuscular hemoglobin concentration (MCHC) and leukocyte count, and increases in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and reticulocytes at 100 mg/kg bw/day were observed in males. Decreases in erythrocyte count, hemoglobin and MCHC, and increases in MCV and reticulocytes at 20 and 100 mg/kg bw/day, and increase in MCH at 100 mg/kg bw/day were found in females. Absolute and relative weights of the spleen were increased in males and females at 100 mg/kg bw/day. Increase in hematopoietic cells, erythrocyte cells, in the bone marrow and hemosiderin deposition in Kupffer cells of the liver and tubular epithelium of the kidney were observed in males and females at 100mg/kg bw/day. Hemosiderin deposition in the spleen was observed in males at 100 mg/kg bw/day. Extramedullary hematopoiesis in the liver was found in females at 100mg/kg bw/day. Extramedullary erythropoietic hematopoiesis in the spleen was found in males at 100 mg/kg bw/day and females at 20 mg/kg bw/day and higher. The NOAELs for repeated dose toxicity were 20 mg/kg bw/day in males and 4 mg/kg bw/day in females.

In a reverse gene mutation assay [OECD TG 471], ETB was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 or *Escherichia coli* WP2 *uvr*A with or without an exogeneous metabolic activation. In a chromosomal aberration test [OECD TG 473], ETB did not induce structural chromosomal aberrations or polyploidy with or without an exogeneous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells. Based on these findings, ETB is not anticipated to be genotoxic *in vivo*.

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.

The above-mentioned combined study [OECD TG 422] showed that the reproductive/developmental parameters, i.e., estrous cycle, copulation index, fertility index, gestation length, or number of corpora lutea, or implantations in dams or number, sex ratio, body weight, or viability of pups, were not affected by administration of ETB up to 100 mg/kg bw/day. No external or internal malformations were noted in pups of any groups. The NOAEL for reproductive/developmental toxicity was 100 mg/kg bw/day in rats.

No information is available for irritation, sensitization, or carcinogenicity.

Environment

ETB is a colourless liquid with a water solubility of 100 g/l at 25 °C and a vapour pressure of 1.03 hPa at 25 °C. Based on a measured log Kow of 0.36, bioaccumulation is not expected. Environmental distribution estimated by a level III Fugacity model indicates that almost all of the ETB partitions into water and soil. A ready biodegradation study showed that ETB was not mineralised (6% by BOD) but about 70% of ETB was transformed to 1-tert-butoxy acetic acid (OECD TG 301C). The degradation products may have similar physical chemical properties and less ecotoxicity to ETB. A study on hydrolysis indicates that ETB is stable in water. In the atmosphere ETB is indirectly photodegraded by reaction with OH radicals with a half-life of 0.849 days.

Ecotoxicity data on this substance were available in aquatic species from three trophic levels. In an algal growth inhibition test (OECD TG 201, *Selenastrum capricornutum*, open system, 72 h), acute toxicity was > 866 mg/L for both ErC_{50} and EbC_{50}. For daphnids, a 48 h EC_{50} of > 891 mg/L was reported (OECD TG 202, *Daphnia magna*, semi-static). For fish (OECD TG 203, *Oryzias latipes*, semi-static) a 96 h LC_{50} > 100 mg/L was available.

Regarding chronic toxicity to algae, a 72 h NOEC (growth rate and biomass) of 291 mg/L (OECD TG 201, *Selenastrum capricornutum*, open system) was reported. For daphnids, a 21 d EC_{50} of > 94.2 mg on reproduction and a 21 d NOEC of 94.2 mg/L on reproduction were reported (OECD TG 211, *Daphnia magna*, semi-static).

Exposure

ETB is produced by a single Japanese manufacturer at one production site. Annual production volume in 2003 was 4,000-5,000 metric tonnes in Japan. ETB is synthesised from butene, isobutylene and ethylene glycol. ETB is used primary as a solvent for dyes and a raw material of inks but also there are many applications including end use products. Exposure to the environment can occur primary through evaporation at production and user sites. Exposure to the general public is expected through dermal contact and inhalation of vapour. This chemical is produced in a closed system in Japan, but used to formulate various products, occupational exposure through inhalation and dermal route is possible in both production and user sites.

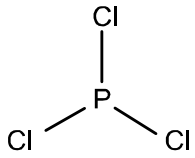
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (repeated dose toxicity by oral route). Exposure to the general public is expected through dermal contact and inhalation of vapour. This chemical is produced in a closed system 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 because of its low hazard potential.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7719-12-2
Chemical Name	Phosphorus trichloride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Phosphorus trichloride is quickly hydrolysed at first contact with water. It is, therefore, very unlikely that phosphorus trichloride will reach tissues distant from the portal of entry and become systemically available. The products of hydrolysis, hydrochloric acid and phosphorous acid, also act at the portal of entry.

The acute toxicity of phosphorus trichloride is high. It is characterised by immediate irritation/corrosion at the portal of entry in experimental animals and humans due to the irritant/corrosive properties of the products of hydrolysis. After inhalation (4h in some studies, unspecified in others) the LC_{50} was determined in rats as 226 to >500 mg/m³. The oral LD50 presumably by gavage in corn oil or vegetable oil (data for mode of application and for vehicle sometimes not given) was 18 to 550 mg/kg bw. in rats showing a very steep dose/mortality-curve in individual studies. The dermal LD_{low} in rabbits is 500 mg/kg bw. The most relevant route of exposure is inhalation. Therefore, the primary target tissues are the mucous membranes of mouth, eyes and respiratory tract. After oral exposure stomach ulceration is to be expected.

Phosphorus trichloride is corrosive to the skin and mucous membranes of the eyes and the respiratory tract. Data on sensitisation for phosphorus trichloride have not been identified. The hydrolysis product hydrochloric acid gave no indication for a sensitising potential in humans and experimental animals. Data on phosphorous acid, the second hydrolysis product, are not available, but no specific effects are expected due to its structure.

After 4-weeks of whole-body inhalation exposure to 0.5, 3, or 10 ppm (2.8, 17.1 or 56.8 mg/m^3) phosphorus trichloride (6h/day, 5d/wk for 4 weeks), irritation of the eyes and the respiratory tract (suppurative inflammation, and inflammation and squamous metaplasia of respiratory epithelium) was observed in rats. There were no other symptoms not related to the irritant properties of phosphorus trichloride. The NOAEC in rats was 3 ppm (17 mg/m³). Chronic bronchitis can develop in humans. Repeated dose toxicity studies employing other routes were not identified in the literature. Because phosphorus trichloride as well as its hydrolysis products are toxicants acting at the portal of entry, and because phosphorus trichloride is unlikely to reach tissues distant from the portal of entry due to rapid hydrolysis, direct systemic toxicity is not likely to occur following exposure to phosphorus trichloride by any route.

Phosphorus trichloride did not show mutagenic activity in a bacterial mutagenicity assay. Neither micronuclei nor chromosomal aberrations were induced in mouse bone marrow and human blood cells in vivo.
As phosphorus trichloride decomposes to acid within seconds in aqueous media the resulting acidity of the hydrolysis products may cause unspecific effects of low pH in in-vitro tests. The change in pH may induce chromosomal aberrations and other DNA damage.

In vivo, reduced pH levels could lead to chromosomal changes and DNA damage at the portal-of-entry of phosphorus

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.

trichloride. However, it is unlikely that systemic changes in pH would occur after exposure to phosphorus trichloride that are sufficient in magnitude to induce this effect in distant tissues or organs. The excess phosphate produced by hydrolysis of phosphorus trichloride may play a role in the development of effects on kidney, bone and calcium levels. Also by other routes (oral, dermal) phosphorous trichloride is expected to produce effects at the site of first contact (irritation, corrosion). The long term effects observed in humans (chronic bronchitis) are considered as sequelae of the irritation in the lungs which after prolonged periods may lead to an impairment of lung function (i.e. oxygen availability).

No carcinogenicity studies with phosphorus trichloride were identified. The hydrolysis product hydrochloric acid (rats and mice) gave no indications for an increased tumour incidence after life-time exposure by inhalation. The other product of hydrolysis and subsequent partial neutralisation of phosphorus trichloride, mono sodium phosphite, gave also no indication of a carcinogenic potential after long term oral exposure. At low concentrations the hydrolysis products, phosphoric and hydrochloric acid, will be neutralized immediately in the physiologic medium at the portal of entry. Nevertheless prolonged irritation could give rise to a constant stimulus to local cell proliferation.

The repeated treatment of male animals with phosphorus trichloride via gavage or inhalation did not induce sperm morphology aberrations in rats and mice. There were no significant effects on intra-uterine development in rats. No malformations were detected. Skeletal development in treated fetuses was retarded but without a dose effect relation. The NOAEL was 19.3 mg/kg bw/day.

Due to the rapid hydrolysis it is unlikely that PCl_3 could reach the reproductive organs or the embryo/fetus. At high concentrations major toxic effects (severe irritation and/or corrosion) on the parents are expected that could influence reproductive success. Specific toxicity to reproduction or developmental toxicity in mammals are not likely to occur following exposure to phosphorus trichloride by any route.

As, due to the corrosive nature of the substance, exposure is limited to the technically feasible extent in industrial settings, no consumer exposure is anticipated and it is unlikely that PCl_3 could reach the reproductive organs, reproductive toxicity studies in animals are not warranted. No recommendation will result for further testing within the context of the SIDS program.

Environment

Phosphorus trichloride is a moisture/water sensitive fluid with a melting point of -93.6 °C, a boiling point of 76.1 °C, and a density of 1.575 g/cm³ at 20 °C. The vapour pressure of the substance is 129.7 hPa at 20 °C. The log K_{ow}, the water solubility and several other parameters cannot be determined due to hydrolysis. Phosphorus trichloride hydrolyzes completely in water with a $t_{1/2}$ of less than 10 seconds at 20 °C, forming phosphonic acid and hydrochloric acid. In the atmosphere, PCl_3 is oxidised by several photooxidants. Any emission into water, air, or the terrestrial compartment would be affected by humidity and also results in the formation of the hydrolysis products. Hydrochloric acid dissociates readily in water causing a pH shift which determines the impact of phosphoryl trichloride on aquatic life. The tolerance of water organisms towards pH is diverse. Recommended pH values for test species listed in OECD guidelines are between 6 and 9. Phosphonic acid (pK_a = 2.0)/ phosphoric acid (pK_a = 2.1) is of medium acidity and partly dissociates in water causing a pH shift. Phosphoric acid and phosphates may affect aquatic life due to eutrophication.

Several aquatic toxicity tests have been undertaken in non-buffered solution. The observed toxicity effects in these studies can be attributed to the acidity of the degradation products and are not used for the hazard assessment. Acute toxicity of phosphorus trichloride (buffered) to fish (*Danio rerio*) tested according to the German guideline proposal "Lethal effects on Brachydanio rerio", was ≥ 1000 mg/l (96 h-LC_0, nominal concentration), which equals a LC_0 of ≥ 597 mg/l of (buffered) phosphonic acid. With *Daphnia magna* an EC_{50} (48 h) of > 100 mg/l in buffered solution was determined (92/69/EEC, method C.2). Algal toxicity was determined in a growth inhibition test with *Desmodesmus subspicatus*(92/69/EEC, method C.3). In buffered solution no effect was observed at 100 mg/l (nominal). There are no results available on chronic toxicity. With activated sludge a 3 h-EC_{50} of 9450 mg/l (nominal) and an EC_0 of 3520 mg/l (nominal) were measured according to the ISO 8192 (pH not reported).

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.

There are test results available for acute testing from three trophic levels (all in buffered media).. Using the lowest acute test result, a 48 h-EC_{50} of $\geq$ 100 mg/l (*Daphnia magna*, nominal concentration of buffered solution), and an assessment factor of 1000, a $PNEC_{aqua} \geq 0.1$ mg/l was obtained.

Exposure

In 2002, the global production capacity of phosphorus trichloride is estimated to be 0.8 million tonnes by about 20 producers. The global distribution of this capacity was approximately 0.5 million tonnes/year in OECD countries and 0.3 million tonnes /year in non-member countries.

Phosphorus trichloride is used as an intermediate for the manufacturing of wide range of chemicals (percentages reported for the USA 2001):

- Pesticide intermediate (70 %)
- Phosphorus oxychloride (12 %)
- Surfactants and sequestrants, including phosphorus acid, used primarily for water treatment chemicals (11 %)
- Plastics additives, including flame retardants, plasticizers, phosphite antioxidants, and stabilizers (5 %)
- Miscellaneous, including lube oil and paint additives (2 %)

At one company in the Sponsor country phosphorus trichloride is manufactured and processed in closed systems. The exhausts from manufacturing and processing (including filling) of phosphorus trichloride are connected to air washing units. Thus, at this company, during production and processing virtually no phosphorus trichloride is emitted into the atmosphere. ue to water-free production, processing, and rapid hydrolysis phosphorus trichloride is not detectable in the wastewater.

In this company, the exposure of workers is well below the maximum admissible concentration of phosphorus trichloride in the workplace air (MAK) of 2.8 mg/m^3 (0.5 ppm). The exposure of workers to the hydrolysis product hydrochloric acid is also well below the MAK value of 8 mg/m^3 (5 ppm) for hydrogen chloride. Immunoglobulines against phosphorus trichloride have been detected.

No direct use of phosphorus trichloride is known. There is no exposure of consumers. Phosphorus trichloride is not listed in the Finnish, Norwegian and Swiss product registers. In the Swedish product register it is listed as an industrial chemical intermediate. Product register entry is confidential for Denmark. Phosphorus trichloride can be converted by chemical synthesis to nerve gases. Therefore the production and export of phosphorus trichloride is stringently controlled under the International Chemical Weapons Convention.

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). Based on data presented by the Sponsor country (relating to production by one producer which accounts for 1-6% of global production and relating to the use pattern in several OECD countries), exposure is limited to the technically feasible extent in occupational settings in the sponsor country. There is no exposure of consumers. No recommendation for further testing within the context of the SIDS program is therefore warranted. Although there are no valid data regarding reproductive effects, due to the fast hydrolysis it is unlikely that PCl_3 could reach organs and tissues distant from the site of first contact, therefore, and due to the corrosive properties studies in animals are not warranted. The chemical is currently of low priority for further work.

Environment: The chemical is currently of low priority for further work due to its low hazard profile. One of the degradation products, hydrochloric acid, has already been assessed within the OECD SIDS-Program.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7758-94-3
Chemical Name	Iron dichloride
Structural Formula	Cl —— Fe —— Cl

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

An acute oral toxicity study (Acute Toxic Class Method OECD TG 423) showed that the LD_{50} of iron dichloride was between 300 and 2000 mg/kg bw. All animals of the 2,000 mg/kg b.w. treatment group and one animal of the 300 mg/kg bw treatment group died. The necropsy showed hemorrage on lymphtic nodes, stomach, intestine and thymus, and hypertrophy of pancreas and spleen. In the 300 mg/kg bw group, the clinical signs such as hypoactivity and piloerection recovered within the test period. For humans, significant gastrointestinal manifestations occur following ingestion of 20 mg of elemental iron/kg bw while systemic toxicity may occur at 60 mg/kg bw. Generally, doses of various ferrous or ferric salts greater than 150 mg/kg bw of elemental iron are considered serious. According to an acute dermal toxicity study, the acute lethal dose (LD_{50}) was greater than 2,000 mg/kg bw. There was no animal death during the test.

The skin irritancy of iron dichloride was low. Only weak edema was induced on application sites. However, the effect of iron dichloride on the eyes was quite severe. In the early stages after application, opacity of cornea was observed and severe edema with redness and swelling were observed in conjunctiva. These pathological changes were not recovered within the test periods. Therefore, iron dichloride is a corrosive irritant to the eyes. No skin sensitization data are available.

In a repeated dose toxicity study performed according to OECD TG 422, Sprague-Dawley rats were treated orally at 0, 125, 250 and 500 mg/kg bw/day. The rate of body weight gain was decreased in males at 250 and 500 mg/kg bw/day compared to the control group. Black colored liver and hemorrhage with diffuse black pigmentation in the stomach were observed in male rats at 500 mg/kg bw/day. In males at 250 and 500 mg/kg bw/day, the organ weights of liver and adrenal glands were increased. According to these results, the NOAEL value was determined to be 125 mg/kg bw/day for male rats. In female at 500 mg/kg bw/day, three (out of 20) rats died during the treatment period. The liver weights and water consumption were increased and there were histopathological differences. Therefore the NOAEL value for female rats was 250 mg/kg bw/day.

In a genetic toxicity test (OECD TG 471), iron dichloride did not show mutagenic effects on *S. tryphimurium* (strains TA 98, TA 100, TA 1535 and TA 1537), and on *E. coli* WP2 *uvr*A up to 5,000 μg/plate. In an oral *in vivo* micronucleus assay (OECD TG 474), no increase of the micronucleus was observed when tested up to 50 mg/kg/day (MTD). Therefore, iron dichloride is not considered to be a mutagen.

A reproduction and developmental study on rats was also performed according to OECD TG 422. For the reproduction toxicity, there was no significant difference in mating data, pre and post implantation loss rate between the control group and the treatment groups. For the developmental study, mean litter size, birth rate, survival rate, and body weights of litters were not affected. In conclusion, the NOAEL of iron dichloride on reproduction and developmental toxicity was 500 mg/kg bw/day for both male and female rats.

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

Iron dichloride is a solid inorganic substance (white rhombohedral crystals), sometimes has a green tint and is very hygroscopic. Its commercial form is liquid. It is freely soluble in water with a solubility of 650 g/L at 25 °C. Vapor pressure, partition coefficient in n-octanol/water and stability in water according to OECD TG 111 are not applicable for the salt of an inorganic substance. Photodegradation and biodegradation are not relevant for an inorganic compound. Environmental fate modeling cannot be performed with the available data. Bioaccumulation is not expected.

The following studies for aquatic organisms were performed:

Green algae (*Selenastrum capricornutum)*: EC_{r50} (72 h) = 6.9 mg/L (growth rate)
EC_{b50} (72 h) = 3.8 mg/L (biomass)
Invertebrates (*Daphnia magna):* EC_{50} (48 h) = 19.0 mg/L.
Fish (*Oryzias latipes*): LC_{50} (96 h) = 46.6 mg/L.

For fish and algae, the observed effects were partially due to the pH changes. For fish, no mortality was observed up to 100 mg/l of iron dichloride in neutralised solutions. For algae, test solutions dropped below pH 7 at concentrations of 12 mg/l and above.

No data were available on terrestrial organisms. From the results of aquatic organisms of three trophic levels, iron dichloride is considered to be moderately toxic in the aquatic environment.

Exposure

In Korea, the estimated production amounts of iron dichloride were approx. 100,000 tonnes/year in 1998. The European production capacity of iron dichloride is estimated to be 250,000 tonnes in 2004.

Iron dichloride is produced by reaction of scrap iron with waste liquid hydrochloric acid in a continuous closed reactor and this chemical is mainly used as a supplementary cohesion agent to treat dye wastewater in textile, dye and paper manufacturing industries and as a raw material for iron trichloride production in Korea. In Europe iron dichloride is used for water treatment, H_2S reduction, as a pigment and for soil immobilization. Further uses are as follows; metallurgy; reducing agent; pharmaceutical preparations; mordant in dyeing; sewage treatment.

Iron dichloride is produced in a closed system and wastewater containing this chemical is recycled in to the manufacturing process. In the wastewater plants of textile, dye and paper manufacturing industries, dye sewage is treated with iron dichloride. Ferrous ion is oxidized to ferric ion which precipitates to form a slurry. The slurry contains ferric hydroxide ($Fe(OH)_3$) and the supernatant of treated dye sewage is discharged. Therefore, environmental exposure of iron dichloride is expected to be very low and mostly ferric ion would be released.

As for human exposure, there is a potential for exposure to workers *via* inhalation and dermal routes during the packaging or processing the raw material, cleaning of reaction tank or filtration after the reaction. But occupational exposure is controlled with personal protective equipments like goggles and gas filter mask and with ventilation in Korea. The substance is not classified as a hazardous chemical which is monitored for workplace exposure in Korea annually. Therefore, monitoring data for occupational exposure is not available. ACGIH TLV of iron dichloride is TWA 1 mg (Fe)/m^3. In the manufacturing factories, workers may be exposed to the mist of hydrochloric acid but monitoring data by personal air sampling of hydrochloric acid were under TLV-ceiling of 5 ppm.

There is no direct use and there are no consumer products containing iron dichloride in Korea.

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.

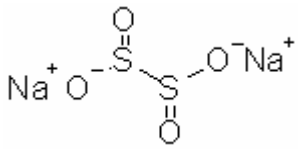
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (corrosivity). The chemical is produced in a closed system and exposure to workers during the processing of the chemical is low. Based on data presented by Sponsor country (relating to labelling), adequate risk management measures are being applied. Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment: The chemical is a candidate for further work. Based on the aquatic toxicity data and the use pattern presented by the sponsor country, member countries are invited to perform an exposure assessment, and if then necessary a risk assessment. Consideration should be given to the ongoing assessment of other iron salts in the OECD HPV Chemicals Programme.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7775-14-6
Chemical Name	Sodium dithionite
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Sodium dithionite is not stable under physiological conditions, with the rate of decomposition increasing with increasing acidity. Upon contact with moisture, it is oxidized to hydrogen sulfite (HSO_3^-), sulfite (SO_3^{2-}) and hydrogen sulfate (HSO_4^-), and under strongly acidic conditions it may liberate sulfur dioxide. Under anaerobic conditions (such as in the lower gastrointestinal tract), hydrogen sulfite (HSO_3^-) and thiosulfate ($S_2O_3^{2-}$) may be formed. Hydrogen sulfite (HSO_3^-) can be absorbed after ingestion. It is efficiently metabolized, and the major part rapidly excreted as sulfate into the urine.

The acute oral LD_{50} of sodium dithionite in rats was about 2500 mg/kg bw, with atony, gastro-intestinal irritation, diarrhea and dyspnea as the main clinical and pathological signs at doses near to or exceeding the LD_{50}. There were no acute dermal and no valid acute inhalation studies available.

Sodium dithionite was slightly irritating to the skin, and strongly irritating to the eyes of rabbits. Under acidic conditions, sodium dithionite may liberate sulfur dioxide, which is known to induce respiratory irritation in humans. There was no animal data available regarding sensitization. In humans, allergic dermatitis from exposure to sulfites is rare and, consequently, sodium dithionite is not considered to possess a significant skin sensitization potential. Although there were no specific reports with regard to sodium dithionite available, the potential for allergoid reactions ("sulfite-asthma") should be assumed in sensitive individuals following oral or inhalation exposure.

Sodium dithionite was not tested for its toxicity after repeated dosing. Due to its rapid degradation under *in vivo* conditions, the toxicity data on its decomposition products were used for the evaluation of this endpoint. The conversion products, including sulfite (SO_3^{2-}), hydrogen sulfite (HSO_3^-), sulfate (SO_4^{2-}) and thiosulfate ($S_2O_3^{2-}$), are considered as substances of very low order systemic toxicity. It should be noted that sulfites, in general, reduce the thiamine content in food. For disodium disulfite, oral NOAELs (30 and 104 weeks) of 942 mg/kg bw/day and 217 mg/kg bw/day were obtained for systemic toxicity and local gastrointestinal toxicity in rats, respectively. These results appear to be sufficiently representative also for the assessment of sodium dithionite. Repeated dose studies in animals using the dermal or respiratory routes were not available.

Sodium dithionite was not mutagenic in standard bacterial tests with and without metabolic activation (OECD TG 471, 472). No experimental data was available on the potential of sodium dithionite to induce chromosomal aberrations *in vitro*. An increase in the frequency of micronuclei in bone marrow cells of mice was found after intraperitoneal injection of high doses (2 x 500 or 2 x 750 mg/kg bw) of a mixture of sodium hydrogen sulfite (HSO_3^-) and sodium sulfite, the degradation products of sodium dithionite under physiological conditions.

No experimental data were available on the carcinogenic potential of sodium dithionite. In 1992, IARC concluded

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.

that degradation products of dithionite, i.e. sulfur dioxide, sulfites, hydrogen sulfites and metabisulfites "are not classifiable as to their carcinogenicity to humans (Group 3)".

Sodium dithionite has not been tested for its effects on reproduction and development. Based on its physico-chemical behavior and its rapid conversion in the body, it is not expected that the intact molecule reaches the reproductive organs, or has any direct effect on reproduction and development. Data relating to the degradation products of sodium dithionite do also not indicate any adverse effects. At high dietary doses, which can cause maternal malnutrition and destruction of thiamine, fetal growth retardation was however observed. In a rat dietary study with sodium sulfite (similar to OECD TG 414), the NOAEL for developmental toxicity was at 5 % (about 1450 mg/kg bw/day; highest tested dose). At this dose clear signs of maternal toxicity were observed (LOAEL, maternal toxicity: 5 % in diet = about 1450 mg/kg bw/day). The NOAEL for maternal toxicity was at 2.5 % in feed (about 850 mg/kg bw/day).

Environment

Sodium dithionite dihydrate is very sensitive towards atmospheric oxygen in the finely crystalline state and oxidizes under heat development: the heat of oxidation can lead to ignition, e.g. upon contact with moisture. The anhydrous salt decomposes exothermically in air on prolonged heating above 90 °C (decomposition/oxidation products: sodium sulfate (Na_2SO_4) and sulfur dioxide (SO_2)). Above ca. 150 °C, in exclusion of air, vigorous decomposition occurs, yielding mainly sodium sulfite (Na_2SO_3), sodium thiosulfate ($Na_2S_2O_3$), sulfur dioxide (SO_2) and a small amount of sulfur. Because of decomposition on heating, boiling point and melting point are not relevant. The vapour pressure is negligible and the Henry constant is near to zero due to the ionic character of the inorganic salt. Biodegradation or elimination tests are not appropriate for the inorganic substance. Hydrolysis occurs within hours at pH 7 and room temperature. There is no indication of a bioaccumulation potential.

Main hydrolysis products are thiosulfate ($S_2O_3^{2-}$) and sulfite (SO_3^{2-}). Small amounts of sulfur and sulfide (S^{2-}) have been detected during oxygen-free hydrolysis. Oxygen dissolved in water is consumed by dissolved sodium dithionite. Final oxidation products are sulfate (SO_4^{2-}) and sulfite (SO_3^{2-}).

Because of the high water solubility at 20 °C of 182 g/l (value related to formula $Na_2S_2O_4$) and 219 g/l (related to formula $Na_2S_2O_4 * 2\ H_2O$) respectively, for hydrated sodium dithionite, aquatic environment is the target compartment. Sodium dithionite is expected not to be stable in soil because of its rapid decomposition in water and the reaction with oxygen.

From acute toxicity test to fish (*Leuciscus idus*), 96-hr LC_{50} was 62.3 mg/l. For algae (*Scenedesmus subspicatus*), 72-hr ErC_{50} was 206 mg/l and 72-hr NOErC was 62.5 mg/l(corresponding values for biomass are 135 and 62.5 mg/l respectively; nominal concentration). For *Daphnia magna*, the acute toxicity value of 48-hr EC_{50} was 98.3 mg/l, and the chronic value of 21-day NOEC was > 10 mg/l. Due to oxygen concentrations < 1 mg/l at test start in high test concentrations in the fish and acute daphnia test, it cannot be excluded that the effect values found in these studies are at least partly caused by oxygen deficiency. A PNEC of 0.1 mg/l for the aquatic organisms was calculated from the chronic value (NOEC for daphnia > 10 mg/l) using an assessment factor of 100.

Exposure

For workers, the main potential routes of exposures to sodium dithionite are the respiratory and dermal route, for consumers the dermal route through the use of household products.

In 2001, the estimates for sodium dithionite production for the world market amounted to approx. 550 000 tonnes/year. These are distributed as follows: 60 000 - 120 000 tonnes in Germany, 40 000 – 80 000 tonnes in the rest of Europe, 100 000 - 150 000 tonnes in NAFTA and 200 000 – 300 000 tonnes in Asia. The production volume is used in dispersive manner, primarily in industrial applications to approx. 90 %. The use pattern is 50 % textile bleaching, 35 % pulp and paper bleaching, 5 % kaolin bleaching, 10 % other applications (e.g. household colour remover). According to Swiss, Danish and Swedish Products Registers sodium dithionite is contained in a large

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.

number of products. Some of them are available to consumers. Release of the substance, its reaction and hydrolysis products into the environment (especially waste water) is likely to occur during the production and processing of sodium dithionite and from the use of the substance itself, as well as from the formulation and use of products containing the substance.

During production and internal processing at one company in the Sponsor country, approx. 115 kg sodium dithionite (dust) were emitted into the air in 2000, where it is expected to be oxidized to sulfate (SO_4^{2-}). No information on the emission into waste water or surface water are available for this site. Emission data from other production and processing sites or literature was not available.

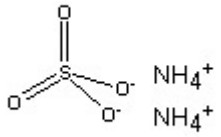
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. Sodium dithionite possesses properties indicating a hazard to human health (sulfite asthma, irritant effects on the eye, chromosomal aberrations *in vivo* were observed following intraperitoneal injection of the degradation products). There is only limited information on the exposure of workers in manufacturing and down-stream industries, and consumers may be exposed through household products (detergents, stain removers). It is therefore recommended to conduct an exposure assessment, 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. These hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure levels. They should nevertheless be noted by chemical safety professionals and users.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7783-20-2
Chemical Name	Ammonium sulfate
Structural Formula	$(NH_4)_2SO_4$ 

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Fertility and developmental toxicity studies with ammonium sulfate were not available. As ammonium sulfate dissociates in biological systems studies with other ammonium and sulfate salts can be used to cover these endpoints: A screening study according to OECD TG 422 with ammonium phosphate as analogue substance, which forms ammonium ions in aqueous solutions is available. Fully valid fertility studies with analogue compounds containing sulfate ions are however lacking. Two limited studies with sodium sulfate can be used for assessment of fertility and developmental toxicity, however, in none of these studies have the fetuses been examined histologically. There are no in vivo data on genotoxicity for ammonium sulfate. To bridge the data gap, data for ammonium chloride, which dissociates in aqueous media to form ammonium ions, as does ammonium sulfate, will be used.

In aqueous media, ammonium sulfate dissociates in the ammonium and sulfate ions (NH_4^+, SO_4^{2-}). These can be taken up into the body by the oral and respiratory routes. Absorbed ammonium is transported to the liver and there metabolised to urea and excreted via the kidneys. Ammonium is also an endogenous substance that serves a major role in the maintenance of the acid-base balance. Minor amounts of ammonium nitrogen are incorporated in the physiological N-pool. Sulfate is a normal intermediate in the metabolism of endogenous sulfur compounds, and is excreted unchanged or in conjugated form in urine.

Ammonium sulfate is of relatively low acute toxicity (LD_{50}, oral, rat: 2000 - 4250 mg/kg bw; LD_{50} dermal, rat/mouse > 2000 mg/kg bw; 8-h LC_{50}, inhalation, rat > 1000 mg/m^3). Clinical signs after oral exposure included staggering, prostration, apathy, and laboured and irregular breathing immediately after dosing at doses near to or exceeding the LD_{50} value. In humans, inhalation exposure to 0.1 – 0.5 mg ammonium sulfate/m³ aerosol for two to four hours produced no pulmonary effects. At 1 mg ammonium sulfate/m^3 very slight pulmonary effects in the form of a decrease in expiratory flow, in pulmonary flow resistance and dynamic lung compliance were found in healthy volunteers after acute exposure.

Neat ammonium sulfate was not irritating to the skin and eyes of rabbits. There is no data on sensitisation available.

A 14-day inhalation study on rats exposed to 300 mg/m^3 , the only tested dose, did not report histopathological changes in the lower respiratory tract. As the respiratory tract is the target organ for inhalation exposure, the NOEL for toxicity to the lower respiratory tract is 300 mg/m^3.
The NOAEL after feeding diets containing ammonium sulfate for 13 weeks to rats was 886 mg/kg bw/day. The only

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.

toxicity sign found was diarrhea in male animals of the high-dose group (LOAEL: 1792 mg/kg bw/day).

Ammonium sulfate was not mutagenic in bacteria (Ames test) and yeasts with and without metabolic activation systems. It did not induce chromosomal aberrations in mammalian or human cell cultures. No in vivo genotoxicity tests are available. Based on the negative results from in vitro studies and the negative results in the micronucleus test in vivo with ammonium chloride a mutagenic activity of ammonium sulfate in vivo is unlikely. Similarly to other salts, high doses of ammonium sulfate may have the capability of tumor promotion in the rat stomach; it is, however, much less potent than sodium chloride when tested under identical conditions.

There are no valid studies available on the effects of ammonium sulfate on fertility and development. Based on data from a similar ammonium compound (diammonium phosphate), which has been tested up to 1500 mg/kg bw in a screening study according to OECD TG 422 in rats it can be concluded that ammonium ions up to the dose tested have no negative effects on fertility. In the 13-week feeding study of ammonium sulfate with rats, no histological changes of testes were observed up to 1792 mg/kg bw. The ovaries were not examined. Fully valid studies with sulfate on fertility are not available.

In a limited study (pretreatment time short, low number of animals, no fertility indices measured) where female mice were treated with up to ca. 6550 mg sulfate/kg bw (as sodium sulfate) no effects on litter size were found.

Studies of developmental toxicity for ammonium sulfate are not available. In the screening study according to OECD TG 422 with up to 1500 mg diammonium phosphate/kg bw no effects on development have been detected in rats. In another limited screening study with exposure of mice to a single dose of 2800 mg sodium sulfate/kg bw no macroscopic effects or adverse effects on body weight gain have been detected in the pups. In both studies fetuses were not examined histopathologically.

Environment

Ammonium sulfate is a white solid, with a solubility in water of 764 g/l at 25 °C. When heated, decomposition starts at temperatures between 150 and 280 °C, depending on the experimental conditions and purity of the test substance, and is complete at 336 - 357 °C. The relative density is 1.77, and the partial pressure of ammonia over solid ammonium sulfate at 25 °C is $4.053*10^{-7}$ Pa. The log Kow was determined as –5.1 in a test according to OECD TG 107; as this method applies only to substances which do not dissociate, the validity of this method for ammonium sulfate is uncertain. Due to the ionic nature of the substance the calculation of sorption onto organic soil matter does not have any practical meaning.

Due to the salt-character of the substance the calculation of a fugacity model and Henrys Law Constant is not appropriate. Based on the physico-chemical properties of ammonium sulfate, water is expected to be the main target compartment. Although ammonium sulfate can be created in the atmosphere from ammonia and sulfur dioxide, this process is limited by atmospheric sulfur dioxide, not by ammonia, which has many natural sources. Particulate ammonium sulfate is removed from air by wet and dry deposition. There is no evidence for photodegradation of ammonium sulfate.

In unsterilized soil, ammonium sulfate is mineralized fairly rapidly, and subsequently nitrified. Nitrification and de-nitrification processes also occur naturally in streams and rivers, as well as in many secondary sewage treatment processes.

Based on the high water solubility and the ionic nature, ammonium sulfate is not expected to adsorb or bioaccumulate to a significant extent. However, mobility in soil may be reduced through ion-ion interactions.

Environmental effects can be assessed in the freshwater and marine environments. In addition, some information is available for soil and sewage treatment micro-organisms, for freshwater sediment, and for the terrestrial environment.

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.

Freshwater Environment

The lowest acute and chronic toxicity values for the three trophic levels are shown in the following table.

Test Type	Trophic Level	Species	Result
Acute	Fish	juvenile *Salmo gairdneri*	LC_{50} (96 h) = 173 mg/l
Acute	Invertebrates	juvenile freshwater snail *Helisoma trivolyis*	LC_{50} (24 h) = 393 mg/l
Acute	Invertebrates	*Daphnia magna*	EC_{50} (96 h) > 100 mg/l
Acute	Aquatic Plants	*Chlorella vulgaris*	EC_{50} (18 d) = 2700 mg/l (cell count)
Chronic	Fish	alevins of *Oncorhynchus gorbuscha*	NOEC (61 d) = 11 mg/l

The PNEC for the freshwater aquatic environment is based upon the lowest observed chronic toxicity result, the NOEC value of 11 mg/l ammonium sulfate for alevins of *Oncorhynchus gorbuscha*. An assessment factor of 100 is appropriate, leading to a freshwater aquatic PNEC of 0.11 mg/l. Supporting information is also available for three juvenile amphibian species. The most sensitive amphibians were 6 week-old *Pseudacris regilla* tadpoles, with a NOEC (10 d) of 82mg/l ammonium sulfate.

Marine Environment

Marine acute data are available for fish, invertebrates and for phytoplankton, the latter being most sensitive. For *Gymnodinium splendens* and *Gonyaulax polyedra* , *growth* reduction was found at concentrations of 0.7 mg/l and above. No EC50 can be derived. For seawater invertebrates the lowest effect value was obtained for green mussel *Perna viridis* (96h-LC_{50} = 47.7 mg/l). For marine fish the lowest effect value was found for larvae of *Sciaenops ocellatus* with a LC_{50} (10 d) of 27 mg/l.

Micro-organisms in sewage treatment

Nitrification during sewage treatment plant operation involves both sensitive (no growth at 4700 but growth at 94 mg/l ammonium sulfate) and insensitive (growth at 4700 mg/l ammonium sulfate) strains of *Nitrobacter spp*. These results indicate that a NOEC for specific nitrifying bacteria will be greater than 94 mg/l.

In the terrestrial environment, the major effect of repeated ammonium sulfate application is a reduction in soil pH. The most toxic results for specific soil bacteria, for cyanobacteria in rice fields, show less than 50% reduction in nitrogen fixation at 330 kg/ha/yr in the absence of liming. Similar results are seen for plants, with 471 kg/ha/y for 6 years affecting drought resistance in *Picea abies*. The soil fauna is less sensitive, with both *Collembolla* and *Cryptostigmata* numbers increasing under 708 kg /ha/year ammonium sulfate application.

Exposure

According to the statistics of the “International Fertilizer Industries Association” in 2002, approx. 0.76 million tonnes were produced in Germany, approx. 3.95 million tonnes in Western Europe, approx. 3.33 million tonnes in the United States and Canada, and approx. 3.95 million tonnes in Asia including Japan. The world wide production amounts to approx. 17.2 million tonnes per year.

Ammonium sulfate is used primarily as a nitrogen source in commercial fertilizer mixtures or as a direct application fertilizer, which accounts for > 90 % of the total amount. It is further used in a variety of industrial applications and is also approved as a direct food additive in the EU. Non-agricultural products containing ammonium sulfate which are intended for use by the general public (e.g. cleaning products, paints), contain ammonium sulfate levels up to 50 %.

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.

Releases into the environment may occur during production, processing and use. According to measurements in a German chemical plant, releases in air are low. During production and internal processing at one company in the Sponsor country, less than 25 kg were emitted into the air in 2001. No quantitative information on the emission into wastewater or surface water is available for this site; however, any waste material is practically quantitatively recycled at this production site. No data about environmental releases at other production and processing sites are available. Releases into the environment from fertilizer applications may result in some leaching to watercourses from sandy soils, whilst monitoring data from representative European catchments have shown negligible leaching from less acidic, clay and clay loam soils.

Consumer exposure is low.

Ammonium salts and sulfates are abundant in the environment. Ammonium sulfate is a neutralization product of ammonia and sulfuric acid in the atmosphere. Levels of sulfate in air in Canada have been found to range from 3.0 - 12.6 µg/m^3 with a mean of 7.0 µg/m^3. In the USA sulfate concentrations in air ranged from 0.5 - 228 µg/m^3, with the means ranging from 0.8-31.5 µg/m^3. The average daily intake from air would amount to 0.02 - 0.63 µg assuming 20 m^3 of inhaled air per day. In winter indoor sulfate levels (21.6 nmol/m^3) were shown to be similar to outdoor sulfate levels (30.6 nmol/m^3) and were predominantly of outdoor origin. The use of kerosene heaters has been shown to increase indoor sulfate levels (82.7 nmol/m^3); the major form of the indoor sulfate was ammonium sulphate.

Sulfate occurs in drinking water with a median concentration of 24 mg/l and the 99th percentile concentration of 560 mg/l as measured by the U.S. EPA in 2001. Sulfates are natural components of food; ammonium sulfate is “generally recognized as safe (GRAS)” and approved as a food additive in the U.S. and in Europe. From these data it can be seen that consumer exposure to sulfate is low: 453 mg per day via food, 48 mg via drinking water assuming 2 l drinking water per day and 0.63 µg per day via air assuming 20 m^3 respiratory volume. Ammonium sulfate intake via food is 20 mg/day. Endogenous production of ammonia (4000 mg/day) is about 2 orders of magnitude higher than exogenous intake (ammonia and ammonium) via food (20 mg/day), air (<1 mg/day) and water (<1 mg/day).

According to the information provided by the Product Registers, exposure of the general public to ammonium sulfate may occur mainly through the use of fertilizer or horticulture products and to a minor extent through the use of paints and cleaning products.

Exposure of workers to dust during production and storage, loading and unloading of trucks was measured. Eight measurements of respirable dust (including fine dust fraction) were carried out within 8 h (personal air samplers and sampling from the working room), but no analysis for ammonium sulfate performed, assumed as 100%. Results: all measurements showed concentrations close to the detection limit. Personal air samplings for respirable dust showed values < 0.354 - 0.360 mg/m^3 (four samples) and for fine dust < 0.442 - 0.455 mg/m^3 (four samples).

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

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

Environment: The chemical possesses properties indicating a hazard for the environment. 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. Although the substance has a low inherent hazard potential for the environment, it degrades in the environment to nitrite. It is recommended that the use of ammonium sulfate as a fertilizer is taken into account when assessing the exposure of nitrite and nitrate to humans through drinking water. The chemical is currently of low priority for further work.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-83-1
Chemical Name	Isobutanol
Structural Formula	$(CH_3)_2$-CH-CH_2OH

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The acute aquatic plant (green algae) toxicity data on isobutanol (IBOH) was supported/addressed-using data from the structural analog, n-butanol (CAS No. 71-36-3).

Human Health

Isobutanol is rapidly absorbed following inhalation and oral exposures. Isobutanol is rapidly metabolised to isobutyraldehyde and isobutyric acid in rodents and humans.

This chemical has low acute toxicity by all routes. The oral LD_{50} in male rats is >2830 mg/kg bw and in female rats was 3350 mg/kg bw. Dermal LD_{50} in male rabbits was >2000 mg/kg bw and 2460 mg/kg bw in female rabbits. Inhalation LC_{50} values for vapor exposures were >6,000 ppm (18,120 mg/m^3) in male and female rats. Isobutanol is a slight to moderate skin irritant and a severe eye irritant.

Repeated exposures to moderate to high concentrations of isobutanol are well tolerated in rats. In a 90-day inhalation study, rats were exposed to isobutanol at 0, 250, 1,000, or 2,500 ppm (760, 3,030 or 7,580 mg/m^3). A reduced response to an external stimulus was noted in the exposed animals only during the exposure period. Repeated exposures did not exacerbate these transient effects. There was no evidence of neurotoxicity based on functional observational battery (FOB), quantitative motor activity, neuropathy and scheduled-controlled operant behavior endpoints. The NOAEL was 1,000 ppm (3,030 mg/m^3) based on increases in erythrocyte count, hemoglobin, and hematocrit measures in the female rats. Based on the definitive measures of neurotoxicity (FOB, motor activity, histopathology), the NOAEL for neurotoxicity was 2,500 ppm (7,580 mg/m^3). A 13-week oral gavage study was conducted with isobutanol with dose levels of 0, 100, 316, and 1,000 mg/kg bw/day. Hypoactivity, ataxia and salivation were noted in the 1,000 mg/kg bw/day dose groups. Hypoactivity and ataxia were resolved by the 4th week of the study. In addition, slight decreases in body weight gain and feed consumption were noted in the first two weeks of the 13-week study in the 1,000 mg/kg bw/day dose group. The NOAEL was 316 mg/kg bw/day.

Several *in vitro* mutagenicity studies indicate that isobutanol is not a genotoxicant. In addition, isobutanol was negative in an *in vivo* mouse micronucleus study.

An inhalation two-generation reproductive toxicity study conducted with isobutanol (up to 2500 ppm (7,580 mg/m^3)) did not cause any parental systemic, reproductive, or neonatal toxicity when administered for two generations via whole-body exposure. The NOEL for reproductive and neonatal toxicity was 2,500 ppm (7,580 mg/m^3). No adverse developmental effects were noted in rats or rabbits exposed by inhalation to 10,000 mg/m^3 isobutanol during gestation. The NOAEL for developmental toxicity was 10,000 mg/m^3.

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

The available physicochemical data are adequate to describe the properties of isobutanol. Isobutanol has a vapor pressure of 13.9 hPa (10.43 mmHg) at 25^0C, a water solubility of 85 g/l at 25^0C and a log K_{ow} of 0.79. The melting and boiling points for isobutanol are approximately -108° and 108° C, respectively. The photochemical removal of isobutanol as mediated by hydroxyl radicals occurs with a calculated half-life of 1.55 days. Isobutanol is readily biodegradable under aerobic conditions. Isobutanol volatilises moderately from moving rivers, but less so from quiescent lakes and other surface water bodies (calculated volatilization half-lives of 43 hours from a river and 23 days from a lake). Isobutanol is not persistent in the environment and is not likely to bioaccumulate in food webs. Based on Level III distribution modelling it is estimated that the majority of isobutanol released to the environment will partition into water (51.6%) and soil (43.5%), with a smaller amount in air (4.85%).

Acute fish and aquatic invertebrate toxicity data are available for isobutanol. Data from the structure analog n-butanol have been used to support/address the acute aquatic plant endpoint. A flow-through test with fathead minnows (*Pimephales promelas*) reported a 96-hour LC_{50} of 1430 mg/L. Static tests were conducted using three water column-dwelling invertebrate species (*Daphnia magna, D. pulex, Ceriodaphnia reticulata*) according to ASTM procedures. Forty-eight hour EC_{50} values of 1300 (96% CI 1200-1400), 1100 (950-1200), and 1200 (1100-1300) mg/L were reported for the three species, respectively. Since no reliable data are available for describing the toxicity of isobutanol to algae, the results of a test on the structurally analogous substance, n-butanol, are presented. The test with *Selenastrum capricornutum* determined a 96-hour EC50 of 225 mg/l.

Exposure

Isobutanol is manufactured at 16 plant sites in the United States and about 35-40 companies or sites worldwide. Production in the United States was reported to be in the range of 100 – 500 million pounds (45-227 thousand metric tons) in 1998. Worldwide production capacity outside the U.S. is about 402 thousand metric tons. The largest uses of IBOH are as follows: production of isobutyl acetate and other chemicals; use as a direct solvent and as an intermediate in the production of lubricant additives. Use as a direct solvent in coatings, lacquers, primers, and adhesives offers the most potential source of human exposure, since some of these applications are open processes, and isobutanol solvent may be released to ambient air through evaporation as the coating or lacquer dries. Consumers may use some of these products. Human exposure to isobutanol may occur in the work place during manufacture, formulation into products or in various industrial applications, such as working with coatings containing isobutanol as solvent. Such exposures can occur through inhalation and dermal contact. Workplace exposure limits have been established for isobutyl alcohol in most OECD countries. Consumers are exposed when working with consumer products, such as coatings, that contain isobutanol, and through ingestion of foods and beverages that contain naturally occurring isobutanol. Consumers may also be exposed to environmental concentrations of isobutanol in the air or water. Almost all human beings are exposed daily to low concentrations of isobutanol from natural sources, such as in foods and from fermentation of carbohydrates. Exposures to artificial sources also occur, primarily in the vicinities of plants that manufacture, process or use isobutanol in many applications.

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

Human Health: Isobutanol possesses properties indicating a hazard for human health (dermal and eye irritation). These hazards do not warrant further work as they are related to reversible, transient effects that may become evident only at high exposure levels. They should nevertheless be noted by chemical safety professionals and users.

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	85535-85-9
Chemical Name	Alkanes, C_{14-17}, chloro-
Structural Formula	$C_xH_{(2x-y+2)}Cl_y$ (Where x = 14-17 and y = 1-17)

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

[to be updated at a later stage, for current conclusions on human health see SIAP from SIAM 10]

Environment

C_{14-17} chloroalkanes – generally known as medium chain length chlorinated paraffins or MCCPs - is a viscous liquid of low volatility and low water solubility (~0.027 mg/l at 20°C), with a log octanol-water partition coefficient (log K_{ow}) of 5.5-8 (depending on the degree of chlorination). The components do not hydrolyse in water, and from the available information can be considered not readily or inherently biodegradable (no data are available from standard tests).

The high log K_{ow} values imply a high potential for bioaccumulation, strong sorption to sewage sludge, soils and sediments and very low mobility in soil. Bioconcentration factors (BCFs) have been reported for a variety of aquatic organisms, but interpretation of the data is complicated by the very low water solubility. The best estimate of a fish BCF is 1,087 l/kg. Uptake via food into fish, via sediment into worms and via soil into earthworms and plants has also been demonstrated.

The ecotoxicity database for MCCPs is complicated because many tests have been conducted at concentrations well above the water solubility. 96-hour LC_{50}s for fish are significantly in excess of water solubility. No effects on mortality, growth or behaviour of Rainbow Trout (*Oncorhynchus mykiss*) were observed at 1 and 4.5 mg/l during a 60-day test. No effects occurred in eggs or larvae of Japanese medaka (*Oryzias latipes*) exposed for 20 days at 0.0029-3.4 mg/l. Several aquatic invertebrate species have been tested, but *Daphnia magna* is the only species to be affected in both short-term tests (48-hour EC_{50} = 5.9 µg/l) and long-term tests (21-day NOEC = 10 µg/l based on mortality and reproductive effects) at concentrations below water solubility. Effects over 96 hours on the alga *Selenastrum capricornutum* occurred at concentrations above solubility, and the NOEC is an order of magnitude greater than that for *Daphnia*. There is no fully valid long-term toxicity study that investigates all of the sensitive early life-stages in fish, but by analogy with the data available for a similar substance (C_{10-13} chloroalkanes) the NOEC for fish early life-stages is unlikely to be lower than the NOEC for *Daphnia*. Although it is possible that the effects seen with *Daphnia* were due to physical adsorption, at least in the acute toxicity tests, direct toxic effects of the MCCPs themselves cannot be ruled out. The PNEC for the aquatic compartment is therefore 1 µg/l, using an assessment factor of 10 on the *Daphnia* NOEC.

Long-term toxicity data are available for three sediment-dwelling organisms (*Chironomus riparius, Lumbriculus variegatus* and *Hyalella azteca*). The lowest NOEC was 50 mg/kg wet weight for both *Lumbriculus* and *Hyalella*. A

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.

threshold concentration of 800 mg/l was measured using a mixed bacterial population from a sewage treatment plant.

For the soil compartment, long-term toxicity data are available for terrestrial plants (*Triticum aestivum, Brassica napus, and Phaseolus aureus*), worms (*Eisenia fetida*) and soil microorganisms. The lowest NOEC was 106 mg/kg wet weight (normalised to a standard soil organic carbon content of 2%) for the worm.

No significant effects were seen in a 5-day dietary study of mallard ducks (*Anas platyrhynchos*) and ring-necked pheasants (*Phasanius colchius*), other than a slight depression of food intake for mallards at the high dose level of 24,063 mg/kg food.

Exposure

MCCPs are a complex mixture of components. Up to 160,000 tonnes are manufactured annually in Europe (1997). They are used mainly as secondary plasticisers for polyvinyl chloride (PVC), with minor uses in metal working fluids, paints, adhesives and sealants, leather processing liquors and rubbers and other polymeric materials.

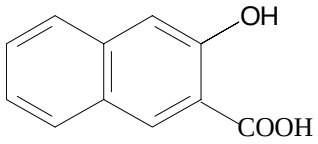
Emissions to the environment can occur both to the atmosphere and waste water. Sources of release include production sites, polymer and rubber processing sites, sites formulating or using metal working/cutting fluids, sites formulating or using paints, sites formulating or using sealants, sites formulating or using leather fat liquors or sites recycling carbonless copy paper. In addition, emissions to the environment (air, water and soil) could occur from finished articles (e.g. plastic or rubber components, painted surfaces and articles containing sealants) during their use and disposal.

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

Environment: The chemical is a candidate for further work. This substance has been assessed in the European Union Risk Assessment program under Regulation EEC/793/93. The assessment concluded that environmental risk reduction measures were needed for production and use of the substance in PVC, other plastics and rubber, paints, metal cutting/working fluids, leather fat liquors and carbonless copy paper. An environmental exposure assessment is therefore recommended as a post-SIDS activity, to determine the need for similar measures in countries outside Europe.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	92-70-6
Chemical Name	3-Hydroxy-2-naphthoic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute oral LD50 of 3-Hydroxy-2-naphthoic acid in rats was 823-1040 mg/kg bw. Clinical signs included reduced activity, accelerated breathing, closure of eyes, and diarrhoea. Gastro-intestinal irritation and dark or mottled livers were seen in the animals that had died during the studies.

A 10% solution of 3-Hydroxy-2-naphthoic acid (approx. 2000 mg/kg bw) was lethal to guinea pigs when applied dermally for 24 hours under occlusive conditions.

Moistened 3-Hydroxy-2-naphthoic acid was slightly irritating to the skin of rabbits in a test performed in accordance with OECD TG 404. Skin necroses and subcutaneous hemorrhages were observed in guinea pigs after occlusive exposures for 24 hours to the 10-12% solutions in mixtures of acetone and olive oil or corn oil. It caused serious damage to the eyes of rabbits (corneal vascularization/opacity) in tests performed in accordance with OECD TG 405. It may also have caused skin and upper respiratory tract irritation in workers.

3-Hydroxy-2-naphthoic acid has skin sensitisation potential.

After repeated administration to rats by the oral route for 28 days, there were indications of a possible effect on the adrenals in females at dose levels of 60 mg/kg bw/day and above. The only effects observed in males were a significantly reduced serum phosphate level and increased levels of bilirubin in serum and urine at a dose level of 300 mg/kg bw/day. The same findings, and, in addition, increased liver weights were reported for females at 300 mg/kg bw/day. NOEL (male): 60 mg/kg bw/day; NOEL (female): 12 mg/kg bw/day.

Poorly documented studies in rats involving repeated administration by the inhalation route gave indications of an effect on the kidneys (kidney necroses were reported after 10-days inhalation of 100 mg/m3).

3-Hydroxy-2-naphthoic acid was judged non- mutagenic in three Ames bacterial tests in Salmonella typhimurium and Escherichia coli strains, but it caused chromosomal damage in V79 hamster cells in vitro (only in the absence, but not in the presence of metabolic activation). No clastogenic activity, and no toxicity was observed in vivo in bone marrow cells of hamsters, dosed with the maximum recommended dose of 2000 mg/kg bw, suspended in starch mucilage. Due to severe limitations (only 50 metaphases were examined per animal and there was no indication that the target tissue was reached by the chemical), the available in vivo study is not sufficient to assess whether the in vitro mutagenic activity is reproduced in vivo.

3-Hydroxy-2-naphthoic acid was tested for its reproductive toxicity in a one-generation study according to OECD TG 415. The administration of the test substance had no adverse effect on the reproductive abilities of the parental

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.

generation. At a dose level of 200 mg/kg bw/day, the body weight of the offspring was decreased. Growth retardation and malformations (brachyury, kinked tail) were observed in the offspring of few litters at a maternally toxic dose (200 mg/kg bw/day). No Effect Level (NOEL) for reproductive toxicity: 200 mg/kg bw/day (highest tested dose); NOEL for toxicity to the offspring: 50mg/kg bw/day. The NOEL for systemic toxicity in males was 12.5 mg/kg bw/day (forestomach lesions at 50 mg/kg bw/day). The NOEL for systemic toxicity in females was 50 mg/kg bw/day (reduced body weight gain, forestomach lesions at 200 mg/kg bw/day).

Environment

3-Hydroxy-2-naphthoic acid has a calculated water solubility of 474 mg/l, a calculated vapor pressure of < 1.4 Pa and calculated log Kow values in the range of 3.4 – 3.59. The calculated data available are estimated for the undissociated acid. As 3-Hydroxy-2-naphthoic acid has a pKa-value of 2.8, under environmental relevant pH conditions the substance is completely dissociated. That means that the physico-chemical properties that are derived for the undissociated acid are not valid for the ionized substance.

The environmental distribution of the substance cannot be estimated with a fugacity model as the available physico-chemical properties were determined for the undissociated acid and not for the dissociated form that is present under environmental relevant pH conditions. However, as both volatilisation and adsorption are not expected for the dissociated substance, it can be assumed that the hydrosphere is the main target compartment for 3-hydroxy-2-naphthoic acid. This is confirmed by a Mackay I model run for the sodium salt.
3-Hydroxy-2-naphthoic acid is not readily biodegradable as was shown in a test according to OECD 301 C (1.3 % after 14 days). In a Zahn-Wellens test (OECD 302 B) with adapted inoculum the chemical was inherently biodegradable (85 % after 21 days). In a 42d bioaccumulation study with Cyprinus carpio BCF values of < 0.5 resp. < 4 were found for 3-hydroxy-2-naphthoic acid concentrations of 1 mg/l and 0.1 mg/l. Therefore, 3-hydroxy-2-naphthoic acid has no potential for bioaccumulation.

For 3-hydroxy-2-naphthoic acid there are short-term tests with fish, daphnids and algae available. In addition, a long-term test with *Daphnia magna* was performed. The following effect values were found:

Brachydanio rerio: 96h-LC_{50} = 68mg/l, *Daphnia magna*: 48h-EC_{50} = 32.9 mg/l, *Pseudokirchneriella subcapitata*: 72h-E_rC_{50} = 65.3 mg/l, 72h-EbC50=26.1 mg/l; 72h-NOEC = 6.8 mg/l; *Daphnia magna*: 21d-NOEC = 10.4 mg/l.

With an assessment factor of 50 a PNECaqua of 136 µg/l was derived from the lowest available NOEC of 6.8 mg/l found for green algae.

Exposure

In the EU the production and import volume is in the range of 10,000 to 50,000 t/a. The worldwide production capacity for 3-hydroxy-2-naphthoic acid is reported to 30,000 t/a . 3-Hydroxy-2-naphthoic acid is mainly used as intermediate for the production of dyes and pigments. Further uses are as intermediate for insecticides and pharmaceuticals.

Occupational exposure may occur during production and processing of 3-hydroxy-2-naphthoic acid, mainly via the dermal route. Workplace measurements are available from one European production plant, ranging up to 1.23 mg/m^3 (mean value: 0.35 mg/m^3). No exposure information is available with regard to processing sites.

3-Hydroxy-2-naphthoic acid is a chemical intermediate for the production of dyes and pigments, which may also be used for pharmaceutical applications. A product containing 100% 3-Hydroxy-2-naphthoic acid is listed in the Swiss Product Register (2002) for industrial use (product category: developer/paints/dyes/laquers). No information on consumer products containing 3-Hydroxy-2-naphthoic acid was located in the Danish, Swedish and Swiss Product Registers (2002) and for Germany.

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.

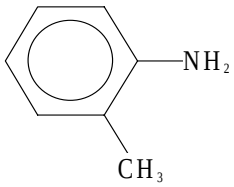
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work, because 3-Hydroxy-2-naphthoic acid was a potent in vitro clastogen in an assay without metabolic activation. Due to severe limitations of the available in vivo chromosomal aberration study (only 50 metaphases were examined per animal and there was no indication that the target tissue was reached by the chemical), it is not possible to finally assess whether the in vitro mutagenic activity is reproduced in vivo. A standard in vivo test (mouse bone marrow chromosome aberration test (OECD TG 475) or an erythrocyte micronucleus test (OECD TG 474)) should therefore be performed as post-SIDS work. It is noted that the chemical is a skin irritant, can cause serious damage to the eye, is a skin sensitiser and there are indications of a teratogenic potential.

Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor Country (that reports that the only known use of the chemical in two OECD countries is as an intermediate, and relating to an unknown fraction of the global production volume), exposure to the environment is anticipated to be low, and therefore, this chemical is of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-53-4
Chemical Name	o-Toluidine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

o-Toluidine is rapidly absorbed via gastrointestinal tract and is rapidly distributed, metabolized and excreted mainly via urine. Although there are no special toxicokinetic data on absorption via skin and respiratory tract, absorption via these administration routes is shown by data from acute toxicity studies.

The LC_{50} (rat) is 852 ppm/4 hrs (approx. 3827 mg/m^3/4 hrs), and oral LD_{50} (rat) is 750 mg/kg bw. The dermal LD_{50} (rabbit) is 3250 mg/kg bw in a limited study. The predominant symptoms after inhalation or oral application were cyanosis, labored breathing, lethargy or loss of consciousness. o-Toluidine is a methemoglobin forming chemical; this was shown in rat and cat as well as in humans.

o-Toluidine is not irritating to the skin of rabbits when tested for 24 hours under semi-occlusive conditions (rabbit, ear) and is moderately irritating when tested 24 hours under occlusive conditions (rabbit, skin). However, skin necrosis developed 72 hours post treatment in 1/6 animals under occlusive conditions. o-Toluidine causes serious damage to the eyes of rabbits.

There are no valid data available to evaluate the sensitization potential of o-toluidine.

Repeated dose studies show that o-toluidine is toxic to erythrocytes and a methemoglobin forming chemical. This was demonstrated in elevated methemoglobin levels up to 19.0 % in the subacute feeding study as well as in the marked splenic toxicity in the subacute gavage and subchronic feeding studies leading to hypercellularity in the bone marrow. Further target organs were liver and kidney (hemosiderin deposition) and urinary bladder (hyperplasia). Based on the hematological findings no NOAEL could be derived, the LOAEL (rat, 14-day feeding study) is 500 ppm (approx. 23.7 and 25.5 mg/kg bw/day for males and females, respectively).

Genotoxicity test results are as typical for the class of aromatic amines. o-Toluidine showed positive as well as negative results in point mutation assays in bacteria and yeast. Results from tests with mammalian cell systems (HPRT, TK, UDS) were inconsistent, too, and appear to be protocol dependent. However, positive and negative results were independent of the presence or absence of a metabolic activation system. In in-vitro tests for chromosomal aberrations o-toluidine yielded positive results in several cell systems and did induce micronuclei in human lymphocytes in-vitro. In in-vivo tests for chromosomal aberrations o-toluidine yielded negative results in bone marrow of mice. o-Toluidine did not induce micronuclei in the in-vivo mouse micronucleus tests following intraperitoneal or oral application. However, SCE assay in mice and UDS-test in rats gave positive results in vivo. o-

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.

Toluidine did not induce point mutations in the in-vivo SLRL-test with *Drosophila melanogaster*. Besides this, there are several, however, less reliable positive test results in *Drosophila*. Overall, o-toluidine showed potential for mutagenic activity in vitro and clastogenic activity in vitro and in vivo.

After oral administration to mice o-toluidine induced and increased incidence of hemangiomas and hemangiosarcomas and hepatocellular carcinomas or adenomas. In rats, oral administration increased the incidence of tumors in multiple organs, including fibromas, sarcomas, mesotheliomas, mammary fibroadenomas and transitional cell carcinomas of the urinary bladder. IARC classified o-toluidine in group 2A (probably carcinogenic to humans).

In the open literature, o-toluidine is suspected to cause urinary bladder tumors in workers. However, this finding cannot definitely be attributed to o-toluidine because of the co-exposure to other arylamines. There is no valid study on reproductive or developmental toxicity available, however, o-toluidine is genotoxic and carcinogenic and therefore it should be regarded as potentially toxic to reproductionaccording to EU Technical Guidance Document. In a subchronic feeding study in male rats o-toluidine hydrochloride led to degeneration of seminiferous tubules and a significant increase in relative weight of testis in systemic toxic doses. In very limited developmental toxicity studies effects on kidneys, ovaries, heart and lungs in progeny were reported that were difficult to interpret. However, due to its methemoglobin forming activity like other structurally related aromatic amino or nitro compunds o-toluidine is anticipated to exert developmental toxicity at least as a secondary consequence of maternal toxicity. As results from further testing would not affect the most stringent exposure control measures being already in place due to genotoxicity and carcinogenicity of o-toluidine, no further tests are warranted.

Environment

o-Toluidine is a light yellow liquid becoming reddish brown on exposure to air and light with a melting point of -24.4 °C for the α-form and -16.3 °C for the β-form, and a boiling point of 200.2 °C. The density of the liquid is 0.9984 g/cm^3 at 20 °C. The vapour pressure is 34.5 Pa at 25 °C. The measured log K_{ow} is 1.40. The solubility in water is 15.0 g/l at 25°C. The dissociation constant is 4.44 - 4.45. The flash point is 85 °C, the auto-ignition temperature 482 °C.

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

With regard to its chemical structure o-toluidine is not expected to hydrolyze under environmental conditions. o-Toluidine is readily biodegradable (MITI, comparable to OECD TG 301 C: biodegradation 65 % after 28 days, OECD TG 301 A: 88 - 90 % after 28 days, OECD TG 301 E: ca. 90 % after 28 days).

According to the Mackay fugacity model level I, the favourite target compartment of o-toluidine is water with 91.8 %, followed by air with 7.8 %. The measured and calculated Henry's law constants (0.20-0.25 Pa m^3/mol at 25 °C) prove a low to moderate potential for volatilisation from surface waters.

The available experimental bioconcentration factors (BCF) for o-toluidine indicate no significant potential for bioaccumulation in Pacific oysters (*Crassostrea gigas*) (BCF = 3.8 - 5.4) or Common bay mussels (*Mytilus edulis*) (BCF = 3.5 - 4.9). The bioconcentration factor BCF = 2.4 for o-toluidine, calculated from the octanol-water partition coefficient, confirms the low bioaccumulation potential also for fish..
K_{oc} values were calculated with PCKOCWIN v. 1.66 (K_{oc} = 74) and with the TGD equation for the anilines (K_{oc} = 52). From the measured coefficient of distribution between the sediment and water (K_d = 0.013) the K_{oc} was calculated to 0.87. These results indicate a low sorption potential of o-toluidine onto the organic phase of soil or sediments. However, adsorption of o-toluidine in soil can be enhanced by ion-ion interactions as the results with clay minerals show.

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

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.

Leuciscus idus: 96 h-LC_{50} = 82.5 mg/l
Poecilia reticulata: 14 d-LC_{50} = 81.3 mg/l
Daphnia magna: 48 h-EC_{50} = 0.52 mg/l
Daphnia magna: 96 h-EC_{50} = 0.249 mg/l
Chlorella pyrenoidosa: 96 h-E_bC_{50} = 55 mg/l
Selenastrum capricornutum: 72 h-E_rC_{50} = 94.5 mg/l (72h-EbC50 = 30.9 mg/l)

Reliable tests on chronic toxicity towards *Daphnia* and algae are available as well:

Daphnia magna 21 d-NOEC = 0.0126 mg/l [Endpoint Reproduction]
Daphnia magna: 21 d-LRCT = 0.1 mg/l [endpoint population growth]; derived NOEC = 0.032 mg/l
Selenastrum capricornutum: 72 h-NOEC = 31.0 mg/l [endpoint growth rate]; (2.9 mg/l [Endpoint biomass])
Microcystis aeruginosa: 8 d-EC_3 = 0.31 mg/l [endpoint cell multiplication], similar to NOEC

Based on the lowest NOEC of 0.0126 mg/l derived for *Daphnia magna* a Predicted No Effect Concentration in water ($PNEC_{aqua}$) of 0.252 µg/l can be calculated with an assessment factor of 50.

Exposure

o-Toluidine is commercially manufactured by reduction of o-nitrotoluene. In 2001, the world wide production volume of o-toluidine is estimated to be 59,000 tonnes by 11 producers. o-Toluidine is an intermediate in chemical synthesis of herbicides, rubber chemicals, dye and pigment intermediates, resin hardeners, fungicide intermediates, pharmaceutical intermediates, and others. By far the largest use is as an intermediate in the manufacture of herbicides.

No direct consumer use is known for o-toluidine. o-Toluidine is listed in the Danish, Finnish, Norwegian, and Swedish product registers as an industrial product. No consumer application is registered. The Swiss product register lists 2 analytical kits, both with a o-toluidine concentration of about 0.1 %, presumably for occupational use. An analytical substance is registered for industrial use with an o-toluidine content of less than 1 %. There are about 10 metallic mordants for industrial use with o-toluidine levels of < 0.1 %.

In the EU, the use of azo dyes releasing o-toluidine on degradation, is not permitted for textiles and other consumer articles. Thus, an exposure of consumers and of the environment due to releases from consumer products appears to be negligible.

At all 5 sites of one company in the Sponsor country o-toluidine is manufactured and processed in closed systems. The effluent concentration from the wastewater treatment plants was below the detection limit of 20 µg/l (one production site), below 25 µg/l (one processing site) and 10 µg/l (two processing sites). For one production site in the Sponsor country only data for the sum of the toluidine isomers are available.

o-Toluidine occurs in certain vegetables, in tobacco leaves and in the aroma of black tea. It is an intermediate in the biodegradation of o-nitrotoluene, e.g. at former munitions sites. Toluidine (isomers not specified, but o-toluidine likely to be present) was detected as a component of coal oil. o-Toluidine is formed during pyrolysis. Most recent detection of o-toluidine in environmental waters in the Sponsor country was in the rivers Rhine and Elbe in 1997and 1998, with the highest o-toluidine concentrations of 0.1 µg/l in the Elbe river at Schmilka.

o-Toluidine releases were up to 4 µg/cigarette. o-Toluidine was detected in contaminated outdoor air. In indoor air there was a correlation between o-toluidine concentration and exposure to environmental tobacco smoke.

In Germany for occupational settings, a Technical Exposure Limit (TRK) of 0.5 mg/m³ is set for o-toluidine. At production and processing sites of the Sponsor company, the exposure of workers is well below this limit.

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.

There are several published reports on biomonitoring of o-toluidine. o-Toluidine concentration in urine and the level of hemoglobin adducts in blood of workers were higher than in the general population in historic studies, but not in recent studies. In general, smokers have higher levels of o-toluidine in urine and of hemoglobin adducts in blood than non-smokers. o-Toluidine was also detected in human milk.

Consumers are exposed to o-toluidine in environmental tobacco smoke, some foodstuffs, and (other) products in contact with smoke. Tobacco smoke is the predominant source of o-toluidine in humans.

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 and subacute toxicity, methemoglobin formation, skin and eye irritation, genotoxicity, carcinogenicity, potential for reproductive toxicity). Based on data presented by the Sponsor country (relating to production by one producer which accounts for 17 – 60 % of global production and relating to the use pattern in several OECD countries as well as occupational monitoring data from several countries), exposure is controlled in occupational settings, and exposure of consumers is negligible. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor.

Environment: The substance is currently of low priority for further work. 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 17 – 60 % of global production and relating to the use pattern in several OECD countries as well as surface water monitoring data from one 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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	25264-93-1 25339-56-4 25377-83-7 27215-95-8 25339-53-1 25378-22-7 85535-87-1 629-73-2 112-88-9
Chemical Names	[in the same order shown above for CAS Nos.] hexene heptene octene nonene decene dodecene alkenes, C10-13 1-hexadecene 1-octadecene
Structural Formula	[in the same order shown above for CAS Nos.] CH_3-CH=CH-$(CH_2)_2$-CH_3[a] CH_3-CH=CH-$(CH_2)_3$-CH_3[a] CH_3-CH=CH-$(CH_2)_4$-CH_3[a] CH_3-CH=CH-$(CH_2)_5$-CH_3[a] CH_3-CH=CH-$(CH_2)_6$-CH_3[a] CH_3-CH=CH-$(CH_2)_8$-CH_3[a] CH_3-CH=CH-$(CH_2)_x$-CH_3[a] (x = 6-9) CH_3-$(CH_2)_{13}$-CH=CH_3 CH_3-$(CH_2)_{15}$-CH=CH_3 [a] Basic structure; position of internal double bond varies and some isomers may be branched

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

This profile includes an evaluation of SIDS-level testing data, using a category approach, with six individual internal olefins (C_6 – C_{10} and C_{12}), a C_{10-13} internal olefins blend and two linear alpha olefins (1-hexadecene and 1-octadecene), all of which are mono-olefins. The internal olefins are predominantly linear, but may contain small amounts of branched materials. For the purposes of the OECD HPV Chemicals Programme, the category was defined as "Higher Olefins." The category designation was based on the belief that internalizing the location of the carbon-carbon double bond, increasing the length of the carbon chain, and/or changing the carbon skeleton's structure from

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.

linear to branched does not change the toxicity profile, or changes the profile in a consistent pattern from lower to higher carbon numbers. While the category is actually defined as $C_6 - C_{18}$ mono-olefins (sponsored chemicals), we included surrogate data from a mixed stream containing C_{20}-C_{24} linear and branched internal olefins. While we realize that sufficient data exist to support the category without the data on the C_{20}-C_{24}, we believe these data provide additional support and strengthen the hypothesis that changing carbon number, location of the double bond or addition of branching does not alter the mammalian health and biodegradation endpoints and helps to indicate increasing or decreasing trends for ecotoxicity data.

Human Health

Olefins (alkenes) ranging in carbon number from C_6 to C_{24}, alpha (linear) and internal (linear and branched) demonstrate low acute toxicity by the oral, inhalation and dermal routes of exposure: Rat oral LD_{50} >5 g/kg; rat 4-hr inhalation LC_{50} range = 110 mg/L (32,000 ppm) to 6.4 mg/L (693 ppm) for C_6 to C_{16}; and rat/rabbit dermal LD_{50} > highest doses tested (1.43 - 10 g/kg).

Repeated-dose studies, using the inhalation (C_6 alpha), dermal (C_{12}-C_{16}), or oral (C_6 alpha and internal linear/branched; C_8 and C_{14} alpha; and C_{16}, C_{18} and C_{20}-C_{24} internal linear/branched) routes of exposure, have shown comparable levels of low toxicity in rats. In females, alterations in body and organ weights, changes in certain clinical chemistry/hematology values, and liver effects were noted (NOELs of $\geq$ 100 mg/kg oral or $\geq$ 3.44 mg/L (1000 ppm) inhalation). In males, alterations in organ weights, changes in certain clinical chemistry/hematology values, liver effects, and male rat-specific kidney damage that is likely associated with the alpha $_{2\mu}$- globulin protein were noted (LOELs $\geq$ 100 mg/kg oral only). The male rat kidney damage was seen in oral studies with C_6, C_8 and C_{14} linear alpha olefins and C_6 internal branched olefins, but was not seen in studies with C_{16}/C_{18} or C_{20} - C_{24} internal linear/branched olefins. The noted liver effects were seen in oral studies with C_{14} alpha olefins (minimal-to-mild hepatocyte cytoplasmic vacuolation with increased liver weight in males and females) and with C_{20}-C_{24} internal olefins (minimal centrilobular hepatocyte hypertrophy with increased liver weight in females only). No effects were present in the study with C_{20}-C_{24} internal olefins following a 4-week recovery period, indicating reversibility of the observed effects. These liver effects seen only with the larger molecules may be indirect effects of an intensified liver burden, rather than a direct toxic effect of the olefin. Based on evidence from neurotoxicity screens included in repeated dose studies with C_6 and C_{14} alpha olefins and with C_6, C_{16}/C_{18} and C_{20}-C_{24} internal linear/branched olefins, the category members are not neurotoxic.

Based on evidence from reproductive/developmental toxicity screens in rats with C_6 and C_{14} alpha olefins and C_6 and C_{18} linear/branched internal olefins, along with the findings of no biologically significant effects on male or female reproductive organs in repeated dose toxicity studies, the category members are not expected to cause reproductive or developmental toxicity.

Based on the weight of evidence from studies with alpha and internal olefins, category members are not genotoxic. No carcinogenicity tests have been conducted on $C_6 - C_{18}$ alpha or internal olefins; however, there are no structural alerts indicating a potential for carcinogenicity in humans.

These materials are not eye irritants or skin sensitizers. Prolonged exposure of the skin for many hours may cause skin irritation. The weight of evidence indicates alpha and internal olefins with carbon numbers between C_6 and C_{24} have a similar and low level of mammalian toxicity, and the toxicity profile is not affected by changes in the location of the double bond or the addition of branching to the structure.

Environment

The potential for exposure of aquatic organisms to members of the Higher Olefins Category will be influenced by their physico-chemical properties. The predicted or measured water solubilities of these olefins range from 50 mg/L at 20°C for hexene to 0.00015 mg/L at 25°C for 1-octadecene, which suggests there is a lower potential for the larger olefins to be bioavailable to aquatic organisms due to their low solubilities. Their vapor pressures range from 230.6 hPa at 25°C for hexene to 0.00009 hPa at 25°C for 1-octadecene, which suggests the shorter chain olefins will tend to partition to the air at a significant rate and not remain in the other environmental compartments for long periods of

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.

time; while the longer chain olefins will tend to partition primarily to water, soil or sediment, depending on water solubility and sorption behaviour. The soil adsorption coefficients (K_{oc}) range from 149 for C_6 to 230,800 for C_{18}, indicating increasing partitioning to soil/sediment with increasing carbon number. Level I fugacity modeling predicts that the C_6-C_{13} olefins would partition primarily to air, while the C_{16}-C_{18} olefins would partition primarily to soil. Results of Level III fugacity modelling suggest that the $C_6 - C_8$ category members will partition primarily to the water compartment; and, as the chain length increases beyond C_{10}, soil and sediment become the primary compartments. These chemicals have a very low potential to hydrolyze and do not photodegrade directly. However, in the air, all members of the category are subject to atmospheric oxidation from hydroxyl radical attack, with calculated degradation half-lives of 1.8 to 4.1 hours. $C_6 - C_{18}$ olefins have been shown to degrade to an extent of approximately 8-81% in standard 28-day biodegradation tests. These results were not clearly correlated with carbon number or any other identifiable parameter; however, the weight of evidence shows that the members of the Higher Olefins Category have potential for degradation in the environment. Volatilization from water is predicted to occur rapidly (hours to days), with Henry's Law Constants (bond method) ranging from 0.423 (C_6) to 10.7 (C_{18}) atm m^3/mol. Consideration of these degradation processes supports the assessment that these substances will degrade relatively rapidly in the environment and not persist. Based on calculated bioconcentration factors, the C_6, C_7, C_{16} and C_{18} category members are not expected to bioaccumulate (BCF = 46, 236, 71 and 3). Although the $C_8 - C_{13}$ olefins have BCFs ranging from 659 to 748, and K_{ow} values ranging from 4.13 to 6.59, and thus are considered to have the potential for bioaccumulation, their physico-chemical properties and fate indicate that there would be limited environmental exposure because of volatility, biodegradability and limited solubility.

Data indicate that acute aquatic toxicity can be observed for C_6 through the C_{10} olefins (C_6: EC/LC_{50} range of 1-10 mg/L; C_7-C_{10}: EC/LC_{50} range of 0.1-1.0 mg/L), and that toxicity increases with increasing carbon number within that range, which is consistent with increasing K_{ow} values (3.07 – 5.07). Above a chain length of 10, toxicity is not observed within the limits of solubility. However, data indicate that chronic aquatic toxicity can be observed in the C_{10} olefins (EC_{10} = 20.0 μg/L, EC_{50} = 28.1 μg/L, NOEC = 19.04 μg/L). Data also suggest that aquatic toxicity does not differ with bond location or presence of branching.

Exposure

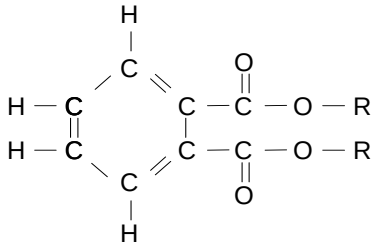
The following U.S. production volumes for 2002 were reported for members of the Higher Olefins Category: 1-10 million pounds for hexene and dodecene, 10-50 million pounds for decene and C_{10}-C_{13} alkenes, 50-100 million pounds for heptene and octene, and 100-200 million pounds for 1-hexadecene and 1-octadecene. Members of the Higher Olefins Category are produced commercially in closed systems and are used primarily as intermediates in the production of other chemicals (including polymers, fatty acids, mercaptans, plasticizer alcohols, detergents, surfactants, additives for lubricants, amine oxides and amines, detergent alcohols and nonionics, and hydraulic fluids and additives). C_{16} and C_{18} olefins are blended with other chemicals for use as drilling fluids for off-shore oil exploration. Non-occupational human exposure is not expected. Any occupational exposures that do occur are most likely by the inhalation and dermal routes. Results from modeled data suggest that on-site waste treatment processes are expected to remove these compounds from aqueous waste streams to the extent that they will not be readily detectable in effluent discharge. The olefins will not persist in the environment because they can be rapidly degraded through biotic and abiotic processes.

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. These chemicals possess properties indicating hazards to human health (reversible mild skin and eye irritation; mild respiratory tract irritation to the lower chain length members) and the environment (acute aquatic toxicity for the C6-C10 category members and chronic aquatic toxicity for C10). Based on exposure data presented by the sponsor country, (four manufacturing sites within the sponsor country which accounts for 47-64% of global production depending on category member) and relating to use pattern in the sponsor country (industrial intermediate in closed systems) this category is a low priority for further work. Countries may wish to investigate any exposure scenarios that were not presented by the sponsor country.

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.

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	High Molecular Weight Phthalate Esters (HMWPE)
CAS Nos.	53306-54-0 68515-41-3 85507-79-5 68515-43-5 3648-20-2 68515-47-9 119-06-2
Chemical Names	1,2-benzenedicarboxylic acid, di-2-propylheptyl ester 1,2-benzenedicarboxylic acid, di-C7-9-branched and linear alkyl esters 1,2-benzenedicarboxylic acid, di-C11-branched and linear alkyl esters 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters 1,2-benzenedicarboxylic acid, di-C11-alkyl ester 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich 1,2-benzenedicarboxylic acid, di-C13-alkyl ester
Structural Formula	Substances in the High Molecular Weight Phthalate Esters Category have the following basic structure with alkyl groups (R) as indicated for the CAS registry numbers (RNs) below:  53306-54-0 R=$C_{10}H_{21}$ (propyl branched) [100% branched] 68515-41-3 R=C_7H_{15} to C_9H_{19} (branched and linear) [>80% linear] 85507-79-5 R=$C_{11}H_{23}$ (branched, essentially methyl, and linear) 68515-43-5 R=C_9H_{19} to $C_{11}H_{23}$ (branched and linear) [>80% linear] 3648-20-2 R=$C_{11}H_{23}$ (branched) 68515-47-9 R=$C_{13}H_{27}$ (branched, essentially methyl) 119-06-2 R=$C_{13}H_{27}$ (branched)

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The High Molecular Weight Phthalate Ester (HMWPE) Category consists of esters with an alkyl carbon backbone with 7 carbon (C) atoms or greater. The category is formed on the principle that substances of similar structure have

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.

similar environmental and toxicological properties. Data are available on substances that meet the category definition and which are, or are not members of the category, to demonstrate that the members of this category have similar biological activities and that, when used, read-across is an appropriate approach to characterize endpoints for select members of this category.

The HMWPE Category contains chemically similar substances, 1,2-benzenedicarboxylic acid reacted with branched and/or linear alkyl alcohols, which are referred to as the alkyl chains in the phthalate ester molecule. A phthalate ester (PE) molecule is produced by esterifying one molecule of benzenedicarboxylic acid (phthalic anhydride) with two alcohol molecules. The seven members of this category contain linear and/or branched diheptyl, dioctyl, dinonyl, didecyl, diundecyl, didodecyl, and/or ditridecyl PEs. The branched alkyl chains are composed of varying mixed isomers. The length of the alkyl chains varies by substance, but the total carbon number of the longest linear C-chain (or backbone chain) is predominantly C7 or greater. For the seven substances in the category described in this submission, the backbones range from C7 to C12. The backbones in all but one category member contain methyl branching, only the bis-propyl heptyl phthalate backbone contains propyl branching.

Due to similar chemical structure, category members are generally similar with respect to select physico-chemical properties or display an expected trend (see Table 1 in SIAR). From the available data, HMWPE members are also similar with respect to their biological activity in that they demonstrate few biological effects.

For PEs, the critical toxicological effects are development and reproduction. These aspects are very structure dependent, and are associated with molecules with a 4 to 6 carbon backbone. By contrast, PEs with 7 or more backbone carbons produce no detectable effects in reproduction and no adverse effects on development. From a very large toxicology database for phthalate esters, a structure activity can be demonstrated that best relates to the linear portion of the phthalate ester, rather than total carbon number. For example, DINP (di-isononyl phthalate ester, CAS No 68515-48-0 and 28553-12-0) and DIDP (di-isodecyl phthalate ester, CAS No 68515-49-1 and 26761-40-0), are not formally part of this category as they have been assessed previously, but satisfy the category definition (as in Table 2 of the SIAR). Furthermore, for environmental effects, PEs do not show any effects from C5 upwards (see reference in SIAR). Hence, the HMWPE Category is valid for both toxicological and environmental endpoints.

As mentioned, DINP and DIDP, meet the category definition in that their backbone lengths are predominantly C7 or above, and produce little, if any, effects of developmental or reproductive toxicity. The DINP and DIDP dossiers have not been included in detail in this category, as they have already been assessed in the OECD HPV program. However select data for these two substances will be used as supportive data to the category.

To correctly characterize selected endpoints for PEs, read-across techniques can be applied. Read-across is typically performed using measured or calculated data for an endpoint of interest for one or more like-substances to predict that endpoint for a similar substance without data.

Two general rules for read-across as they apply to PEs include:

- Chemical relatedness - the substance without data as well as the substance(s) with data are similar such that their physicochemical, biological, and toxicological properties would be expected to behave in a predictably similar manner or logically progress across a defined range. It is shown that for the environment assessment, read-across can be performed with HMWPE having a backbone chain length longer than 5 carbons. Indeed, since their water solubility is so low, there is no toxicity in fish, invertebrates, and algae for the HMWPE members at their limit of solubility. Read-across for the health assessment is performed with HMWPE having a backbone chain length of 7 carbons or greater.
- Structural similarity - the substance without data possesses small incremental structural differences from the reference substance(s) or the difference between the two will not affect the property sufficiently that it cannot be accurately predicted.

For PEs in general, read-across can be applied across increasing/decreasing carbon (C) numbers in the alkyl side-chains. For example, data for dinonyl (di-C9) phthalate and a diundecyl (di-C11) phthalate might be used to read-across to a didecyl (di-C10) phthalate or a phthalate diester with constituents that contain combinations of C9 to C11 alkyl groups. For purposes of discussion, the following general abbreviations will be used in this document to refer to

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.

PE members of this category:

- Di-phC10 PE (CAS No 53306-54-0)
- Di-C7-9 PE (CAS No 68515-41-3)
- Di-C11 PE (CAS No 3648-20-2 or 85507-79-5)
- Di-C9-11 PE (CAS No 68515-43-5)
- Di-C13 PE (CAS No 68515-47-9 or 119-06-2)

Human Health

Data are not specifically available on the toxicokinetics, metabolism, or distribution of the HMWPE covered under this category. However, data developed for DINP are considered to be representative, in a qualitative point of view, of other HMWPE. When orally administered to rodents, DINP is rapidly metabolized in the gastrointestinal tract to the corresponding monoester (MINP), absorbed and excreted, primarily in the urine. Shortly after administration, it is found primarily in liver and kidneys, but it does not persist or accumulate in any organ or tissue. It is very poorly absorbed from the skin, but once absorbed it behaves in the same way as the orally administered substance. The results of these rodent studies contrast with data from studies involving humans or other primates, which indicate low absorption at low oral doses and even more limited total absorption at high doses. Indeed primates appear to be less efficient at metabolizing phthalates to the corresponding monoester, and at high doses absorption of monoester by primates is saturated. One reason for this difference is that there are differing hydrolysis rates for the phthalates between primates and rodents. Consequently, less HMWPE is likely to be absorbed in humans than in rodents.

HMWPE have a low order of acute toxicity by the inhalation, dermal, intraperitoneal and oral routes of exposure. Members of the HMWPE Category are not irritating to the skin or eyes (only slight conjunctival irritation for CAS RN 68515-47-9), neither are they skin sensitizers (Maximization Test or comparable, or Buehler Method). Although some data for these endpoints are older and the peer reviewed publications may not include all desirable methodology, the weight of evidence is consistent.

The primary findings in the repeated dose rat studies were in the liver and kidney and to a lesser degree in the thyroid. Effects to the liver, besides some minor and probably adaptative effects, are indicative of peroxisomal proliferation, including increased PCoA, liver weights, and liver hypertrophy and are not relevant for humans. Indeed, it has been shown that these effects are mediated through the peroxisome proliferation-activated receptor alpha (PPARα) and that levels of PPARα are much higher in rodents than humans. Thus, one would expect humans to be substantially less responsive than rodents to peroxisome proliferating agents. Empirical evidence for this hypothesis has been provided by studies in primates in which repeated administration of DINP had no effects on liver, kidney or testicular parameters, including peroxisome proliferation. The kidney effects were a result of a dose-dependent α-2μ-globulin nephropathy. Such effects are sex- and species-specific to male rats and also are not relevant to humans. The relevance of sporadically observed increased kidney weights in female rats is unclear. Thyroid effects are likely to be a compensatory effect associated with the peroxisomal proliferation in the liver. The results were consistent for all members of the Category, with NOAEL ranging between 10 and 282 mg/kg/day. It should be noted that the 10 mg/kg/day value comes from an OECD 422 study, where rats were dosed for 45 days and the effect observed at 50 mg/kg/day was liver weight increase. This is likely to be related to peroxisome proliferation. The spread in this data is driven by the dose level selection in the various tests. All the NOAELs are driven by liver and/or kidney (common) effects.

HMWPE Category members have been tested in the Ames reverse mutation assay using *Salmonella typhimurium* and all were non-mutagenic with and without metabolic activation. Similarly, a range of substances covering the majority of the carbon numbers in this category were found to be inactive in the mouse lymphoma tests. Additional testing of di-C13 PE showed that the test substance did not induce either structural chromosomal aberrations or polyploidy in CHL cells up to the limit concentration of 4.75 mg/ml, in the absence or presence of an exogenous metabolic activation system. These substances are non-genotoxic based on the negative genotoxicity data for the category as a whole. Although some data for these endpoints are older and the peer reviewed publications may not include all desirable methodology, the weight of evidence is consistent.

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.

Although the HMWPE have not been tested for carcinogenic properties (i.e. chronic toxicity or bioassay studies), previous experience with a wide range of phthalates suggests that high doses might produce liver changes in rodents, but these are not relevant to humans and not indicative of a potential human risk. Three chronic toxicity/carcinogenicity studies of DINP have been conducted; two in rats and one in the mouse. In the rat studies, the major findings were liver and kidney changes principally related to the induction of peroxisome proliferation. There was an increase in liver tumors in both male and female rats and also a small increase in kidney tumors in the male rats. Both of these tumors are considered to be rat specific and without relevance to humans. In the mouse study, there were liver tumors as well, also the consequence of peroxisomal proliferation, but no tumors of other types.

Although not all members of the category have been tested for reproductive toxicity, (di-phC10 PE, di-C11 PE, or di-C13 PE - CAS No 68515-47-9), there are data for the lower (di-C7-9 PE), intermediate (di-C9-11 PE) and higher (di-C13 PE - CAS No 119-06-2) molecular weight representatives that have shown no significant reproductive toxicity at doses up to 500 mg/kg/day or 250 mg/kg/day (di-C13 PE). Effects included transiently decreased body weights or slightly decreased ovary and epididymidal weights. These effects are minor and are not directly related to reproductive toxicity. Furthermore, category members di-C7-9 PE and di-C9-11 PE have been recently shown not to be associated with detectable reproductive effects and do not affect fertility, similarly to DINP and DIDP.

Data from the developmental toxicity tests for the HMWPE conducted in rats, on di-phC10, di-C7-9, di-C9-11, and di-C13 PEs, have shown minimal maternal toxicity, at doses up to 1,000 mg/kg/day (limit dose) or 250 mg/kg/day (in di-C13 PE). Either no effects were produced or the effects were associated with decreased food consumption and body weight loss in dams. Only the di-phC10 PE showed maternal toxicity at the limit dose and associated effects of resorptions, decreased litter size, or fetal survival associated with the above two symptoms of maternal toxicity. In the two-generation study on DIDP, a decrease in offspring survival, more marked in F2, was observed. In the di C13 PE (CAS RN 119-06-2) 1 generation study (F1 generation) a decrease in survival indices was observed leading to a NOAEL of 50 mg/kg/day for offspring rats whereas NOAELs for parental rats were 250 mg/kg. These may be considered related to developmental effects. No such changes were seen in either generation of the separate studies on di-C7-9 PE and di-C9-11 PE; these results are consistent with results from DIDP studies.

However, none of the HMWPE substances tested produced developmental effects. Increased frequencies of developmental variants including dilated renal pelvis and supernumerary lumbar ribs were produced in the studies on di-C7-9 PE and di-C9-11 PE, but are common findings in rats. Although not all members of the HMWPE Category have been tested for developmental toxicity, there are data for the lower (di-phC10 and di-C7-9), intermediate (di-C9-11) and higher (di-C13) molecular weight representatives. Like DINP and DIDP, they have shown no significant developmental toxicity. It is reasonable to conclude that other members of the category would behave similarly, as shown by the weight of evidence. Thus, it can be concluded that this category of HMWPE induces no biologically significant developmental effects in rodents.

In conclusion, as demonstrated in the SIAR (sections 3.1.2 to 3.1.8), the weight of evidence shows that members of the HMWPE Category have a low order of acute and subchronic toxicity. They are not irritating to the skin or eyes. They are not skin sensitizers. They are not mutagenic. No or only minimal developmental toxicity and no adverse effects on reproductive capability have been observed in rodent studies. Thus, there is minimal concern about those PEs resulting in reproductive toxicity in humans.Although not tested for carcinogenicity, the members of this category do not show the potential for producing genetic effects. Also, the same mechanism of action through peroxisome proliferation can be anticipated for induction of liver tumors in rodents, and this is presumed not to be relevant to humans.

The results were consistent for all members of HMWPE Category in all endpoints and the toxicity has been well characterized. No further studies are proposed.

Environment

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.

Members of the HMWPE Category are liquid at 25°C. Most of their physico-chemical properties were obtained by calculation using chemical structures that best characterize the range of constituent chemicals. They demonstrate relatively similar properties or progressive change across a range of values with melting point ranging from -48°C to -9°C, boiling point ranging from 398°C to 501°C (at 1,013 hPa), density ranging from 0.950g/cm^3 to 0.965 g/cm^3, vapour pressure ranging from 3.63E-10 hPa to 9.33E10-7 hPa at 25°C, water solubility values less than 0.0001 mg/l, and log P_{ow} values cited as greater than 6 and ranging up to 12.1.

Results of distribution modeling, using a Mackay Level I model, suggest that members of the HMWPE Category will partition primarily to the soil compartment (approximately 98%) with a small amount partitioning to sediment (approximately 2%). Volatilization to air from aqueous and terrestrial habitats will be negligible because category members have low vapor pressure (<9.33E-7 hPa at 25°C). However, the small fraction that may partition to air has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals with calculated degradation half-lives ranging from approximately 4 to 7 hours depending on hydroxyl radical concentration. Aqueous photolysis and hydrolysis will not contribute to the transformation of phthalate esters in aquatic environments because they are poorly or not susceptible to these reactions. Hydrolysis half-lives of >3 years are estimated for category members.

Members of the HMWPE Category have the potential to biodegrade from 12.8% to 75% biodegradation within 28 days, in ready biodegradability tests. Members of the category, as well as DIDP, have not been shown to be readily biodegradable. Although the two highest molecular weight members of this category, di-C13 PEs with CAS RN 119-06-2 and 68515-47-9, exhibited lower relative extents of biodegradability at 28 days when compared to the other category members, the extant database for these substances show that they can be biodegraded to levels similar to the other lower molecular weight members of this category over an extended test duration (56 days). Data for DINP show that it is readily biodegradable within 28 days. Additionally, studies show that HMWPEs do not inhibit microbial respiration in terrestrial and sewage systems. Category members are expected to sorb to organic matter in soil, sediment, and wastewater solids based on calculated log K_{oc} values that range between 4.5 and 7.7.

The acute and chronic aquatic toxicity of HMWPEs has been evaluated using numerous species. These data clearly show that category members do not exhibit acute and chronic aquatic toxicity at or below their maximum attainable water solubility. The solubility of these substances is equal to or less than 0.017 mg/L. As such, aqueous exposure to these substances will be very limited.

Concerning terrestrial environments, the compartment of primary interest as indicated by partitioning data, studies on members of the HMWPE Category are not available. However, they are not expected to exhibit toxicity based on results from earthworm studies for an analog substance, DIDP, which was applied at a concentration as high as 7,994 mg/kg soil, dry weight. The two lower molecular weight category members, di-C7-9 PE and di-C9-11 PE, may cause effects in plants at very high concentrations, greater than 8,000 mg/kg soil, dry weight, based on data for DINP, which contains constituents that can be found in the two category members. Results from sediment toxicity studies with two freshwater invertebrates that showed no effects at relatively high concentrations (up to 2,900 mg/kg sediment, dry weight) suggest that category members will not produce toxicity to sediment invertebrates. Although the phthalate esters tested, DINP, DIDP, and a di-C7-11 PE, do not belong to the HMWPE Category, select category member constituents have overlapping carbon number ranges and similar structures. Finally, it has been demonstrated that HMWPEs have a low potential to bioaccumulate in aquatic species, demonstrated by a food web study on DINP, and bioconcentration studies on DINP, DiC11-PE and di-C13 PE. Metabolic transformation is the most likely reason why these substances exhibit decreasing concentrations from lower to higher trophic levels.

Exposure

Estimated European production is approximately 60 to 100k tonnes per year (European Council for Plasticisers and Intermediates - personal communication). This is likely to represent a third of world production.

HMWPEs are used primarily as industrial chemicals associated with polymers, mainly as additives to impart flexibility in polyvinyl chloride (PVC) resins, but are also used as synthetic base stocks for lubricating oils. Polymer

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.

applications can be divided into PVC-related uses and uses involving other non-PVC polymers. PVC-containing phthalate ester applications can include wire and cable insulating, furniture and automobile upholstery, flooring, wall coverings, coil coatings, pool liners, roofing membranes, and coated fabrics. Polymer containing phthalate ester applications that are non-PVC based, include thermoplastics, rubbers and selected paints and adhesives. Members of the HMWPE Category are not used for PVC-medical or toy applications. Due to their high viscosity, slow fusion and high costs, members of the HMWPE Category are not preferred for the manufacture of toys.

Essentially all HMWPEs released from their manufacture, which can occur when cleaning manufacturing systems, enter wastewater treatment facilities where they can be biodegraded or sorbed to sewage sludge.

The majority of HMWPEs found in the environment likely come from the slow release of these chemicals from phthalate ester-containing polymer products as a result of weathering processes. Once phthalates are produced and used in various products, emissions can occur during the end-use of these products. Unlike industrial point sources, emissions during product end-use represent a diffuse emission source. In both polymer uses the phthalate ester serves as a plasticiser that enhances the flexibility of the product as a result of the positioning of the phthalate ester molecules between the polymer chains. However, since the phthalate ester molecules are not covalently bound to the polymer matrix, user or consumer exposure, or migration and subsequent release to the environment may occur. Since most HMWPEs are sandwiched within a polymer matrix, emissions are retarded during the life of the polymer product.

Exposure to HMWPEs may occur at workplaces where they are manufactured. Based on physical properties, the primary workplace exposure in production activities would be dermal and there may be a potential for formation of aerosols during some applications. However, HMWPEs are handled only in industrial manufacturing facilities and the majority of the applications involve incorporation of the phthalate ester into a matrix. Therefore, minimal consumer exposure is foreseen, since the consumer is only indirectly exposed through the use of products, which may contain HMWPEs and uptake is expected to be low.

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 because of their low hazard profile.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2807-30-9, 111-76-2(surrogate only), 112-07-2, 112-25-4
Chemical Name	Monoethylene glycol ethers category (Mono EGEs)
Structural Formula	$HOCH_2\ CH_2OCH_2CH_2CH_3$ Ethylene glycol propyl ether (EGPE, CAS No. 2807-30-9), $HOCH_2\ CH_2O\ CH_2\ CH_2CH_2\ CH_3$ Ethylene glycol butyl ether (EGBE, CAS No. 111-76-2), $CH_3C(=O)OCH_2\ CH_2O\ CH_2CH_2CH_2CH_3$ Ethylene glycol butyl ether acetate (EGBEA, CAS No. 112-07-2), $HOCH_2\ CH_2OCH_2CH_2\ CH_2CH_2\ CH_2CH_3$ Ethylene glycol hexyl ether (EGHE, CAS No. 112-25-4)

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The four substances of this category all have similar molecular structures, functionality and metabolic pathways. The category members demonstrate similar physicochemical properties and mammalian toxicity. EGBE is included in the category only to fill data gaps for mammalian toxicity. A separate dossier on EGBE is not included as this chemical's data set was previously agreed to at SIAM 6. The reader should refer to the existing SIDS dossier for additional information on EGBE. The acetylated glycol ether, EGBEA, although rapidly metabolized *in vivo* to its corresponding glycol ether, is not expected to hydrolyze rapidly to EGBE in the aqueous environment. Therefore, EGBEA aquatic toxicity data are not extrapolated to the other category members.

Toxicokinetics

EGPE, EGBE and EGHE are substrates for alcohol dehydrogenase isozyme ADH-3, which catalyzes the conversion of their terminal alcohols to aldehydes (which are transient metabolites). Further, rapid conversion of the aldehydes by aldehyde dehydrogenase produces alkoxyacetic acids, which are the predominant urinary metabolites of mono substituted glycol ethers; for example, 2-propoxy acetic acid (PAA) is a metabolite of EGPE and butoxy acetic acid (BAA) is a metabolite of EGBE. At equivalent concentrations, metabolism of EGPE is less rapid than EGBE and more rapid than EGHE.

Human Health

Oral LD_{50} values in rats for all category members range from 739 (EGHE) to 3089 mg/kg bw (EGPE), with values increasing with decreasing molecular weight. Four to six hour acute inhalation toxicity studies were conducted for these chemicals in rats at the highest vapour concentrations practically achievable. Values range from $LC_0 > 85$ ppm (508 mg/m^3) for EGHE, $LC_{50} > 400$ppm (2620 mg/m^3) for EGBEA to $LC_{50} > 2132$ ppm (9061 mg/m^3) for EGPE. No lethality was observed for any of these materials under these conditions.Dermal LD_{50} values in rabbits range from 435 mg/kg bw (EGBE) to 1500 mg/kg bw (EGBEA). Overall these category members can be considered to be of low to

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.

moderate acute toxicity. All category members cause reversible irritation to skin and eyes, with EGBEA less irritating and EGHE more irritating than the other category members. EGPE and EGBE are not sensitizers in experimental animals or humans.

Signs of acute toxicity in rats, mice and rabbits are consistent with hemolysis (with the exception of EGHE) and non-specific CNS depression typical of organic solvents in general. Alkoxyacetic acid metabolites, PAA and BAA, are responsible for the red blood cell hemolysis. Signs of toxicity in humans deliberately ingesting cleaning fluids containing 9-22% EGBE are similar to those of rats, with the exception of hemolysis. Although decreased blood hemoglobin and/or hemoglobinuria were observed in some of the human cases, it is not clear if this was due to hemolysis or hemodilution as a result of administration of large volumes of fluid. Red blood cells of humans are many-fold more resistant to toxicity from EGPE and EGBE *in vitro* than those of rats. Accepted PBPK models are available for rats and humans which predict the distribution and metabolism of EGBE. These demonstrate that even at saturated vapor concentrations of EGBE, it is not possible to reach haemolytic blood concentrations of BAA in humans by the inhalation route of exposure.

Evaluation of hemolysis and its associated effects in the liver, spleen, and kidney of rodents and rabbits was done by repeatedly exposing rats via inhalation to 100, 200, or 400 ppm EGPE (425, 850, or 1700 mg/m^3) 6h/day, 5d/week for 14 weeks or to EGBE (rats and mice) at 31, 62.5, 125, 250, 500 ppm (150, 302, 603, 1207 or 2415 mg/m^3) and to EGHE (rats) at 20, 41 or 71 ppm (120, 245 or 425 mg/m^3). The NOAEL for EGPE in rats was 100 ppm and those for EGBE were less than 31 ppm (150 mg/m^3) in rats and 62.5 ppm (302 mg/m^3) in mice, respectively. For EGHE the NOAEL was 41 ppm (245 mg/m^3). Orally administered EGPE to rats at gavage doses of 195, 390, 780, or 1560 mg/kg bw/day for 6 weeks, generated a NOAEL of 195 mg/kg bw/day. Hemolysis and histopathological changes in the liver and kidney were not seen in rats exposed for 14 weeks with up to 71 ppm (425 mg/m^3) EGHE by inhalation, suggesting that this material is not as potent a hemolytic agent as EGBE. In the case of EGBE and EGPE, the hemolytically active agents have been shown to be the acid metabolites, BAA and PAA, respectively.

The fact that the NOAEL for repeated dose toxicity of EGBE is less than that of EGPE is consistent with red blood cells being more sensitive to EGBE than EGPE. Blood from mice, rats, hamsters, rabbits and baboons were sensitive to the effects of BAA *in vitro* and displayed similar responses, which included erythrocyte swelling (increased hematocrit and mean corpuscular hemoglobin), followed by hemolysis. Blood from humans, pigs, dogs, cats, and guinea pigs was less sensitive to hemolysis by BAA *in vitro*.

In the absence and presence of metabolic activation, EGBE tested negative for mutagenicity in Ames tests conducted in *S. typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 and EGHE tested negative in strains TA98, TA100, TA1535, TA1537 and TA1538. *In vitro* cytogenicity and sister chromatid exchange assays with EGBE and EGHE in Chinese Hamster Ovary Cells with and without metabolic activation and in vivo micronucleus tests with EGBE in rats and mice were negative, indicating that these glycol ethers are not genotoxic.

The US National Toxicology Program (NTP) conducted a 2-year inhalation chronic toxicity and carcinogenicity study with EGBE in rats and mice. A significant increase in the incidence of liver hemangiosarcomas was seen in male mice and forestomach tumours in female mice. The data were evaluated by IARC in June 2004 and EGBE was classified as IARC Group 3 (inadequate evidence of carcinogenicity in humans and limited evidence of carcinogenicity in animals). In 2000, the EU classification of EGBE was reviewed under the European Commission process for the classification and labeling of dangerous substances. It was decided that based on the mode of action data available, there was no significant hazard for human carcinogenicity and there was no support for a category 3 (carcinogen) classification. This decision was reconfirmed in 2004.

The results of reproductive and developmental toxicity studies indicate that the glycol ethers in this category are not selectively toxic to the reproductive system or developing fetus, developmental toxicity is secondary to maternal toxicity. Results of the 2-generation, continuous breeding study in CD1-mice exposed by drinking water to 700, 1,300, or 2,100 mg/kg bw/day EGBE show that parental toxicity was observed at all doses tested (significantly reduced liver and kidney weights at the lowest dose, severe toxicity, including death at the mid and higher doses) and fertility was affected at the two highest doses. Although there was no effect of 700 mg/kg bw/day on fertility, live pup weights from animals in this group were slightly but statistically significantly reduced. The parental and offspring

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.

LOAELs were 700 mg/kg bw/day but the NOAEL can be considered close to this value. The repeated dose toxicity studies in which reproductive organs were examined indicate that the members of this category are not associated with toxicity to reproductive organs (including the testes).

Results of the developmental toxicity studies conducted via inhalation exposures during gestation periods on category members EGPE (rabbits -125, 250, 500 ppm or 531, 1062, or 2125 mg/m^3 and rats - 100, 200, 300, 400 ppm or 425, 850, 1275, or 1700 mg/m^3), EGBE (rat and rabbit - 25, 50, 100, 200 ppm or 121, 241, 483, or 966 mg/m^3), and EGHE (rat and rabbit - 20.8, 41.4, 79.2 ppm or 124, 248, or 474 mg/m^3) indicate that the members of the category are not teratogenic.

Inhalation of a maternally toxic concentration of EGBE [100 ppm (or 483 mg/m^3) in the rat and 200 ppm (or 966 mg/m^3) in the rabbit] throughout gestation was associated with embryotoxicity, as evidenced by an increased number of resorptions, and a decreased number of implantations. An increase in the number of fetuses with skeletal variations was noted in offspring of rats exposed to maternally toxic concentrations of EGPE by inhalation (≥ 200 ppm or 966 mg/m^3). In rats exposed to EGHE and rabbits exposed to EGHE or EGPE by inhalation, no effects on the fetus were noted (even at concentrations that produced maternal toxicity).

The NOAELs for developmental toxicity are greater than 500 ppm or 2125 mg/m^3 (rabbit-EGPE), 100 ppm or 425 mg/m^3 (rat-EGPE), 50 ppm or 241 mg/m^3 (rat EGBE) and 100 ppm or 483 mg/m^3 (rabbit EGBE) and greater than 79.2 ppm or 474 mg/m^3 (rat and rabbit-EGHE). Based on the structural similarities between the members, developmental toxicity data for the tested glycol ethers are expected to be predictive of data for EGBEA.

Environment

Members of the category are high boiling liquids (boiling points in the 150-208ºC range), with low melting points (-70 to -50°C). Vapor pressures are in the range of 0.067-1.3 hPa at room temperature. Water solubility values range from soluble (EGHE 9.9 g/L, EGBEA 15 g/L) to miscible (EGPE and EGBE). Octanol-water partition coefficients range from 0.79 to 1.97. Henry's Law Constants range from 7.38×10^{-8} to 6.38×10^{-6} atm-m^3/mole. Hydroxyl radical induced photodegradation half-lives range from 4.9 – 6.0 hours.

EGPE and EGHE, like other simple glycol ethers, possess no functional groups in their molecular structures that are readily subject to hydrolysis in the presence of water. EGBEA, however, possesses an ester group that is estimated to have a half-life of about 30 days in neutral ambient water under abiotic conditions. Level III fugacity modeling indicates that category members, when released to air and water, will partition predominately to water and, to a lesser extent, to air and soil. Estimates of soil and sediment partition coefficients (Kocs ranging from 1 – 10) suggest that category members would exhibit high soil mobility. Estimated bioconcentration factors (log BCF) range from 0.463 to 0.732. Biodegradation studies indicate that all category members are readily biodegradable. The physical chemistry and environmental fate properties indicate that category members will not persist or bioconcentrate in the environment.

The aquatic toxicity data for ethylene glycol ether acetate (EGBEA) and the glycol ethers (EGPE, EGBE and EGHE) are considered separately because glycol ether acetates do not hydrolyze rapidly into their corresponding glycol ethers in water under environmental conditions. The LC_{50} or EC_{50} values for EGHE (which has the longest chain length and highest log Kow value) are lower than those for EGPE and EGBE (which have shorter chain lengths and lower log Kow values). Overall, the LC_{50} values for the glycol ethers in aquatic species range from 94 to > 5000 mg/L. For EGHE, the 96-hour LC_{50} for *Brachydanio rerio* (zebra fish) is between 94 and215 mg/L, the 48-hour EC_{50} for *Daphnia magna* was 145 mg/L and the 72-hour EC_{50} values for biomass and growth rate of algae (*Scenedesmus subspicatus*) were 98 and 198 mg/L, respectively. LC_{50}/EC_{50} values for EGPE and EGBE in aquatic species are 835 mg/l or greater.

Aquatic toxicity data for EGBEA show a 96-hour LC_{50} of 28.3 mg/L for rainbow trout (*Oncorhynchus mykiss),* a 48-hour LC_{50} of 37-143 mg/L for *Daphnia magna,* a 72-hour EC_{50} of greater than 500 mg/L for biomass or growth rate of algae (*Scenedesmus subspicatus* and *Pseudokirchneriella subcapitata,* respectively), and a 7-day EC_{10} of 30.4

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.

mg/L and a NOEC of 16.4 mg/L for reproduction in *Ceriodaphnia dubia* .

Exposure

Annual U.S. production volumes for EGPE and EGBEA are each in the range of 4,540 – 22,700 metric tons. The production volume for EGHE is 450 – 4,500 metric tons. The use patterns for these materials are similar, with qualitative differences. All are used predominately as solvents or coalescing aids for surface coatings, printing inks, metal cleaners, detergents, fire foams, oil field chemicals, pharmaceutical manufacture, agricultural chemicals, leather manufacture and finishing cleaners and adhesives. They are also used as chemical intermediates and in hair dyes. Most applications are industrial, but these materials may also be present at the 1-10% range in some consumer products.

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 use, solvent application conditions may vary widely, and atmospheric releases are expected through solvent evaporation.

Consumers may be exposed through use of products containing category members and also from environmental concentrations. Because category members degrade readily in the environment, environmental exposure should not be a major concern. Exposure monitoring information is not readily available.

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

These chemicals are currently of low priority for further work.

Human Health: The substances in the category possess properties indicating a hazard for human health (reversible eye and skin irritation, reversible CNS depression). These hazards do not warrant further work. However, they should nevertheless be noted by chemical safety professionals and users. Hemolysis and associated organ toxicity are noted in rats, mice and rabbits exposed to EGPE and EGBE. Humans are many-fold less sensitive to these effects and associated organ toxicity. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: EGPE, EGBE, and EGHE are of low priority for further work because of their low hazard profile. EGBEA possesses properties indicating a hazard for the environment. These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure level and the substance is readily biodegradable. However, they should be noted by chemical safety professionals and users.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7631-86-9 (Silica)[1)] 112945-52-5 (Silica, amorphous, fumed, crystalline-free) 112926-00-8 (Silica gel and precipitated silica, crystalline-free) 1344-00-9 1344-95-2
Chemical Name	Silicon dioxide (7631-86-9, 112945-52-5, 112926-00-8) Silicic acid, aluminum sodium salt (1344-00-9) Silicic acid, calcium salt (1344-95-2)
Structural Formula	SiO_2 / SiO_4 tetrahedron (base unit of the structure of the macromolecular network)

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The similarity in the chemical structure, composition, production and processing as well as the similarity in physico-chemical properties and the available toxicological and health data, strongly suggest that the impact on the living organism and environment should not differ considerably between the category members: synthetic amorphous silica (SAS) [CAS No 7631-86-9] and synthetic amorphous silicates, Na-Al silicates (NAS) [CAS No 1344-00-9] and Ca silicates (CS) [CAS No 1344-95-2]. They all form fine powders of amorphous particles between 1 and 350 µm with high surface areas.

Human Health

Absorption, disposition, elimination: SAS forms [CAS No 7631-86-9] are rapidly eliminated from the lung tissue during and after prolonged inhalation exposure of experimental animals with no disproportionate disposition occurring in the mediastinal lymph nodes, whereas crystalline forms exhibit a marked tendency to accumulate and persist in the lung and lymph nodes. Intestinal absorption of SAS appears to be insignificant in animals and humans. There is evidence of ready renal elimination of bioavailable fractions.

Acute toxicity: Following inhalation exposure of rats to the highest technically feasible concentrations of 140 to ~2000 mg/m^3 SAS, no lethal effects were observed. Oral and dermal administration of SAS and amorphous silicates failed to cause mortality at the highest doses tested: LD_0 values ranged from 3300 to 20000 mg/kg in rats. No inhalation data are available for NAS [CAS No 1344-00-9] and CS [CAS No 1344-95-2] and no dermal data for CS. By analogy to SAS [CAS No 7631-86-9], and NAS, respectively, they are assumed to be void of significant acute hazards.

Irritation/Sensitisation: The tested silica/silicate materials [CAS No 7631-86-9; CAS No 1344-00-9] are not irritating to skin and eyes. It is assumed that these results also hold for SAS and CS for which corresponding studies

[1] Note: Silicon dioxide (CAS No. 7631-86-9) is the general CAS No. which includes all forms of silicas (e.g. also crystalline and natural forms) (see family tree SIAR). Only the silica sub-classes, the synthetic amorphous silicas, are subject of this evaluation.

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.

are not available. No experimental data is available on sensitisation. There is no evidence of skin sensitisation in workers over decades of practical experience.

Repeated dose toxicity: The *inhalation* of respirable particles of SAS produces a time- and dose-related inflammation response of the lung tissue in animal studies. Thirteen-weeks exposure to an average concentration of 1.3 mg/m^3 of a pyrogenic SAS resulted in mild reversible pro-inflammatory cell proliferation rather than a pathologically relevant tissue change. Given the low-grade severity of this common lung-tissue response, 1 mg/m^3 can be established as NOAEL and LOEL (sub-chronic, 13 weeks). The LOAEL was 5.9 mg/m^3, the mid concentration, which produced clear signs of histopathological adverse effects (stimulation of collagen production, increase in lung weight, incipient interstitial fibrosis, slight focal atrophy in the olfactory epithelium). All these effects were reversible following discontinuation of exposure. No lung-tissue effects were observed following exposure of 5 days to 1 mg/m^3 of the same silica [NOEL (short-term)]. The LOAEL (5 d) was 5 mg/m^3.

In the absence of experimental data for NAS and CS, an effects profile similar to that of SAS is supposed to also hold for amorphous silicates, based on the assumption that the particle size and morphology rather than particle composition is the determinant of inflammatory response in the lung. This implies that synthetic amorphous silicates would not provoke a more severe pulmonary response under same test conditions.

After long-term *oral application in the diet (2 years)*, no adverse effects were demonstrable for SAS and CS only occasional growth depression or slight elevation of organ weights at the highest doses [NOAEL(chronic, oral) = approx. 2500 mg/kg bw/d)]. Following feeding of 0.625 to 10 % NAS in the diet for 14 d, no substance-related clinical and histopathological findings at any dose level were observed in rats and mice.

Medical surveillance reports failed to reveal significant pathological lung effects attributable to occupational long-term exposure to SAS and/or synthetic amorphous silicates: in particular, no signs of pneumoconiosis, silicosis and fibrosis were evident.

Mutagenicity: There is no evidence that SAS or CS induce mutations either *in vitro* or *in vivo* in standard methods. There was also no evidence for a mutagenic activity in an ex-vivo HPRT gene-mutation assay on isolated alveolar type-II cells after long-term inhalation exposure of rats to a distinctly noxious/inflammatory SAS concentration of 50 mg/m^3 (13 weeks). Likewise, based on structure analogy, no genotoxic effects are expected to occur from exposure to NAS for which corresponding studies were not located.

Carcinogenicity: Negative findings in a rat carcinogenicity model after comparative intra-pleural treatment with various types of materials (including a NAS) and the absence of a mutagenic potential underline that the cancerogenic potential of synthetic amorphous silicas/silicates can be considered as negligible.

Based on the negative results after long-term oral administration of SAS (up to 5 % in the diet given to rats and mice) and CS (up to 10 % in the diet given to rats), there is no evidence of a carcinogenic potential arising from ingestion of these amorphous minerals. Likewise, based on structure analogy, no cancerogenic effects are expected to occur from exposure to NAS for which a corresponding study is not available.

Reproduction: An early limited one-generation study on rats gave no evidence of adverse effects on *reproduction performance* at 500 mg SAS/kg bw/d, the highest dose tested (NOAEL). But the reliability is poor due to the small group size of animals.

Numerous subchronic studies as well as a dominant lethal study with a CS failed to demonstrate any histopathological changes or deleterious effects in the reproductive organs of treated animals. Furthermore, given the inherent physico-chemical properties and ubiquitous nature of this class of compounds, there is no structural alert to indicate a potential for reproductive and developmental toxicity. Therefore, based on the weight of evidence, prolonged exposure to synthetic amorphous silica, applied before and during pregnancy at high doses, is not expected to produce harmful effects on the reproductive performance or embryonic/foetal development in experimental animals.

Based on structure analogy, no impairment of fertility/reproductive performance is expected to occur likewise from exposure to NAS and CS, for which corresponding studies are not available.

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.

The experimental data on *intra-uterine development* gained in four animal species (rat, mouse, hamster and rabbit) across all three types of synthetic amorphous silica and silicates allow the conclusion that there is no potential for adverse effects on embryonal/foetal development arising from oral exposure to these silica/silicates. The NOEL for maternal and developmental toxicity is the highest tested dose of 1600 mg/kg bw/d.

Environment

SAS, NAS and CS are solids in powder form which have a low water solubility, based on the sum of soluble SiO_2 and cations (water-soluble fraction): ≤70 mg/l (SAS), approx. 70 – 80 mg/l (NAS), and approx. 260 mg/l (CS) at 20 °C. They are not volatile and have no lipophilic character. These compounds will be distributed mainly into soils/sediments and weakly into water and are expected to combine indistinguishably with the soil layer or sediment due to their chemical similarity with inorganic soil matter. The bioavailable forms of silica are dissolved silica [$Si(OH)_4$] almost all of which is of natural origin. The ocean contains a huge sink of silica and silicates where a variety of the marine habitat (diatoms, radiolarians, and sponges) is able to exploit this resource as a construction material to build up their skeletons. Based on the chemical nature of silica and silicates (inorganic structure and chemical stability of the compound: Si-O bond is highly stable), no photo- or chemical degradation is expected. Biodegradation is not applicable to these inorganic substances.

Studies on fish, Daphnia and algae using excess loadings of SAS or NAS showed no acute toxicity, although physical effects on Daphnia were observed in tests using unfiltered test medium. Test results, based on loading rates, are as follows: 96h LL_0 *(Brachydanio rerio)* = 10000 mg/l for SAS and NAS; 24h EL_{50} (*Daphnia magna)* >10000 mg/l for SAS; 72h NOEL (*Scenedesmus subspicatus)* = 10000 mg/l for NAS. Since SAS, NAS and CS have similar chemical structures and physico-chemical properties, the conclusion of low acute aquatic toxicity applies to the whole category.

There are no chronic aquatic toxicity data, but due to the known inherent physico-chemical properties, absence of acute toxic effects as well as the ubiquitous presence of silica/silicates in the environment, there is no evidence of harmful long-term effects arising from exposure to synthetic amorphous silica/silicates.

Tests have been conducted on the German cockroach and Grain weevil which demonstrate a lethal effect on these animals due to sorption of the lipid cuticle followed by dehydration. However, the validity of these studies could not be confirmed.

Exposure

The worldwide production in 1992 was estimated at around 100,000 metric tons *(pyrogenic SAS)*, about 800,000 metric tons *(precipitated SAS)*, about 115,000 metric tons *(silica gels and sols).* The European consumption in 2000 (including imports and excluding exports) was approx. 408,500 metric tons with 368,000 metric tons for SAS and 40,450 metric tons for silicate, respectively; in 2002 the overall consumption amount to about 481,050 metric tons.

SAS, NAS and CS are used in a wide variety of applications, including consumer products. They are used to thicken pastes and ointments, to maintain flow properties in powder products and as a carrier for fragrances or flavours and are present in cosmetics (especially toothpaste), pharmaceuticals and food. They are also used in animal feed, rubber and silicones (as fillers), paints (as pigments), lacquers (as flattening agents) and plastics (to prevent plastic films from sticking together and for thixotropy control). SAS is registered as a biocide in the EU and has been successfully employed against juvenile and adult store-product pests, predominantly exerting lethal activity on juvenile and adult forms by sorption of the cuticular lipid layer, thus causing dehydration of the insects.

Potential *occupational sources* of inhalation exposure to SAS dusts are the manufacture itself and various down-stream applications producing product that contain synthetic amorphous silica and silicates as auxiliary agents (production of rubber/silicons, paints/laquers, plastics, papers, cosmetics and pharmaceuticals, as well as animal feed and beverages). In a recent monitoring program in five silica production plants, the highest mean values were

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.

observed for job categories involved with packaging and loading operations (up to 3 mg/m³ inhalable and up to 1 mg/m³ respirable dust).

The *general population* that may come into contact with finished, silica-containing articles is unlikely to be exposed to dusty silica/silicates, as the silica compounds are bound into the matrix of the article and not freely available.

Synthetic amorphous silica and silicates possess properties indicating a hazard for human health following inhalation. These hazardous effects appear to resemble those pulmonary tissue reactions known from exposure to respirable dust. Under practical occupational conditions, these materials tend to form agglomerated particle sizes which will not reach the peripheral area of the lung. This implies that the toxicologically relevant, respirable fraction will be much lower at the workplace than under experimental conditions where the powders are actively atomized shortly before exposure. The concentration of the toxicologically relevant particle fraction at the workplace is estimated to be at least 50 times lower than commonly applied in animal inhalation studies. This would allow estimating a higher workplace-relevant No-Effect-Level for total dust than found in animal studies.

With this in mind and due to the high standard of current control measures that are in place to minimise exposure (automatic and closed packaging operation equipped with local exhaust ventilation, standard protective working clothes, routine observance of occupational exposure level), it is assumed that occupational exposure to synthetic amorphous silica and silicates is low.

Emission to the environment may occur during production and use of SAS, NAS and CS although the potential amount of anthropogenic SAS released into the aquatic environment is estimated to represent only a small fraction of the dissolved silica naturally present in rivers.

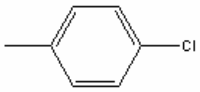
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals in this category are currently of low priority for further work. They possess properties indicating a hazard for human health (repeated inhalation toxicity). Based on data presented by the Sponsor country, relating to 5 production plants in one country, which account for an unknown percentage of global production and relating to the use pattern in several OECD countries, the exposure to humans to respirable dust 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 chemicals in this category are currently of low priority for further work due to their low hazard potential.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-43-4
Chemical Name	p-Chlorotoluene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Since there is no developmental toxicity study with p-chlorotoluene, the data from o-chlorotoluene are taken into account to fill the data gap. The comparison of the two isomers showed a rather high degree of qualitative similarity with respect to available data on absorption, excretion and metabolism, toxicity after acute and repeated exposure, Overall o-chlorotoluene and p-chlorotoluene have a similar toxicity profile. o-Chlorotoluene (CAS No 95-49-8) was already discussed and concluded at SIAM 11, 2001; and the initial assessment was published by UNEP in 2004.

Specific toxicokinetic studies with p-chlorotoluene are not available. The available information indicates that absorption of p-chlorotoluene is rapid via gastrointestinal tract or respiratory tract but is limited via dermal contact. Excretion occurs mainly via urine as p-chlorobenzoic acid derivatives by rabbits or as the corresponding hippuric acid by dogs. Exact data on tissue distribution are not available. Thus, p-chlorotoluene as well as o-chlorotoluene are absorbed via the gastrointestinal tract, the lungs and to a lesser extent via skin. For both isomers excretion takes place principally via urine, and in small amounts with faeces and exhaled air. In the metabolism o- and p-chlorotoluene are oxidized at the methyl group leading to chlorobenzyl alcohol glucuronide, chlorobenzoic acid and mercapturic acid.

The LC_{50} of p-chlorotoluene was not determined but an Inhalation Hazard test showed that exposure of rats against 4183 ppm (approximately 22 mg/m³) for 4 hours was not lethal, but signs of intoxication were observed. Exposure for 8 hours resulted in the death of all exposed rats within the 14-day observation period. The dermal LD_{50} (rabbit) is > 2000 mg/kg bw and LD_{50} (rat) is > 5000 mg/kg bw. Following oral application to rats the LD_{50} values ranged between 2100 mg/kg bw and 2389 mg/kg bw. The predominant symptoms were body tremor, accelerated breathing rate, cyanosis, decreased motor activity and palmospasms. With regard to o-chlorotoluene the acute oral toxicity is LD_{50} (rat, male): 3227 mg/kg bw; the acute inhalation toxicity is LC_{50} (rat): 37,517 mg/m³ (4 hrs) and the acute dermal toxicity LD_{50} (rat) is > 1083 mg/kg bw and LD_{50} (rabbit): > 2165 mg/kg bw. Based on the available data of o- and p-chlorotoluene it can be concluded that the acute toxicity of monochlorotoluene in general is low.

p-Chlorotoluene is slightly irritating to the skin when 0.5 ml undiluted substance is applied to intact and abraded skin of rabbits under occlusive conditions for 24 hours. p-Chlorotoluene is slightly irritating to eyes of rabbits when 0.1 ml undiluted substance was applied into the conjunctival sac. o-Chlorotoluene, tested according to OECD TG 404, is slightly irritating to the skin. However, when tested under occlusive conditions, the substance is corrosive. o-Chlorotoluene, tested according to OECD TG 405, was irritating to the eye in 1 out of 3 animals. Based on the available data it can be concluded that monochlorotoluene in general is slightly irritating the skin and eyes of rabbits. However, o-chlorotoluene seems to be a stronger skin irritant under occlusive conditions.

p-Chlorotoluene is a skin sensitizer when tested in the guinea pig maximization test according to OECD TG 406. o-Chlorotoluene, tested according to OECD TG 406, is not sensitizing to the skin of guinea pigs. However the higher

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.

sensitizing potential for para-substituted substances is a known effect.

Repeated dose toxicity of p-chlorotoluene was examined in sub-acute (29 days) and sub-chronic (90 days) gavage studies with rats using dosages of 50, 200 and 800 mg/kg bw/day. The liver and the kidney are the main target organs. Based on liver impairment in the sub-acute as well as in the sub-chronic study, which also revealed an increase in chronic progressive nephropathy at the highest dose level of 800 mg/kg bw/day, the NOAEL for both studies was determined to be 200 mg/kg bw/day.

With respect to o-chlorotoluene the NOEL for repeated dosing (3 months) by gavage in rats is 20 mg/kg bw/day. In higher dosages (80 or 320 mg/kg bw/day) unspecific signs of toxicity were observed, e.g. reduced body weight gain in male animals as well as elevated BUN, elevated WBC count, reduced prothrombine time in both sexes.

The NOEL for repeated dosing via capsule (3 months) in dogs is 20 mg/kg bw/day. In higher dosage (80 mg/kg bw/day) one animal showed vomiting, and red blood was detected in faeces which might be due to the slightly irritating property of o-chlorotoluene.

In range finding study tests, the LOAECs after inhalation were 4 mg/l (4000 mg/m³, 14 d) in rats and 8 mg/l (8000 mg/m³, 23 d) in rabbits. There is no NOEC from these data.

Based on the test conditions in the repeated dose toxicity studies which were taken into account for comparison, o-chlorotoluene is at least as toxic as p-chlorotoluene after repeated dosing.

p-Chlorotoluene was not mutagenic in the *Salmonella typhimurium* TA97, TA98, TA100, TA1535, TA1537, TA102, and TA104 and in *Escherichia coli* WP2uvrA, *Escherichia coli* WP2uvrA/pKM101 with and without a metabolic activation system nor did it induce micronuclei in mice after a single intraperitoneal injection in a study according to OECD TG 474. o-Chlorotoluene showed no mutagenic activity in bacterial and in mammalian cell test systems *in vitro*. o-Chlorotoluene showed no clastogenic activity (chromosome aberration) *in vitro* and *in vivo*. Based on the available data on o- and p-chlorotoluene it can be concluded that both monochlorotoluenes do not reveal mutagenic activity, neither *in vitro* nor *in vivo*.

There are no studies on the possible carcinogenicity available.

There are no specific studies on reproductive toxicity. However, in the repeated dose-toxicity studies which were taken into account for comparison, o-chlorotoluene is at least as toxic as p-chlorotoluene. Furthermore, in the metabolism o- and p-chlorotoluene are oxidized at the methyl group leading to chlorobenzyl alcohol glucuronide, chlorobenzoic acid and mercapturic acid. Thus, the use of o-chlorotoluene to fill data gaps is justified.

There are no specific studies on reproductive toxicity (fertility assessment) available with p-chlorotoluene or with o-chlorotoluene. Evaluation of the reproductive organs in the available repeated dose toxicity studies with p-chlorotoluene or with o-chlorotoluene give no indication of possible impairment of these organs.

With regard to developmental toxicity conclusion should be drawn from developmental toxicity studies in rats and rabbits with o-chlorotoluene as there is no specific study with p-chlorotoluene available. Developmental toxic effects in rats and rabbits occur mostly in the presence of maternal toxicity and without a clear dose-response relationship, however, as a specific malformation, brachydactyly. Thus, for o-chlorotoluene, the NOAEL (rat) is 1.1 mg/l (1100 mg/m³, maternal toxicity), but no NOAEL for developmental toxicity could be derived, the LOAEL (developmental toxicity, rat) is 1.1 mg/l (1100 mg/m³) In rabbits, the NOAEL (maternal toxicity) is 1.5 mg/l (1500 mg/m³) and the NOAEL (developmental toxicity) is 4 mg/l (4000 mg/m³).

The results of the developmental studies with o-chlorotoluene (brachydactyly mostly in maternal toxic doses and without clear dose-response relationship: 1 rabbit fetus at the highest dose; 1 rat fetus at the lowest dose and 6 rat fetuses at the highest dose) lead to the assumption that monochlorotoluene in general might cause malformations in offspring by high dose treatment (i.e. at 1.1 mg/l = lowest dose tested, and 9.0 mg/l).

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

p-Chlorotoluene is a clear colorless liquid with a melting point of 7.5 °C, and a boiling point of 162 °C. The density of the liquid is 1.0697 g/cm^3. The vapor pressure is in the range of 310 to 379 Pa at 20 /25 °C. The measured log K_{OW} is 3.33. The solubility in water is 40 mg/l at 20 °C. The flash point is 51.9 °C, the auto-ignition temperature 595 °C.

With regard to the chemical structure, p-chlorotoluene is not expected to hydrolyze under environmental conditions. According to the Mackay fugacity model level I calculation, the favourite target compartment of p-chlorotoluene is air with 99.67 %, followed by water with 0.25 %. A Henry's law constant of 446.8 Pa x m³/mol at 25 °C calculated according to the Bond method indicates that the compound has a high potential for volatilization from surface waters. The calculated half-life of p-chlorotoluene in air due to indirect photodegradation is $t_{1/2}$ = 8.8 days. Due to the low absorption in the UV-B range, no direct photodegradation is expected.

p-Chlorotoluene is not readily biodegradable, but can be eliminated in industrial wastewater treatment plants. In a modified Zahn-Wellens-test, comparable to the OECD TG 302 B, elimination of p-chlorotoluene of 86 % after 28 days occurred, 68 % of which occurred in the first three hours and is attributed to physical-chemical effects (adsorption, stripping). A manometric respirometry test (in accordance with OECD TG 301 F) was performed with a concentration of p-chlorotoluene of 100 mg/l. After 28 days 1 % of the test substance had been degraded. Aerobic ready tests were performed according to the national Japanese MITI test, comparable to the OECD TG 301 C. After a period of 14 days, the %-age biodegradation from the oxygen consumption was zero or did not exceed 30 % after 2 weeks from the beginning of the test, respectively. At a concentration of 200 mg/l p-chlorotoluene was metabolized in 3 days by a blend of microorganisms able to degrade a range of halogen substituted aromatic compounds.

The bioconcentration factor BCF = 73.13 for p-chlorotoluene, calculated from the octanol-water partition coefficient, indicates a moderate potential for bioaccumulation of p-chlorotoluene in fish. The available experimental data concerning bioaccumulation of p-chlorotoluene in *Cyprinus carpio*, confirm potential for bioaccumulation in fish. The BCF values obtained for concentrations of 0.3 and 0.03 mg/l were in the range of 14 - 101.6 and 21.9 - 76.5, respectively.

Experimentally obtained adsorption coefficients (K_{OC}) revealed a mid sorption potential of p-chlorotoluene. The experimentally achieved K_{oc} values following the OECD TG 106 were in the range of 327 to 512 depending on soil properties. In addition, a K_{OC} value of 434 was calculated with PCKOCWIN v. 1.66 .

Concerning the toxicity of p-chlorotoluene to aquatic species reliable acute and chronic 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 chronic toxicity test are (n = nominal concentration; m = measured concentration; m* = geometric mean of analytical values ; s = static test type; ss = semistatic test type):

Danio rerio:	28 d-$NOEC_{growth}$	= 1.9 mg/l (m, ss)
Poecilia reticulata:	14 d-LC_{50}	= 5.92 mg/l (n, ss)
Oryzias latipes :	48 h-LC_{50}	= 5.2 mg/l (n, s or ss)
Daphnia magna:	16 d-$NOEC_{reproduction}$	= 0.32 mg/l (n, ss)
Ceriodaphnia dubia:	48 h-EC_{50}	= 1.7 mg/l (n, s)
Desmodesmus subspicatus:	72 h-$EC_{50growth\ rate}$	= > 0.96 mg/l (m*, s)
Desmodesmus subspicatus:	72 h-$NOEC_{growth\ rate}$	= 0.43 mg/l (m*, s)
Desmodesmus subspicatus:	72 h-$EC_{50biomass}$	= > 0.96 mg/l (m*, s)
Desmodesmus subspicatus:	72 h-$NOEC_{biomass}$	= > 0.96 mg/l (m*, s)

Based on the lowest effect concentration observed for *Daphnia* in a semistatic test the Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 10. Using the effective 16 d-$NOEC_{reproduction}$ of 0.32 mg/l found for the invertebrate *Daphnia magna* a $PNEC_{aqua}$ = 32 µg/l was determined.

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.

Exposure

p-Chlorotoluene is produced by catalytic conversion of toluene with chlorine under moderate temperature and normal pressure. The composition of the crude product, a chlorotoluenes isomers mixture, depends on temperature and the catalyst. The chlorotoluene isomers are separated by fractional distillation.

For 2002, the global monochlorotoluenes output by about a dozen producers is estimated to be approximately 75 000 tonnes (including unseparated isomers). The global p-chlorotoluene production volume in 2002 (tonnes/a) is estimated by region as follows: Western Europe 13 500, Ukraine 1000, Japan 4500, and China 5000 (total 24 000). In the Sponsor country there is one company with a manufacturing volume of 10 000 to 50 000 tonnes/a. Three quarters of the global manufacturing volume stems from OECD member countries.

Pure p-chlorotoluene is solely used as an industrial intermediate for the synthesis of organic chemicals. The main derivatives are intermediates, e.g. in the production of pesticides, pharmaceuticals, and pigments, like 4-chlorobenzotrichloride (ca. 45 %), 4-chlorobenzyl chloride (ca. 21 %), 4-chlorobenzaldehyde (ca. 18 %), 2,4-dichlorotoluene (ca. 6 %), 4-chlorobenzonitrile (ca. 8 %), and 4-chlorobenzoic (ca. 2 %).

Chlorotoluene isomer mixtures, especially those containing a relatively high amount of o-chlorotoluene, are used as solvents in industry. In the USA p-chlorotoluene is listed as "other" (inert) ingredient in pesticide formulations, however, production of chlorotoluene was ceased in 2001. In the Sponsor country, p-chlorotoluene is not used in any pesticide formulation.

For the Sponsor country, use as a solvent is not known. Also, no direct consumer use is known for p-chlorotoluene in the Sponsor country. No products containing p-chlorotoluene are listed in the Danish, Finnish, Norwegian, Swedish, and Swiss Product Registers.

From the manufacturing site of the Sponsor company virtually no p-chlorotoluene (< 25 kg) was emitted into the environment in 2003. In the Sponsor country for occupational settings no workplace limit concentration is laid down. Workplace air sampling shows that the exposure is below 1 mg/m³ at the Sponsor company. Except from the Sponsor company, no exposure data is available.

p-Chlorotoluene was detected in construction and demolition waste in waste recycling facilities in Florida. p-Chlorotoluene occurs in volcanic gases and is formed in the atmosphere. In most recent studies on its occurrence in the environment, p-chlorotoluene was not detectable in environmental media.

p-Chlorotoluene is exclusively used as an intermediate in chemical processes. No consumer use is known for p-chlorotoluene. In products made from p-chlorotoluene by the Sponsor company, no p-chlorotoluene could be detected. Exposure of consumers to p-chlorotoluene via the environment is low.

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.

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

Human Health: The chemical possesses properties indicating a hazard (skin sensitization, indications for reproductive toxicity) to human health. Based on 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 low. 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.

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 approx. 44 - 56 % of global production and relating to the use in several OECD countries), exposure 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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-21-4
Chemical Name	Isopropyl Acetate
Structural Formula	CH_3-C(=O)-O-CH(CH_3)-CH_3

SUMMARY CONCLUSIONS OF THE SIAR

Analogue justification

Based on rapid and complete conversion of isopropyl acetate to isopropyl alcohol in vivo, isopropyl alcohol toxicity data have been used to support the health effects of isopropyl acetate. Exposure to isopropyl acetate via dermal, inhalation, and oral routes is expected to result in the rapid appearance of isopropyl alcohol in the systemic circulation. Therefore, systemic toxicity of isopropyl alcohol is relevant in identifying hazards associated with isopropyl acetate exposure. The toxicokinetics of the hydrolysis reaction is documented and explained below. In addition, based on their structural similarities to isopropyl acetate, analog data for propyl acetate and n-butyl acetate, a chemical whose toxicity was evaluated at SIAM 13, have been used for ecotoxicity endpoints.

Human Health

Respiratory bioavailability studies showed that inhalation of 2000 ppm isopropyl acetate in a closed chamber resulted in isopropyl acetate whole blood levels up to 54 μM and isopropyl alcohol levels up to 268 μM. Within 5 minutes into exposure, isopropyl alcohol whole blood levels exceeded that of isopropyl acetate. Isopropyl alcohol levels were between 2 and 10-fold higher than isopropyl acetate levels throughout the 90-minutes exposure period. Therefore, toxicity studies conducted with direct isopropyl alcohol administration are relevant to identifying hazards associated with isopropyl acetate exposures.

Isopropyl acetate has low acute toxicity by all routes. The oral LD50 in female rats is 12,500 mg/kg bw and in rabbits was 6,945 mg/kg bw. Dermal LD50 in male rabbits was >17,436 mg/kg bw. Inhalation LC_{50} values for vapor exposures were 12,114 ppm (50.6 mg/L) in female rats (8 hours of exposure). Isopropyl acetate is a slight skin irritant and a severe eye irritant. Data for skin sensitisation are not available.

Repeated inhalation exposures for 13-weeks to 500 to 5000 ppm (1.23 to 12.23 mg/L) concentrations of isopropyl alcohol caused depressed central nervous system function (e.g. narcosis, hypoactivity, ataxia, loss of startle reflex) in rats and mice. Exposure of female rats to 5000 ppm (12.25 mg/L) also increased motor activity during nine and 13 weeks of the study. No persistent neurotoxicity was noted in the neurotoxicity study conducted in rats. The NOAEL in the 13-week rat study was 500 ppm (1.23 mg/L) based on decreases in red blood cell parameters in the male and female rats and the during-exposure clinical signs noted in the 1500 and 5000 ppm (3.68 and 12.23 mg/L) groups. The NOAEL in the 13-week study in mice was 500 ppm (1.23 mg/L) based on during-exposure clinical signs (male and female mice) and increased relative liver weights (female mice only) at 1500 and 5000 ppm (3.68 and 12.23 mg/L). A NOAEL of 500 ppm isopropyl alcohol corresponds to 394 ppm (1.65 mg/L) isopropyl acetate and a LOAEL of 1500 ppm isopropyl alcohol corresponds to 1181 ppm (4.9 mg/L) isopropyl acetate after correcting for differences in total respiratory bioavailability.

An *in vitro* mutagenicity study in bacteria indicates that isopropyl acetate is not a genotoxicant. In addition, isopropyl alcohol was negative in an *in vivo* mouse micronucleus study and in inhalation cancer bioassays conducted with rats and mice. Based on these results, isopropyl acetate is unlikely to possess carcinogenic potential.

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.

The reproductive toxicity of isopropyl alcohol has been investigated in a one-generation drinking water study and a two-generation oral gavage study. Data from a developmental neurotoxicity study provides additional information on litter size and postnatal survival. A parental NOAEL of 100 mg/kg bw/day (170 mg isopropyl acetate/kg bw/day) was determined based on increased liver and kidney weights, centrilobular hepatocyte hypertrophy and hyaline droplet degeneration of the proximal convoluted tubular cells of the kidney at 500 mg/kg bw/day. Using a weight-of-evidence approach, a NOAEL for reproductive/developmental toxicity (decreased litter size and decreased postnatal survival) of 1338 mg/kg bw/day from a drinking water study for isopropyl alcohol was determined. The corresponding value for isopropyl acetate would be 2275 mg/kg bw/day. No effects were reported in an oral gavage developmental neurotoxicity study (NOAEL 1200 mg/kg bw/day; corresponding to 2040 mg/kg bw/day for isopropyl acetate).

The NOAEL from a rat developmental toxicity study in rats—conducted with 400, 800, or 1200 mg/kg/day isopropyl alcohol during days 6-15 of gestation—was 400 mg/kg bw/day for both maternal and fetal endpoints based on death in the dams and reduced fetal body weights noted at 800 mg/kg bw/day and above. No developmental effects were noted in rabbits exposed to 120, 240, or 480 mg/kg bw/day isopropyl alcohol by oral gavage during gestation days 6-18. Exposure of rats to vapor levels of isopropyl alcohol of 3500 ppm and above caused a decrease in fetal body weights, and the 10,000 ppm group had an increased incidence of failure of implantation, fully resorbed litters, increased resorptions per litter, and increased incidence of cervical ribs when administered 7 hr/day from gestation days 1 through 19. Maternal toxicity (decreased rate of weight gain) was noted at all exposure concentrations and the effect on fetal weight at the 3500 ppm group was slight (<5%) and correlated with increased litter size in that group. An inhalation exposure of 3500 ppm isopropyl alcohol is calculated to equal 2760 ppm (11.5 mg/L) isopropyl acetate after correcting for differences in respiratory bioavailability. Isopropyl alcohol was not a developmental neurotoxicant in rats when exposed by oral gavage at dose levels of 200, 700, or 1200 mg/kg bw/day. The NOAEL for isopropyl alcohol for developmental endpoints (400 mg/kg bw/day) from oral exposures would equal 680 mg/kg bw/day for isopropyl acetate after correcting for differences in gram molecular weight.

Environment

Isopropyl acetate is a liquid with a melting point of –73.4 ^{o}C and a boiling point of 88.6 ^{o}C. It has a vapor pressure of 80.5 hPa at 25^{0}C, a water solubility of 30,900 mg/l at 20^{0}C and a log K_{ow} of 1.02. The photochemical removal of isopropyl acetate as mediated by hydroxyl radicals occurs with a calculated half-life of 3.073 days. Isopropyl acetate is readily biodegradable under aerobic conditions. Isopropyl acetate volatilises easily from moving rivers, but volatilises only moderately from quiescent lakes and other surface water bodies (calculated volatilization half-lives of 3.285 hours from a river and 5.024 days from a lake). Isopropyl acetate is not persistent in the environment and is not likely to bioaccumulate in food webs. Using the Log K_{ow} value, the BCF is 1.2. Based on Level III distribution modelling it is estimated that the majority of isopropyl acetate released to the environment will partition into water (45.3%) and soil (37.8%), with a smaller amount into air (16.8%). The stability of isopropyl acetate in water is pH dependent: at neutral pHs (7) the $T_{1/2}$ = 2.418 years at 25^{0}C and at higher pHs (8) the $T_{1/2}$ is shortened to 88.3 days.

Since the duration of the isopropyl acetate study with green algae was longer than current OECD guidelines, green algae data for an analogous compound, n-butyl acetate (CAS# 123-86-4) is presented. The rationale for the use of the analogous compound n-butyl acetate is based on the log Kow and water solubility values. The log Kow values are 1.02 and 1.82 for isopropyl acetate and n-butyl acetate, respectively. The water solubility values are 30,900 mg/L and 14,000 mg/L for isopropyl acetate and n-butyl acetate, respectively. For isopropyl acetate, a static test with fathead minnows (*Pimephales promelas*) was conducted and a 96-hour LC_{50} of 390 mg/L (ECOSAR 96-h LC_{50} = 632.4 mg/L) was reported. For n-butyl acetate, a flow-through test with fathead minnows (*Pimephales promelas*) gave a 96-hour LC_{50} of 18 mg/L (ECOSAR 96-h LC_{50} = 22 mg/L). The invertebrate (*Artemia salina*) study with isopropyl acetate reported a 48-h LC50 of 110 mg/L (ECOSAR daphnid 48-h EC50 = 51.7 mg/L). The invertebrate (*Artemia salina*) study with n-butyl acetate reported a 48-h LC_{50} of 32 mg/L (ECOSAR 48-h EC_{50} = 135 mg/L), while the study for green algae (*Scenedesmus subspicatus*) reported a 72-h EC_{50} of 674.7 mg/L. Based on physical properties data and valid ecotoxicity studies for both isopropyl acetate and n-butyl acetate, data for n-butyl acetate can be used to reliably and conservatively predict the toxicity of isopropyl acetate to green algae.

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.

Exposure

Environmental release during manufacture is limited by the enclosed nature of the process and equipment. Inhalation and dermal exposure may occur during manufacture, transport, processing into formulations containing isopropyl acetate as solvent (e.g., coatings and inks), and the use or application of formulations and products containing isopropyl acetate. U.S. manufacturers indicate that exposure to isopropyl acetate in the workplace is limited during manufacture and formulation of products by the enclosed nature of these processes. The American Conference of Governmental Industrial Hygienists (ACGIH) has established an 8 hour Time Weighted Average Threshold Limit Value (TLV) of 1040 mg/m^3 (250 ppm) and a Short Term Exposure Limit (STEL) of 1290 mg/m^3 (310 ppm). Greater exposure potential exists during use as an industrial solvent, especially in coatings applications or printing where the processes may be more open. Exposure is typically limited in these cases by the use of engineering controls. Isopropyl acetate is present at 1-5 % concentrations in some consumer products, such as insecticides, shellacs and lacquers, which offer opportunity for occasional exposure. Perfumes containing isopropyl acetate as a diluent/fragrance can result in exposure of low concentrations to this substance. General population exposure may occur through industrial releases via inhalation of ambient air, and through ingestion of drinking water. Ingestion of foods naturally containing isopropyl acetate or due to its use as a food additive (21 CFR § 175.105 and 21 CFR § 172.515) is a further source of general population exposure.

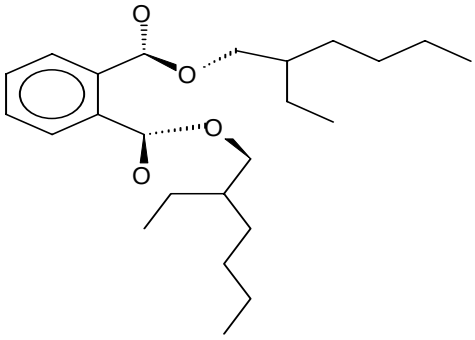
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (eye irritation, reproductive and developmental toxicity at high doses, repeated-dose toxicity at high doses). These hazards do not warrant further work as they are related to reversible effects (eye irritation) or effects seen at high doses. They should nevertheless be noted by chemical safety professionals and users.

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	117-81-7
Chemical Name	Bis(2-ethylhexyl)phthalate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Bis(2-ethylhexyl)phthalate (DEHP) is readily absorbed and distributed in the body, but there is no evidence of accumulation. The metabolism of DEHP involves several pathways and yields a variety of metabolites. The major step in the metabolism of DEHP is hydrolysis by lipases to MEHP (mono(2-ethylhexyl)phthalate) and 2-EH (2-ethylhexanol). The substance is excreted via the urine, mainly as MEHP-metabolites, but some excretion via bile also occurs in rodents. Additionally, there are animal and human data showing that DEHP is transferred to mothers' milk. The relative extent to which different metabolites are produced and excreted is very complex and may depend upon the species, the age of the animal, sex, inter-individual differences, nutrition state, prior exposure to DEHP, the amount of DEHP administered, and the route of administration.

Acute toxicity studies indicate a low acute toxicity of DEHP. The oral LD_{50} is >20,000 mg/kg b.w in rats and >10,000 mg/kg bw in mice. An inhalation LC_{50} of about 10,600 mg/m^3 for 4 hours in rats has been reported. Although there are no adequate acute dermal toxicity data, a low acute dermal toxicity is assumed.

Animal studies performed to current guidelines have shown a slight skin and eye irritation after administration of DEHP, but DEHP is not corrosive to the skin or eyes. DEHP has not been found to induce skin sensitisation in animals.

Numerous studies have investigated the toxicity of DEHP following repeated oral administration to experimental animals. Critical organs for DEHP-induced toxicity in laboratory animals are the **testis** (see below) and the **kidney**. The effects on the kidneys include increased: absolute and relative kidney weights, incidence and severity of mineralization of the renal papilla, incidence of tubule cell pigments, and incidence and/or severity of chronic progressive nephropathy. The lowest NOAEL for kidney toxicity is 29 mg/kg/day in the males and 36 mg/kg/day in females, derived from a chronic 2-year study in rats. In the liver, hepatomegaly due to hepatocyte proliferation, peroxisome proliferation and hepatocellular tumours are observed in experimental animals, but the hepatic effects are not believed to be relevant for humans.

Concerning the genotoxicity of DEHP, several different short-term tests, comparable to guideline studies and performed according to GLP, are available. The results are negative in the majority of the *in vitro* and *in vivo* studies performed with DEHP and its metabolites for detection of gene mutation, DNA damage, and chromosomal effects.

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.

Some positive results are obtained in the in vitro test systems which are also sensitive to several non-mutagenic substances. Overall, taking all data into account, DEHP and its major metabolites can be considered as non-mutagenic.

In rodent studies, liver tumours, Leydig cell tumours, and leukaemia have been observed. The liver tumours are most likely caused by peroxisome proliferation, and are therefore not considered relevant for humans. As to the other two tumours types, a relevance to humans can not be ruled out, although the evidence is inconclusive for this endpoint.

A conservative NOAEL value of 4.8 mg/kg/day has been set for testicular toxicity, based on a three-generation reproductive toxicity study, showing a low incidence of small male reproductive organs and minimal testis atrophy at 14 mg/kg/day and complete atrophy and aspermia at doses of 359 mg/kg/day. Developing and prepubertal rats have been found to be more sensitive to the DEHP-induced testicular toxicity than adults, and the NOAEL for testicular toxicity is therefore also used for developmental toxicity (4.8 mg/kg/day). Studies indicate that DEHP may also interfere with the male endocrine function and also influence the male sexual development. Testicular toxicity and developmental toxicity, observed in different animal species and at relatively low dose levels are considered relevant to humans. Effects on fertility has been observed at slightly higher exposure levels in mice and rats, with a NOAEL of 20 mg/kg/day observed in mice.

Environment

DEHP is a colorless liquid at room temperature The vapour pressure is estimated to $3.4x10^{-5}$ Pa at 20°C. A large range of values on the water solubility (0.0006 – 1.3 mg/L at 20-25°C) is available in the literature. The probable explanation is that DEHP easily forms more or less colloidal dispersions in water. An estimated value of 0.003 mg/L was used for non-colloidal solubility. The Henry´s law constant for DEHP is 4.43 Pa m^3/mol. The octanol-water partition coefficient, log Kow, is 7.5. However, in the model calculations the highest recommended value of 7.0 is used.

DEHP enters the environment mainly via direct release to air, from sewage sludge and from solid waste. In air, DEHP may occur both in vapour phase and as solid particles. The nature of these particles can be either aggregated pure DEHP or polymer particles containing DEHP. The log Koc for DEHP is 5.2 L/kg. Hence, DEHP will be strongly adsorbed to the sludge, in sewage treatment plants. Particles formed by weathering of polymer products probably represent an important route of DEHP distribution.

Photodegradation of DEHP (reaction with OH radicals) is important in the atmosphere ($T_{½}$=1 d) but is assumed to be of little importance in water and soil. DEHP does not hydrolyse in water. The biodegradation of DEHP is varying in available studies. Based on the results of standard biodegradation test DEHP is rapidly biodegradable. Experimental data indicate biodegradation half-life for DEHP in surface water of 50 days, and 300 days in aerobic sediment. Anaerobic conditions and low temperature further reduce the degradation rate. Results from degradation studies of DEHP in agricultural soil are variable, but indicate moderate to low biodegradation rates. MEHP is the primary biodegradation product of DEHP.

DEHP is found to bioaccumulate in aquatic organisms, and the highest BCF values are observed for invertebrates, e.g. 2700 for *Gammarus* (BCF_{fish} 840). This indicates that uptake via the food chain might be an important exposure route (secondary poisoning). BCF as well as monitoring data for different trophic levels, indicate that DEHP does not bio-magnify. This may in part be due to a more effective metabolisation rate in higher organisms. For exposure via the food a NOEC of 33 mg/kg_{food} for mammalian predators is determined, based on studies showing testicular damage in rats. For effects on bird reproduction a NOEC of 1700 mg/kg_{food} is calculated.

Several reliable short-term and long-term studies on effects of DEHP on aquatic organisms exist. There are no studies indicating effects on organisms only exposed to DEHP via water, and at concentrations below the water solubility. However, effects have been shown on fish exposed to DEHP via food. Therefore a NOEC for fish of 160 mg/ kg_{food} has been determined. Studies with sediment organisms showed no effects at 1000 mg/kg dwt, the highest tested concentration. Only one study, on respiration in activated sludge, is considered valid for the risk assessment of

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.

DEHP in STPs. No effects were observed at the highest tested concentration, 2007 mg/L (NOEC).

There are four valid tests with soil organisms, from three trophic levels, all showing no effects. From these studies a NOEC ≥ 130 mg/kg dwt is obtained.

The large amount of DEHP accumulated in the technosphere indicates a considerable potential for formation and distribution of MEHP. However, the formation rate and fate of MEHP in the environment is not known. MEHP causes reproductive toxic effects in studies on mammals. There are no other data on ecotoxicological properties of MEHP available.

There is a Priority Substance List Assessment Report Bis(2-ethyl hexyl) Phthalate produced by Canada in 1994 (http://www.ec.gc.ca/substances/ese).

Exposure

The global production of DEHP in 1994 was estimated to be between 1 and 4 million tonnes per year. The production volume of DEHP in Western Europe was 595,000 tonnes per year in 1997.

The main use of DEHP is as a plasticizer in polymer products, mainly in flexible PVC. The content of DEHP in flexible polymer materials varies but is often around 30 % (w/w). Flexible PVC is used in many different articles e.g. toys, building material such as flooring, cables, profiles and roofs, as well as in medical products like blood bags, dialysis equipment etc. DEHP is also used in other polymer products and in non-polymer formulations and products. This implies multiple sources of DEHP emissions. The main part of DEHP emissions originates from use and disposal of polymer products. These emissions are widely dispersed, and monitoring data of DEHP in environmental samples confirm a widespread occurrence.

Occupational exposure to DEHP, mainly through inhalation but also via the dermal route, occurs in the production of DEHP, industrial use of DEHP as an additive, and at industrial end-use of semi-manufactured products and end-products containing DEHP. The general population can be divided into sub-populations, as the extent of exposure is expected to be different in different sub-populations (e.g. adults, young/children), partly caused by a suspected higher bio-availability of DEHP in children than in adults. The exposure can be via many different sources, such as indoor air, car interiors, toys, medical equipment, and indirectly via the environment or via breast milk. Due to the multiple pathways of exposure, the combined exposure should be considered. Urinary biomonitoring of the total human exposure to DEHP has shown considerable exposure.

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

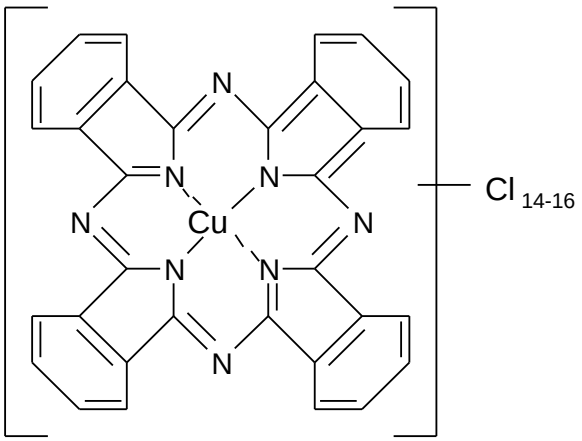
Human Health: The chemical possesses properties (testis, kidney, and reproductive toxicity) indicating a hazard to human health. Due to the widespread use of the substance, leading to continuous exposure at low level, member countries are invited to perform an exposure assessment, and if necessary, a risk assessment for human health.

Note: A risk assessment performed in the European Union in the context of the EU Existing Substances Regulation reveals concern for several toxicological endpoints in occupational settings, but also for consumers as a consequence of use of toys and some medical technical equipment. In addition, there are concerns for effects on humans via the local environment outside plants producing or using DEHP.

Environment: Based on the chemical's properties (bioaccumulation, effects in fish after dietary exposure and the low NOAEL for reproductive toxicity) member countries are invited to perform an exposure assessment specifically investigating secondary poisoning.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1328-53-6
Chemical Name	C.I. Pigment Green 7 Copper, [tetradecachloro-29H,31H-phthalocyaninato(2-)-N{29},N{30},N,{31},N{32}]-
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

C.I. Pigment Blue 15 (CAS-No. 147-14-8) will be used as an analogue for C.I. Pigment Green 7 (CAS-No. 1328-53-6). Both pigments belong to the same class of organic pigments bearing the same core structure (Cu-Phthalocyanine). While C.I. Pigment Blue 15 represents the unmodified version of the molecule, C.I. Pigment Green 7 is chlorinated 14 to 16 fold per phthalocyanine. They both are of high molecular weight and show extremely low water solubility. Furthermore, data from subchronic toxicity studies and genetic toxicity *in vitro* support the analogy.

Data on C.I. Pigment Blue 15 will be used to address the reproduction and developmental toxicity endpoints, as well as biodegradability.

Human Health

C.I. Pigment Green 7 is of low acute oral toxicity (LD_{50}, oral, rat: > 2000 mg/kg bw). The available data concerning the inhalation route are not sufficient to provide a well founded assessment of the inhalation toxicity of the substance. No data are available on the dermal route.

C.I. Pigment Green 7 is not irritating to the rabbit skin and eye. One isolated case of positive patch reaction to C.I. Pigment Green 7 (10 % in pet.) was reported for humans. However, there are no reliable references on a sensitizing potential of C.I. Pigment Green 7.

In a 28-day gavage study on rats with C.I. Pigment Green 7, doses up to 1000 mg/kg bw/day resulted in no adverse effects in clinical observations, hematology, urine analysis, clinical chemistry as well as macro- and microscopical

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.

pathology. The NOEL determined was 1000 mg/kg bw/day for both sexes. In a 28-day feeding study on rats with the analogue C.I. Pigment Blue 15 slight but significant changes in some blood parameters were detected in the 200 and 1000 mg/kg bw/day male groups and increases of absolute organ weights in the 1000 mg/kg bw/day group. Due to the minor severity of the effects a NOAEL of 1000 mg/kg bw/day is derived.

90-day feeding studies on rats and mice with C.I. Pigment Green 7 showed no adverse effects with NOAELs of 4600 mg/kg bw/day for male rats and 5000 mg/kg bw/day for female rats and 16,000 mg/kg bw/day for female mice and 20,000 mg/kg bw/day for male mice. The NOAELs from the rat and mouse studies are the highest tested doses.

In vitro genotoxicity tests indicated that the substance has no genotoxic activity. C.I. Pigment Green 7 was not mutagenic in bacteria (Ames test) with and without metabolic activation systems. Furthermore, it did not induce chromosomal aberrations or aneugenic activity in mammalian cell cultures. Data for *in vivo* genotoxicity tests are not available. These data were partly supported by Ames test results with the analogue C.I. Pigment Blue 15.

Data from subchronic studies showed no changes in the reproductive systems of both sexes in terms of organ weights, gross pathology and histopathology. Additionally, data derived from a reproduction toxicity screening test in rats with the analogous substance C.I. Pigment Blue 15 showed no effects on mating performance, fertility and during autopsy of the pups. Therefore, and taking the low bioavailability of the compound into account, an induction of effects on fertility and development by C.I. Pigment Green 7 is not indicated.

Environment

In the Sponsor country C.I. Pigment Green 7 contains < 2.5 ppm of HCB. This quantity may not be representative for other production sites.

C.I. Pigment Green 7 is a dark green crystalline powder. It has a very low calculated water solubility ($7 * 10^{-18}$ - $2 * 10^{-16}$ mg/l at 20 °C), and a low measured n-octanol solubility (0.07 mg/l at 20 °C). C.I. Pigment Green 7 has a calculated log K_{OW} of 17.4 and a vapour pressure of < 0.001 Pa at 25 °C. The relative density is 1.8 – 2.47 and the melting point is 480 °C. For the boiling point, no data or reliable calculations are available, it is assumed to be >1000 °C.

The degradation in the atmosphere through reaction with hydroxyl radicals was calculated for a chlorinated phthalocyanine without metal complexation using SRC-AOP v3.10. The half-time was calculated to 1.9 hours (12 hour day, $1.5 * 10^6$ OH/cm^3) and 5.9 hours (24 hour day, $0.5*10^6$ OH/cm^3).

C.I. Pigment Green 7 is expected to sorb readily to soils and sediments. Thus, the mobility in soil is likely to be limited.

Modelling of the distribution behaviour in the environment is not possible since several physical parameters are not available and standard calculations are not useable for metal-complexed dye-stuffs. However, as C.I. Pigment Green 7 is almost insoluble in water and volatility is estimated to be negligible due to its physical state, it may be expected that soil and sediment will be the main target compartments.

Biodegradation test results are not available. According to the structure and the low solubility in water, C.I. Pigment Green 7 is not expected to be biodegradable. C.I. Pigment Blue 15 was not biodegradable in a test conducted according to OECD TG 301C (0 % degradation after 14 days). Hydrolysis at environmental pH conditions is not expected due to the structure of the molecule.

The BCF has been measured to be < 2.1 to 74 at an exposure concentration of 0.01 mg/l, although this was above water solubility. Thus, a relevant bioaccumulation is not expected.

Several studies for freshwater organisms and one study for terrestrial organisms are available. The lowest effect concentrations are summarized below:

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.

Fish:
Salmo gairdneri (*O. mykiss*) LC_{50} (96h) = 355.6 mg/l (nominal)

Invertebrates:
Daphnia magna EC_{50} (48h) = 153.6 mg/l (nominal)
Daphnia magna NOEC (21d) > 1 mg/l (nominal)
These investigations were performed well above the estimated water solubility limit. Effects occurred only far above the water solubility limit, it is possible that these effects could have also been caused by physical effects of the substance.

Algae:
For growth rate and biomass the EC_{50} for *Desmodesmus subspicatus* after 72 h lies above the water solubility. Due to the test design the raw eluate has to be diluted (8:1:1) due to the addition of algal suspension and enriched medium. At the highest technically feasible concentration of the eluate (due to the test design, 80 % of the water solubility) 9.1 % effect on growth rate and 28.4 % effect on biomass appeared. The NOEC lies at 1/10 of the water solubility for both endpoints.

Based on these data, C.I. Pigment Green 7 is considered as not harmful to aquatic organisms.

One study for soil dwelling organisms is available. The NOEC (14d) for *Eisenia fetida* was > 1000 mg/l.

Exposure

The uses of C.I. Pigment Green 7 include colorants in inks, paints and plastics. It is also used in textile printing, spin dying, ball-point pen inks, colouring of detergents, soaps, coating of glass fibers, greases, stains and xerographic imaging. Further uses for wallpaper, rubber, paper surfacing, book cloth, Linoleum are described. C.I. Pigment Green 7 is approved for food contact applications and is approved by EPA for seed dressings. C.I. Pigment Green 7 has a FDA approval for use as a contact lens colorant. In 2002 the estimated world production amounts to about 17 000 tonnes.

Releases into the environment may occur during production and processing of C.I. Pigment Green 7, as well as from the use of the substance or products containing it. Pigments released from production sites and not having been eliminated mechanically, will probably absorb to sewage sludge. C.I. Pigment Green 7 is not monitored in the effluent of the waste water treatment plant of one company in the Sponsor country. Via production and further processing, less than 25 kg of C.I. Pigment Green 7 were emitted into the air in 2000 at the plant of one company in the Sponsor country according to the German Emission Register.

Emission data from other production and processing sites are not available.

In the Swiss Product Register (status May 2002), about 331 products are listed under different names, about 74 of them are consumer products. In the Danish product register 633 products with a total quantity of 773 t/a are mentioned (year not given). In the Swedish product register 304 products with a total quantity of 133 t/a are listed, 33 of these are available to consumers. The SPIN database lists for the year 2001 for Norway 186 products (261 tons), for Denmark 733 products (909 tons), for Finland 4 products (0.1 tons). For Sweden 302 products are given for the year 2000 (111 tons). The preparations listed for Norway and Sweden include products for consumer use, in Denmark and Finland, none of the products is for consumer use (SPIN database, 2004).

According to an exposure assessment for copper from the manufacture, processing and use of three copper phthalocyanine pigments which has been established 1988 by the US EPA, releases to the air occur primarily during conditioning of the pigments. Estimations of the exposure of populations 100 meters from the source to free copper via inhalation gave an airborne concentration of < 0.001 mg/m^3 for manufacture and 0.002 mg/m^3 for conditioning. The inhalation exposure was estimated to 1.7 mg/year and 3.97 mg/year, respectively.

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.

Concerning consumer exposure the above cited report gives the following estimations:
Human exposure via drinking water to Cu released from manufacturing was estimated using site-specific surface water flow rates for a known manufacturing site. Exposure of an individual drawing water 10 km downstream was estimated to be 7.3 µg/year. Releases from conditioning at the same site resulted in a drinking water exposure of < 1 µg/year.

Human exposure via drinking water to free copper released from paint manufacturing operations were estimated and gave a mean drinking water exposure of < 0.001 mg/year (50 %ile) and 0.004 mg/year (10 %ile), respectively, assuming no removal at the waste water treatment.

An exposure assessment for significant releases and consumer uses of the pigments was conducted regarding exposure to the copper as an impurity in the pigments. The estimation was performed for Pigment blue 15 using the worst-case consumer scenario "use of a pigment containing interior housepaint". The annual exposure to the pigment was estimated to be approximately 412 mg/year.

As the substance has no relevant bioaccumulation potential, human exposure through the environment is not expected. No monitoring data are available.

C.I. Pigment Green 7 produced in the Sponsor country contains small amounts (< 2.5 ppm) of HCB (hexachlorobenzene, CAS: 118-74-1) as impurity. Environment Canada is continuing work on HCB in pigments to determine the use and distribution as well as what, if any, levels of HCB releases may occur from these uses. The collection of information related to the incidental presence of HCB in pigments will be used to make a decision on the appropriate actions to be taken in the future. HCB is internationally recognized as to be hazardous to both human health and the environment.

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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	15630-89-4
Chemical Name	Sodium percarbonate
Structural Formula	$2Na_2CO_3 \cdot 3H_2O_2$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Sodium percarbonate is an inorganic, water soluble solid of relatively low molecular weight. Dermal absorption is assumed to be low due to the hydrophilic character and the ionic structure of the substance. When sodium percarbonate is getting into contact with body fluids it will dissociate into hydrogen peroxide, carbonate and sodium ions which are all naturally present in the human body. For hydrogen peroxide a high degradation capacity is present in the blood and tissues, making it unlikely that hydrogen peroxide is systemically available. As carbonate is a part of the natural buffer systems in the organism it is unlikely that it is absorbed through sodium percarbonate exposure in amounts that would disturb the normal acid/base balance of the body. Similarly for sodium percarbonate exposure is not expected to contribute significantly to the sodium load of the body. The mode of action is characterized by the local irritation potential in particular to mucous membranes. No systemic effects are anticipated because it is unlikely that the substance is systemically available.

Acute oral LD50 values ranged between 1034 and 2200 mg/kg bw, while the acute dermal LD50 was > 2000 mg/kg bw. The existing animal data on acute toxicity show that sodium percarbonate has a local effect and that systemic effects are not to be expected. In animal tests a slight irritating effect on the skin was reported for solid sodium percarbonate and it was highly irritating to the rabbit eye (not rinsed). Sodium percarbonate did not have sensitizing properties in a test with guinea pigs. The acute studies indicate that most of the acute and local effects can be explained by the release of hydrogen peroxide.

Although a repeated dose study is not available for sodium percarbonate, an additional repeated dose toxicity study in rats with sodium percarbonate is not necessary because the effects can be predicted based on the release of hydrogen peroxide, carbonate and sodium. As it is expected that repeated dose toxicity of sodium percarbonate will mainly be mediated by hydrogen peroxide, no observed adverse effect levels can be defined on the basis of its hydrogen peroxide content. Based on the 90-day drinking water study according to OECD guidelines and GLP with hydrogen peroxide and catalase deficient mice, the predicted NOAEL of sodium percarbonate would be 308 ppm (81 to 115 mg/kg bw/day for males and females, respectively).

Data on the mutagenicity of sodium percarbonate are not available but it is likely that any test results for sodium percarbonate will be similar to those of hydrogen peroxide due to the release of hydrogen peroxide in aqueous media. The available studies on hydrogen peroxide, most of them, in particular the *in vivo* studies, were performed according to OECD guidelines and GLP, are not in support of significant genotoxicity/mutagenicity under *in vivo* conditions. Therefore sodium percarbonate is also unlikely to have any *in vivo* genotoxic potential. For hydrogen peroxide a wider database in particular with regard to local genotoxicity was however, considered desirable in the EU risk assessment report, once suitable validated methods become available.

Carcinogenicity studies with animals and sodium percarbonate are not available. The only component that could give rise to some concerns with regard to this endpoint is hydrogen peroxide. A local carcinogenic effect was observed in the duodenum of a catalase-deficient mouse strain administered 0.4 % hydrogen peroxide in drinking water. Although

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.

an underlying genotoxic mechanism cannot be excluded, the weight of evidence at this time does not suggest that the carcinogenic properties of hydrogen peroxide should be regarded as practically significant.

Neither an animal study on toxicity to reproduction nor a study on developmental toxicity is available for sodium percarbonate. A developmental toxicity study with sodium carbonate, which was well documented and meets basic scientific principles, revealed no substance related fetotoxic, embryotoxic or teratogenic effects. From the nature of the substance it is to be anticipated that neither sodium percarbonate nor hydrogen peroxide and sodium carbonate will be systemically available under human exposure conditions and are thus unlikely to reach the gonads and the developing embryo or fetus. Therefore the substance is unlikely to have any relevant potential for toxicity to reproduction or developmental toxicity and no further animal testing is warranted for those endpoints.

Environment

The water solubility of sodium percarbonate is 140 g/l at 20 ºC. Sodium percarbonate rapidly dissolves in water and dissociates into sodium ions, carbonate ions and hydrogen peroxide. Sodium carbonate and hydrogen peroxide are very water soluble and will therefore remain in the water phase. Hydrogen peroxide is a naturally occurring substance (typical background concentrations < 1 - 30 µg/l). Almost all cells with the exception of anaerobic bacteria produce it in their metabolism. Hydrogen peroxide is a reactive substance in the presence of other substances, elements, radiation, materials and can be degraded by micro-organisms or higher organisms. Hydrogen peroxide is rapidly degraded in a biological waste water treatment plant. Hydrogen peroxide adsorbs poorly to sediment particles and is rapidly degraded, thus accumulation in the sediment is also not expected.

A standard guideline study has been done with a freshwater fish species and sodium percarbonate and this study revealed an acute LC50 value of 71 mg/l for fathead minnow (*Pimephales promelas*). A standard guideline study has been done also with a water flea (*Daphnia pulex*) and in this case an acute EC50 value of 4.9 mg/l was found. Based on a comparison of the results of acute toxicity tests with sodium carbonate, hydrogen peroxide and sodium percarbonate, the acute toxicity of sodium percarbonate can be explained by the formation of hydrogen peroxide. Chronic toxicity studies with sodium percarbonate are not available. However, the chronic toxicity of sodium percarbonate can be predicted from the chronic toxicity of hydrogen peroxide. A chronic toxicity study with invertebrates (zebra mussels) and hydrogen peroxide revealed a NOEC of 2 mg/l. The PNEC of hydrogen peroxide is equal to 10 µg/l and algae are the most sensitive species for hydrogen peroxide. The algal EC50 of hydrogen peroxide was 1.6-5 mg/l, while the NOEC was 0.1 mg/l. Both sodium carbonate and hydrogen peroxide (log Kow < -1) are inorganic chemicals which do not bioaccumulate.

Exposure

The estimated world-wide demand of sodium percarbonate was 300,000 – 500,000 tonnes in 2003. Globally sodium percarbonate is produced at 12 – 24 production sites and about half of them are located in Europe.

The main user of sodium percarbonate is the household cleaning products industry, which is expected to use more than 95 % of the global sodium percarbonate demand. Sodium percarbonate is mainly used as a bleaching chemical in laundry detergents (tablets, compact or regular powders), laundry additives and machine dishwashing products. Minor amounts of sodium percarbonate may be used in products for drain cleaning, multipurpose cleaning, denture cleansing and tooth whitening. Furthermore sodium percarbonate may be used for preservation of raw milk by use of the lactoperoxidase system, when cooling facilities of raw milk are not available. The pure product (100 %) is available for consumers as a laundry additive.

During production and formulation possible routes of exposure for workers are direct skin contact and inhalation of dust. Consumer exposure may occur through direct skin contact with the solid, through skin contact with solutions (e.g. hand wash) and via inhalation of dust particles. Furthermore accidental or intentional overexposure may occur in certain cases for consumers and/or workers.

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.

An emission of sodium percarbonate to the environment could potentially occur during production, formulation and use of the substance. However, hydrogen peroxide is rapidly degraded in a biological waste water treatment plant, while sodium carbonate will be neutralised by such a treatment.

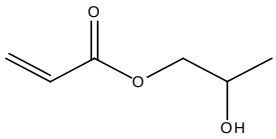
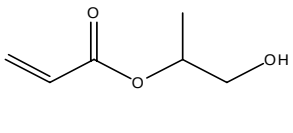
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health and the environment. These hazards do not warrant further work as they are related to reversible effects (irritation) and acute toxicity which may become evident at high exposure level. They should nevertheless be noted by chemical safety professionals and users.

Note: Member states assessing the exposure of hydrogen peroxide should take into account the sources from the use of sodium percarbonate.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	25584-83-2
Chemical Name	Hydroxypropyl Acrylate (Acrylic Acid, Monoester with Propane-1,2,-Diol)
Structural Formula	 2-Hydroxypropyl acrylate  1-Methyl-2-hydroxyethyl acrylate A typical commercial sample of hydroxypropyl acrylate contains approximately 75-80% 2-hydroxypropyl acrylate and 20-25% 1-methyl-2-hydroxyethyl acrylate. The purity of the salable product is at least 97% combined isomers

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The kinetics of hydroxypropyl acrylate have not been studied. However, results from oral, inhalation, and dermal single dose studies with the closely related, hydroxyethyl acrylate (CAS No. 818-61-1), indicated rapid metabolism via hydrolysis of the ester functionality, similar to many other acrylic acid esters. For hydroxyethyl acrylate, rapid metabolism to CO_2 and urinary metabolites was not route-dependent. The half-lives of elimination of radioactivity were approximately 14 hours for urine and 17 hours for CO_2. The half-life of elimination of radioactivity from plasma was approximately 26 hours. Based on the similarity of the results for hydroxyethyl acrylate with other acrylic acid esters, similar kinetics of hydroxypropyl acrylate is anticipated.

Acute toxicity studies with experimental animals indicate oral and dermal LD_{50} values of 820 mg/kg bw (rat) and 306 mg/kg bw (rabbit), respectively. In an acute inhalation study, exposure to a saturated vapor for eight hours did not result in deaths. In standard primary irritation studies, hydroxypropyl acrylate is a severe skin irritant. Upon eye contact, hydroxypropyl acrylate may cause severe irritation with corneal injury which may result in permanent impairment of vision or blindness. Skin sensitization studies in animals and humans indicate that hydroxypropyl acrylate is likely to be a sensitizer and will cross-react with other acrylates in some exposed individuals.

Repeated exposure to vapors of hydroxypropyl acrylate (6 hr/day, 5 days/week for 21 or 20 exposures to rats and mice and rabbits and dogs, respectively) results in severe irritation of the upper respiratory tract, resulting in death due to respiratory failure at higher concentrations and concentration-related local irritation at sublethal exposures. The LOAEC for subchronic exposure, based on irritation, was 5 ppm (27 mg/m^3) for hydroxypropyl acrylate. Except for irritant effects, no systemic toxicity was observed.

Hydroxypropyl acrylate was not mutagenic to *Salmonella typhimurium* (bacterial reverse mutation assay) *in vitro* with or without metabolic activation but was positive with metabolic activation when tested with two *E. coli* strains. In mammalian cells *in vitro*, hydroxypropyl acrylate was negative in a gene mutation assay but had clastogenic activity in cytogenetic and chromosomal aberration assays. In these mammalian cell assays, positive results occurred only at concentrations that resulted in significant cell death. Thus, the positive results are considered equivocal. Hydroxypropyl acrylate was not mutagenic in an *in vivo* mouse micronucleus study. Overall, hydroxypropyl acrylate

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.

is considered not to have mutagenic potential *in vivo* based on available data.

Hydroxypropyl acrylate had no effect on male reproductive organs in four species following repeated exposures via inhalation for 30 or 31 days (20 or 21 exposures). The principal treatment-related effects observed following 18 months exposure of laboratory rats to 5 ppm of the closely related, hydroxyethyl acrylate, were related to irritation of the respiratory tract, without significant evidence of systemic toxicity. Histopathological examination of the reproductive organs revealed effects in the arteries of the testes (fibrinoid degeneration in the vascular channels — an age-related lesion) and uterus (inflammation) which were interpreted as neither treatment-related nor adverse to reproduction.

In a well-conducted inhalation study exposing pregnant rats to hydroxypropyl acrylate from gestation day 6 to 20, maternal body weights were reduced at the two highest exposure concentrations (5 and 10 ppm; 27 and 53 mg/m^3), but no embryo-fetal or developmental toxicity was observed. Overall, based on the available studies, hydroxypropyl acrylate does not show evidence for developmental toxicity.

Environment

The melting point is – 23.4°C and the boiling point is 205.7°C. The vapor pressure is 0.038 hPa at 25°C. The measured log Kow is 0.35. The water solubility of hydroxypropyl acrylate is estimated to be 307 g/L (25°C) and specific gravity is 1.049 g/cm^3 at 25°C.

Hydroxypropyl acrylate is photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 7.4 hours (calculated). The hydrolysis rate of hydroxypropyl acrylate is pH dependent with hydrolysis half-lives of > 490 days and >230 days at pH 3 and pH 7, respectively. The hydrolysis half-life at pH 11 is 0.056 days.

Distribution modeling using Mackay Level I indicates hydroxypropyl acrylate released into the environment partitions almost completely (99.8%) to the water phase. Fugacity model Level III with 100% of the hydroxypropyl acrylate release to air distribution is: <1% (air), 27% (water), 73% (soil) and <0.1% (sediment). Fugacity model Level III distribution with 100% of the hydroxypropyl acrylate release to water is: <0.1% (air), 100% (water), <0.1% (soil) and <1% (sediment). Fugacity model Level III distribution with 100% of the hydroxypropyl acrylate release to soil is: <0.1% (air), 21% (water), 79% (soil) and <0.1% (sediment). Fugacity model Level III distribution with equal distribution of hydroxypropyl acrylate release to air, water and soil is: <0.1% (air), 45% (water), 55% (soil) and <0.1% (sediment)

A low bioaccumulation potential is expected based on the partition coefficient of Log Kow of 0.35. Based on an OECD Guideline 301C study, hydroxypropyl acrylate is readily biodegradable (83% degraded over 28 days).

The 96-hour LC_{50} for fathead minnow was 3.1 mg/L (measured), the 48-hour EC_{50} for *Daphnia magna* was 24 mg/L (nominal) and the 96-hour EC_{50} values for biomass and growth rate of algae (*Selenastrum capricornutum*) were 3.53 and 6.67 mg/L (nominal), respectively.

Exposure

The worldwide production volume of hydroxypropyl acrylate is estimated to be 6000 to 7000 tonnes per year. The US production is estimated to be 5000 tonnes per year. Hydroxypropyl acrylate is produced and primarily used in closed systems. Its principle use is either as a co-monomer in the manufacture of polymers or as a chemical reactant in the manufacture of chemical intermediates. The polymers and chemical intermediates made with hydroxypropyl acrylate find applications in automotive top coatings, architectural coatings, photocure resins, and adhesives.

Based on the use pattern of the substance, significant environmental releases are unlikely. Impact on the environment is expected to be low due to photolysis, biodegradation and lack of bioaccumulation. Results from workplace measurements at a US production site indicated that hydroxypropyl acrylate did not exceed the TLV of 0.5 ppm in 87 samples collected over 20 years. Worker exposure is limited by the use of enclosed processing systems, industrial hygiene controls and personal protective measures. Hydroxypropyl acrylate has a characteristic

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.

acrylic odor, which can provide a measure of warning of the presence of vapors. End-use consumer products contain only trace levels of acrylic acid and esters (as a result of polymerization). Therefore, consumer exposure to acrylate monomers is not anticipated.

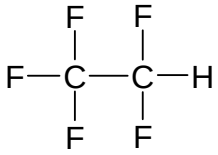
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical has properties indicating a hazard for human health (severe eye irritation with corneal injury, which may result in permanent impairment of vision, even blindness, skin and upper respiratory tract irritation, potential skin sensitization, and acute toxicity from inhalation exposure). Based on exposure data presented by the Sponsor Country (relating to production in one country which accounts for approximately 80% of global production and relating to the use pattern in several countries), this chemical is currently of low priority for further work. Countries may wish to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: This chemical has properties indicating a hazard for the environment (fish, invertebrate, algae). However, the chemical is of low priority for further work for the environment because of its ready biodegradability and the limited potential for bioaccumulation.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	354-33-6
Chemical Name	1,1,1,2,2-pentafluoroethane (HFC-125)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Analog Rationale

HCFC-141b (1,1-dichloro-1-fluoroethane; CAS No. 1717-00-6) and HCFC-142b (1-chloro-1,1-difluoroethane; CAS No. 75-68-3) are used to supplement the data for pentafluoroethane for the aquatic toxicity endpoints. These substances are justified as analogs because they have molecular weights, functional groups, and Log Kow values that are similar to pentafluoroethane (HFC-125).

Human Health

In an inhalation toxicokinetics study, exposure by rats to concentrations of 1,000, 5,000, and 50,000 ppm (4,909, 24,544, and 245,440 mg/m^3) for 6 hours did not result in significant absorption or distribution in the body. In an acute inhalation toxicity test, HFC-125 administered to rats at a concentration of 800,000 ppm (3,927,000 mg/m^3) did not result in death. However, ataxic gait and abnormal respiration were observed during exposure and ceased one hour after exposure ended. No signs of dermal or ocular irritation were observed during acute exposure (up to 800,000 ppm) or repeated whole-body exposure (up to 50,000 ppm, 245,440 mg/m^3). Skin sensitization was not observed during repeated-dose studies.

In a 28-day inhalation study, rats were administered doses up to 50,000 ppm (245,440 mg/m^3) 6 hours per day, 5 days per week. Ten rats per sex per dose were used in the study. No clear treatment-related effects were observed and the highest tested concentration was considered to be the NOAEC. In a 90-day inhalation study, groups of ten males and ten females were also administered HFC-125 at doses of 5,000, 15,000, and 50,000 ppm (24,544, 73,630, and 245,440 mg/m^3) by inhalation for 6 hours/day for 5 days/week. Gross pathological effects observed at the highest dose included a cyst in the kidney of one animal, a cyst in the ovary of another, enlarged lymph nodes of a third animal, and white patches in the liver of a fourth animal. Due to the limited number of animals and different organs affected as well as the lack of statistical significance, these effects were considered incidental. Therefore, the highest dose (50,000 ppm) was considered the NOAEC for the 90-day study.

In vitro genotoxicity studies (a bacterial reverse mutation test and two mammalian chromosomal aberration tests) and an *in vivo* study (a mammalian erythrocyte micronucleus test) showed negative results at non-cytotoxic concentrations.

Fertility studies are not available. Results of organ weight and tissue analyses of male and female reproductive organs in both the 28-day and 90-day studies did not reveal any treatment-related effects.

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.

In a developmental study in rats, groups of 40 females were exposed to concentrations up to 50,000 ppm (245,440 mg/m^3) HFC-125 during days 6 to 15 of pregnancy for 6 hrs/day. Twenty-four rabbits per exposure group were also dosed with concentrations up to 50,000 ppm during days 6 to 18 of pregnancy for 6 hours/day. No changes in embryo-foetal viability, incidence of malformations, anomalies or variants were observed. Therefore 50,000 ppm (245,440 mg/m^3) can be considered as both the maternal and the foetal NOAEC in the developmental studies.

A study on cardiac sensitisation was carried out in dogs exposed to HFC-125 and concurrently injected with adrenaline. Cardiac sensitisation was observed in animals exposed to an atmosphere containing 100,000 ppm (490,880 mg/m^3) HFC-125 and above. The NOAEC for this study was 75,000 ppm (368,160 mg/m^3).

Environment

HFC-125 is a gas with a melting point of -103 °C, a boiling point of -48 °C, a vapor pressure of 1.4 x 10^4 hPa at 25°C an estimated water solubility range of 432-1071 mg/l at atmospheric pressure and a Log K_{ow} of 1.48.

According to the Level III Fugacity-based Multimedia Environmental Model, HFC-125 will partition almost exclusively into the atmosphere in an exposure scenario using 100 percent release into the air. No experimental data on abiotic degradation are available. However, calculated half-lives for hydrolysis are 1166 days at pH7 and 117 days at pH 8. Due to its vapor pressure and Henry's Law constant (28.2 KPa m^3/mol), the estimated volatilization half life 1 hour for a river and 105 hours for a lake. HFC-125 was not readily biodegradable in a closed-bottle test. Hydroxyl radical-mediated photodegradation in the troposphere results in a calculated global atmospheric lifetime of 29 years. Because of the low atmospheric degradation rate, HFC-125's potential to form ozone in the troposphere is considered negligible. Based on the ozone depletion potential value of 3 x 10^{-5} compared to CFC-11 (ODP = 1), HFC-125 does not contribute to atmospheric ozone depletion. Its global warming potential relative to CO_2 is 3,400 for a time horizon of 100 years and thus it has the potential to contribute to global warming upon release. Using the Log K_{ow} value, the estimated BCF is 2.75. Therefore, HFC-125 is not expected to bioaccumulate in aquatic organisms to any appreciable extent.

No ecotoxicity experimental data are available for HFC-125. ECOSAR calculations predicted the hazard potentials shown in the following table. This estimation is supported by the low aquatic toxicity of HFC-125 structural analogs. The analogs are likely to be more biologically reactive because of the presence of chlorine atoms in the chemical structures as well as the higher water solubilities.

	HFC-125	HCFC-141b	HCFC-142b
Fish (mg/L)	96-hr LC_{50} 274 (QSAR calculation)	96-hr LC_{50} 126 (experimental)	96-hr EC_{50} 220 (experimental)
Daphnia (mg/L)	48-hr LC_{50} 283 (QSAR calculation)	48-hr LC_{50} 31.2 (experimental)	48-hr LC_{50} 160 (experimental)
Algae (mg/L)	96-hr LC_{50} 172 (QSAR calculation)	72-hr EC_{50} >44 (experimental)	No data

Exposure

Greater than 99 percent of HFC-125 is used as a blend component for commercial refrigeration and air conditioning systems, while the rest is used as a fire extinguishing agent, as minor applications in plastic foam blowing, and as a solvent in special applications. The production of HFC-125 from three producers was approximately 16,000 tonnes in 2002. Occupational exposure to HFC-125 may occur during production and mainly during repair/maintenance operation in refrigeration systems. Since refrigeration units and fire extinguishing systems are hermetically sealed, consumer exposure would occur most likely from slow leaks. However, when used to extinguish fires, there may be

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.

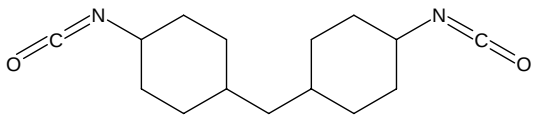
some short term exposure to HFC-125 as well as thermal degradation products such as hydrogen fluoride. Environmental monitoring data performed between 1998 and 2000 detected a maximum mixing ratio of 1.4 ppt HFC-125 in the atmosphere. The use and disposal of equipment containing HFC-125 is regulated in the USA under the Clean Air Act (FR V68, 162, 2003).

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, invertebrates, and algae). Its global warming potential is acknowledged and being addressed by other programs.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	5124-30-1
Chemical Name	4,4´-Methylenedicyclohexyl diisocyanate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

4,4´-Methylenedicyclohexyl diisocyanate is of low oral and dermal acute toxicity with an oral LD_{50} (rat) of 9900 mg/kg bw and a dermal LD_{50} (rabbit) > 10,000 mg/kg. Toxic symptoms after oral administration included severe diarrhea, loss of appetite and increasing weakness. Assessment of the acute inhalation toxicity data indicates that exposure to respirable aerosols of 4,4´-methylenedicyclohexyl diisocyanate confined predominantly to the respiratory tract. Clinical signs (salivation, bradypnea, stridor) indicated respiratory distress. A haemorrhagic lung edema was considered to be causative for mortality. An animal study according to OECD TG 403 gives a LC_{50} (4 h, rat) of 434 mg/m^3.

4,4´-Methylenedicyclohexyl diisocyanate is moderately to severely irritant to the skin of rabbits (OECD TG 404). Irritant effects were observed after instillation of 4,4´-methylenedicyclohexyl diisocyanate into the eyes of rabbits (OECD TG 405). The repeated dose studies indicate that 4,4´-methylenedicyclohexyl diisocyanate causes irritation of the respiratory tract.

Animal data are not uniform however they frequently provide evidence of a skin sensitizing potential of 4,4´-methylenedicyclohexyl diisocyanate. Human case reports describe allergic contact dermatitis due to 4,4´-methylenedicyclohexyl diisocyanate exposure. Although no validated animal model is available to assess the potential for respiratory sensitization or asthma in humans animal data support to some extent the hypothesis that respiratory hypersensitivity may be induced by 4,4´-methylenedicyclohexyl diisocyanate.

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure. A subacute inhalation study (1, 6 and 36 mg/m^3; 6 hours/day on five days/week for 4 weeks) with rats (OECD TG 412) indicates the respiratory tract to be the target organ of respirable 4,4´-methylenedicyclohexyl diisocyanate aerosol. The reported NOAEL for effects governed by respiratory tract irritation is 1 mg/m^3; the LOAEL is 6 mg/m^3 (i.e. histopathological changes in nasal passages, larynx and bronchi). The results of a reproduction/developmental toxicity screening test (OECD TG 421) corresponds to the results of the subacute study.

4,4´-Methylenedicyclohexyl diisocyanate did not induce gene mutations in bacteria (OECD TG 471) and demonstrated no potential to induce chromosome aberrations in Chinese hamster V79 cells *in vitro* (OECD TG 473) either with or without metabolic activation.

Data from an inhalative reproduction/developmental toxicity screening test according to OECD TG 421 with rats (1, 6 and 36 mg/m^3) did not reveal substance related impairment of reproduction up to a 4,4´-methylenedicyclohexyl diisocyanate concentration of 6 mg/m^3. A slightly reduced fertility index was observed at an exposure level (36 mg/m^3) that was associated with parental toxicity. NOAELs were considered to be 1 mg/m^3 in males and females for general toxicity. NOAEL for reproductive toxicity is 6 mg/m^3.

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.

Pre-natal inhalation toxicity testing in rats (OECD°TG°421) indicates the absence of selective toxicity to the development at levels up to 36°mg/m^3. No findings indicate any specific developmental effects such as live birth index, viability index and apparent malformation. The reported $NOAEL_{(developmental)}$ for 4,4´-methylenedicyclohexyl diisocyanate in a developmental toxicity study according to OECD TG 414 (1, 6 and 36 mg/m^3) is 6 mg/m^3/day. At the 36 mg/m^3 level that caused clear maternal respiratory tract toxicity ($NOAEL_{(maternal)}$ = 1 mg/m^3) increased incidences of ventricular septal defects of the heart and slight dilation of lateral brain ventricles were observed, which lay marginally above the upper or within the normal range of scattering of the rat strain used respectively.

Environment

4,4'-Methylenedicyclohexyl diisocyanate is a slightly yellowish, moisture/water sensitive liquid with a melting point of 15 °C. 4,4'-Methylenedicyclohexyl diisocyanate has a relative density of 1.07 at 25 °C, a boiling point of 167 - 168 °C (at 2 hPa), and a vapor pressure of 2.13 x 10^{-5} hPa at 25 °C [Directive 92/69/EEC, A.4]. A water solubility and a log K_{OW} are not determinable due to the instability of 4,4'-methylenedicyclohexyl diisocyanate in water. The flash point of 4,4'-methylenedicyclohexyl diisocyanate is 200 °C [DIN 51758], the ignition point is 225 °C and the viscosity is approximately 30 mPa x s at 25 °C [DIN ISO EN 3219/A.3]. The calculated half-life of 4,4'-methylenedicyclohexyl diisocyanate in air due to indirect photodegradation is about 15.0 h.

4,4'-Methylenedicyclohexyl diisocyanate hydrolyses rapidly in the presence of water, the major product in the aqueous phase is methylene bis(4-cyclohexylamine). In water, a half-life for 4,4'-methylenedicyclohexyl diisocyanate of approximately 2 hours was determined experimentally. Due to the rapid hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate, a transport of the substance between environmental compartments is unlikely. Consequently, a calculation of the Henry Law Constant and of the distribution between the environmental compartments according to the Mackay fugacity model level 1 is not suitable.

However, several aquatic toxicity tests have been undertaken with 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products. Because of the rapid hydrolysis the assessment of the substance should be based on the hydrolysis products and not on 4,4'-methylenedicyclohexyl diisocyanate. The hydrolysis product methylenebis-p-cyclohexylamine was assessed by the EU PBT Working Group. The hydrolysis product was not classified as a PBT substance.

4,4'-Methylenedicyclohexyl diisocyanate is not readily biodegradable.

Due to the rapid hydrolysis 4,4'-methylenedicyclohexyl diisocyanate is neither persistent in the water compartment nor bioaccumulative. The calculated K_{oc}-value indicates that 4,4'-methylenedicyclohexyl diisocyanate may strongly adsorb to soil but due to its rapid hydrolysis any emission to the terrestrial compartment would be affected by humidity and therefore, geoaccumulation of 4,4'-methylenedicyclohexyl diisocyanate is not expected to occur.
Concerning the toxicity of 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products towards aquatic species, reliable experimental results of tests with fish, *Daphnia*, and algae are available (* = determined as TOC and back-calculated to parent substance, n = nominal concentration).

Danio rerio (fish):	96 h-LC_{50} > 8.1 mg/l*,	[Directive 92/69/EEC, C.1]
Daphnia magna (aq. invertebrate):	48 h-EC_{50} > 8.3 mg/l*,	[Directive 92/69/EEC, C.2]
Scenedesmus subspicatus (algae):	72 h-E_rC_{50} > 5 mg/l*,	[Directive 92/69/EEC, C.3]
Activated sewage sludge (bacteria):	3 h-EC_{50} = 191 mg/l (n),	[Directive 88/302/EEC, Part C (corresponds to the OECD TG 209)].

It has to be considered that the toxicity observed in the reported aquatic studies was caused both by the 4,4'-methylenedicyclohexyl diisocyanate as well as by the hydrolysis products due to the instability of the test substance.
Based on the acute aquatic toxicity data on three trophic levels (fish, *Daphnia*, algae), the Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000 applied to the lowest acute effect concentration. The lowest 72 h-E_rC_{50}-value of > 5 mg/l obtained for the alga species *Scenedesmus subspicatus* was used to derive a $PNEC_{aqua}$ of > 5 µg/l.

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.

Exposure

Commercial 4,4'-methylenedicyclohexyl diisocyanate manufacturing starts with hydrogenated methylenedianiline (methylenebis-p-cyclohexylamin) which is phosgenated. The global production capacity of 4,4'-methylenedicyclohexyl diisocyanate is 10 000 - 20 000 tonnes/a, with most of it in the USA. In Germany, the only producer has a manufacturing capacity of 1000 - 5000 tonnes/a of 4,4'-methylenedicyclohexyl diisocyanate.

4,4'-Methylenedicyclohexyl diisocyanate is an intermediate in the chemical industry, used for the manufacture of binders or hardeners for coating materials or adhesives (60 %), prepolymers (20 %), and for other applications, e.g. for the production of elastomers (20 %). 4,4'-Methylenedicyclohexyl diisocyanate is not used for "Do It Yourself" applications or in other consumer products. 4,4'-Methylenedicyclohexyl diisocyanate is registered as a component in approximately 50 industrial products listed in the Danish, Finnish, and Swedish Product Registers with a consumption of about 30 tonnes/a in 2000 and 2001 (last years of record). 4,4'-Methylenedicyclohexyl diisocyanate is confidentially listed in the Norwegian Product Register. There is no registration for a consumer product. The main use category is "non-dispersive use". For 4,4'-methylenedicyclohexyl diisocyanate the Swiss Product Register lists 34 industrial products (with concentrations of up to 100 % 4,4'-methylenedicyclohexyl diisocyanate), but no consumer product.

By the producer in Germany, 4,4'-methylenedicyclohexyl diisocyanate is manufactured and processed (including filling) in closed systems at the same industrial site. To the customers most of the 4,4'-methylenedicyclohexyl diisocyanate is transported in ISO containers, and to a minor part, in drums.

During 4,4'-methylenedicyclohexyl diisocyanate manufacturing and processing, virtually no 4,4'-methylenedicyclohexyl diisocyanate (< 25 kg/a) is emitted into the atmosphere from the Bayer plants. Waste from the manufacturing and processing of 4,4'-methylenedicyclohexyl diisocyanate is disposed off in an incinerator for hazardous wastes. Due to wastewater-free manufacturing and processing, and to rapid hydrolysis, no emissions into the aquatic environment are expected.

Surveys of the workplaces have been performed also according to German Technical Guidance TRGS 402, TRGS 430, and TRGS 900 by the producer in Germany. To protect workers from exposure, several precautionary and protective measures are taken, e.g., sampling takes place in a widely closed system. In Germany for occupational settings, the maximum permissible concentration for 4,4'-methylenedicyclohexyl diisocyanate is 0.054 mg/m³. At the producer in Germany, all exposure data were below the maximum permissible concentration.

No environmental monitoring data have been identified. Traces of 4,4'-methylenedicyclohexyl diisocyanate (up to 2 µg/m^3) were detected as a thermolytic degradation product during joint welding of polyurethane floor covering in a small room with no ventilation.

The exposure of consumers to 4,4'-methylenedicyclohexyl diisocyanate is unlikely to occur, because no consumer product is known to contain 4,4'-methylenedicyclohexyl diisocyanate. An exposure via the environment is also unlikely to occur because there are virtually no emissions of 4,4'-methylenedicyclohexyl diisocyanate, and 4,4'-methylenedicyclohexyl diisocyanate released to environment would rapidly be degraded by photooxidants and water.

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.

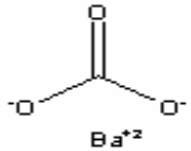
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (severe irritation of skin, eye and respiratory tract, sensitization of skin and predicted to be a respiratory tract sensitizer because it is a diisocyanate). Based on data presented by the Sponsor country (relating to production by one producer which accounts for approximately 5 % to 50 % of global production and relating to the use pattern in several OECD countries), occupational exposure is anticipated to be low and there are no known consumer uses. 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 (including its hydrolysis products) 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 approximately 5 % to 50 % 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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	513-77-9
Chemical Name	Barium carbonate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The toxicity of barium compounds depends on their solubility. Barium carbonate is less soluble than barium chloride. Since the toxicity of barium salts is mainly depending on the Ba^{2+} ion, barium carbonate is less toxic than barium chloride. So in nearly all sections the studies of barium chloride are used as surrogate to estimate the toxicity of barium carbonate. Distribution studies in rats showed barium, as chloride or carbonate, to be rapidly absorbed and distributed. 24 Hours after gastric intubation of barium chloride to rats, tissue concentrations ranked in the order of heart > eye > skeletal muscle > kidney > blood > liver, indicating retention in some tissues. Following intra-muscular injection of barium carbonate to rats, barium carbonate left the injection site very rapidly but resided in the bones with a biological half-life of 460 days.

Barium is not an essential element in human tissues. The metabolism of barium in mammals has been shown to be similar to calcium and strontium (all group II metals). The principal physiological activity of barium is stimulation of all types of muscles, irrespective of their innervations. The average daily human intake of barium is about 1.3 mg (0.65 - 1.7 mg). The human adult body contains 22 mg of barium of which 66 % is present in bones and estimated to have a half-life of 50 days. Excretion of barium is both fecal and urinary. Within 24 hours, 20 % of an ingested dose appears in feces and 5 - 7 % is excreted via the urine. Injection of a soluble barium salt results in increased urinary excretion compared to an ingested dose, but fecal excretion is still greater. Within 21 days, 90 % of the dose is excreted in a 1:9 ratio of urine vs. feces. Barium is found in newborn babies at concentrations higher than in adults; it crosses the lactational and placental barriers.

The acute oral LD_{50} of barium chloride in rats is 419 (males) and 408 (females) mg/kg bw. Ninety percent of deaths occurred within 5 hours of administration, and hemorrhagic areas in the stomach and inflammation of the intestines were observed in the primary necropsy. A second single dose study was conducted at three dose levels of 30, 100 and 300 mg/kg bw. At 300 mg/kg, 8 of 10 males and 7 of 10 females died within 24 hours, and the effects on body, liver and kidney weights after a single dose of 300 mg/kg bw appeared to be related to barium chloride. The same symptoms of the small and large intestines observed in the previous study (to determine the median lethal dose) were also seen at the high dose in both sexes. There were no chemical-related changes at doses of up to 100 mg/kg bw. Studies in dogs with infused barium chloride demonstrated the toxicity of barium ion, which is relevant to barium carbonate. The data showed that barium caused a reduction in plasma potassium, resulting in hypokalaemia and that barium also caused hypertension. There were no reliable animal acute toxicity studies by dermal and inhalation routes available.

The barium carbonate poisoning in humans initially stimulates striated, cardiac and smooth muscles and depresses serum potassium, which is forced intracellularly. Subsequent muscle weakness may result from a direct depolarizing

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.

effect and neuromuscular blockade. Symptoms are vomiting, severe abdominal pain, diarrhea, slow irregular pulse, muscle paralysis, dilated pupils, increasing somnolence, and cardiac arrest.

No reliable skin/eye irritation and skin sensitization studies were available.

In repeated dose toxicity studies, barium chloride dihydrate was given to F334/N rats and $B_6C_3F_1$ mice in drinking water for 13 weeks at concentrations of 0, 125, 500, 1,000, 2,000 and 4,000 ppm. The NOAEL value was estimated to be approximately 2,000 ppm, corresponding to an average daily dose of 110 and 115 mg Ba/kg bw to male and female rats, respectively, and 205 and 200 mg Ba/kg bw to male and female mice, respectively. This was based on mortality, decreased final mean body weights and mean body weight gains, decreased water consumption and renal toxicity. A similar study was conducted in the same species with the same concentrations of barium chloride dihydrate in drinking water for 92 days. The NOAEL of this study was 2,000 ppm (rats: 61 – 81 mg Ba/kg bw/day, mice: 165 – 166 mg Ba/kg bw/day) in the drinking water (based on depressed body weight gains and chemically related lesions in the kidney and lymphoid tissue for both species).

There are no *in vitro* or *in vivo* genotoxicity studies and no carcinogenicity studies of barium carbonate available. However, a number of in vitro genotoxicity studies of barium chloride dihydrate were conducted. Barium chloride dihydrate showed negative results in a bacterial reverse mutation test with *Salmonella typhimurium* strains (TA 97, TA98, TA100, TA1535 and TA1537) with and without S9 at concentrations of up to 10,000 µg/plate. In contrast, barium chloride dihydrate at concentrations of 250 µg/ml and above induced gene mutation at L5178Y mouse lymphoma cells in the presence of S9 mix while mutagenic activity was not observed without S9 mix. *In vitro* tests for sister chromatid exchange and chromosome aberration in Chinese hamster ovary (CHO) cells showed that barium chloride dihydrate did not induce chromosome changes up to the concentration of 3,000 µg/mL with or without S9 mix. No *in vivo* genotoxicity data was available. In conclusion, all except one *in vitro* genotoxicity studies were negative. The mouse lymphoma test gave an equivocal result only in the presence of an S9 activation system.

Concerning the carcinogenic potential, there was no evidence of carcinogenic activity of barium chloride dihydrate in drinking water to either sex of rats or mice that received up to 2,500 ppm for 2 years, corresponding to an average daily dose of 60 and 75 mg Ba/kg bw to male and female rats, respectively, and 160 and 200 mg Ba/kg bw to male and female mice, respectively.

Concerning the effect of Barium on reproduction and fetal development, the NOAEL for barium chloride dihydrate on fertility and developmental toxicity was 4,000 ppm for rats (the average dose was 201.5 mg Ba/kg bw/day for males and 179.5 mg Ba/kg bw/day for females) and 2,000 ppm for mice (the average dose was 206 mg Ba/kg bw/day for males and 199.8 mg Ba/kg bw/day for females). There were no treatment-related effects on pregnancy rates, pup survivals, pup weights, external abnormalities in both species except rats receiving 4,000 ppm exhibited marginal reduction in pup weights. No effect of barium chloride dihydrate could be detected on epididymal sperm counts, sperm motility, sperm morphology, testis or epididymal weight or vaginal cytology in either species up to 4,000 ppm in rats and 2,000 ppm in mice.

Environment

Barium carbonate is an odorless white inorganic solid. It occurs in nature as the mineral witherite. It is soluble in water at 24 mg/L at 25 °C, soluble in acids (except sulfuric acid) and in ethanol. It has a density of 4.3 g/cm^3 at 20 °C and negligible vapor pressure.

There is no evidence that barium carbonate undergoes environmental biotransformation other than dissolving to a divalent cation. Photodegradation and biodegradation are not relevant transformation processes. Under natural conditions barium will form compounds in the +2 oxidation state. Environmental fate modelling cannot be performed with the available data. Soil adsorption of barium was studied in a sandy soil and a sandy loam soil. Sludge solutions appeared to increase the mobility of elements in soil. Barium adsorption in algae increased proportionally with decreasing barium concentration in the medium. Bioconcentration of barium in fish was studied. BCF value for *Lepomis macrochirus* in male carcass was 74.4 (ug/g wet weight of bluegill tissue)/(ug/mL unfiltered water) so barium has a low potential for bioaccumulation.

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.

In an acute toxicity test with barium carbonate on *Gambusia affinis*, a 96 hour TLm of >10,000 mg/L was determined. For *Daphnia magna*; a 48 hour EC_{50} of 32 mg/L was determined with barium. Barium was phytotoxic to the common duckweed, the 96 hour IC_{50} varying from approximately 100 mg/L to > 400 mg/L barium, the variability dependent upon site-specific water quality and in particular, the sulfate concentration. Chronic toxicity to aquatic organisms was studied. In a static renewal test using rainbow trout embryos and larvae, 4 day LC_{10} and LC_1 values of 9.5 and 2.8 mg/L were determined for barium (salt not specified). 30 day LC_{50} values of *Orconectes limosus* and *Austropotamobius pallipes pallipes* (crayfish) for barium chloride were 59 mg/L and 39 mg/L, respectively. 21 days LC_{50} value of *Daphnia magna* for barium chloride was 13.5 mg/L.

Exposure

Barium is the 16th most abundant non-gaseous element of the Earth's crust, constituting approximately 0.04 %. The two most prevalent naturally occurring barium ores are barite (barium sulfate) and witherite (barium carbonate).

In 2001, 542,000 tonnes of barium carbonate were produced globally. In Korea the estimated production volume of barium carbonate was 26 626, 10 681, and 16 452 tonnes/year in 2002, 2003, and 2004, respectively.

Barium carbonate has a wide variety of uses; it is used in the production of television glass, crystal glass and special glass, frits and enamels, brick and tile, ceramic, magnets, electrodes, barium salts, paper, rubber, marble substitute and paints. It is also used for removing sulfates mainly in phosphoric acid production and chlorine alkali electrolysis and it is used as a rodenticide, an additive for glaze, an analytical reagent, oxidizing agent and filler.

In the production and processing facilities, workers might be exposed to barium carbonate dust by inhalation during handling, mixing or packaging the raw material. But in Korea and the EU, occupational exposure is controlled with personal protective equipments like goggles and dust filter masks and with ventilation. Korea has periodically collected monitoring data of occupational exposure. Based on the monitoring data from glass manufacturing factories, air concentration levels of total dust for workplace were less than 0.4 mg/m^3, which was below the permissible exposure limit of 10 mg/m^3 in Korea. In addition, the recorded airborne barium ranged from 0.0002 to 0.0004 mg/m^3, which is below the American Conference of Governmental Industrial Hygienists Threshold Limit Value (0.5 mg Ba/m^3).

The legal emission limits for barium carbonate range from 20 to 660 mg/m^3 for dust to air depending on the geographic location. There is no limit for waste to water outside a production plant.

The general population is exposed to barium primarily through ingestion of drinking water and consumption of food and beverages. Concentration of barium in seawater is 6µg/L and in fresh water 7 – 15,000 (average 50) µg/L. Ambient barium concentrations ranged from 0.0015 to 0.95 µg mg /m^3 in a USA survey. Barium concentrations of < 0.005 to 1.5 µg mg /m^3 have also been detected in the air of 18 cities and 4 suburban areas in the USA. Barium content in milk was found to range between 45 and 136 ug/g and in edible crops ranges from 10 ug/g in wheat to 3 - 4 mg/g in brazil nuts.

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

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health and the environment. These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure level. They should nevertheless be noted by chemical safety professionals and users.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	60-24-2
Chemical Name	2-Mercaptoethanol
Structural Formula	$C_2 H_6 O S$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No data are available on toxicokinetics and metabolism of 2-mercaptoethanol in experimental studies. However, systemic toxic effects after exposure via different application routes suggested absorption and distribution after oral and dermal administration. The metabolite 2-mercaptoacetate was detected in the urine of a person who died from ingesting 2-mercaptoethanol.

The LD_{50} was 131 mg/kg bw in rats after acute oral exposure (OECD TG 401). The estimated LC_{50} after 4-hour inhalation exposure of rats was ca. 2000 mg/m^3. In rabbits the LD_{50} after acute dermal exposure to 2-mercaptoethanol was 251 mg/kg bw. The clinical signs of systemic toxicity were mainly sedation, tremor and convulsions.

2-Mercaptoethanol was moderately irritating to rabbit skin in a 4-hour occlusive patch test. 2-Mercaptoethanol is corrosive to the rabbit eye, which was tested in studies according to the principles of the Draize test. Skin sensitizing effects were reported in a guinea pig maximization test (OECD TG 406).

In a study according to OECD TG 422 and 407 repeated oral application of 2-mercaptoethanol at 15, 50 and 75 mg/kg bw/day via gavage to rats for ca. 7 weeks resulted in clinical symptoms (excessive salivation, decreased body weight in males) and effects on the liver (organ weight increased and vacuolated liver cells in both genders) and the heart (degenerative cardiomyopathy in females at 50 and 75 mg/kg bw/day, in males at 75 mg/kg bw/day). The NOAEL was 15 mg/kg bw/day. 2-Mercaptoethanol neither induces gene mutation in *Salmonella typhimurium* nor chromosome aberration in human lymphocytes, both endpoints investigated in studies according to current guidelines (OECD TG 471 and 473, respectively). No mutagenic activity was detected in a mouse lymphoma assay (limited validity). Negative results were also obtained in a yeast recombination/mutation assay. Inconsistent results were reported in sister chromatid exchange (SCE) assays with CHO cells. No aneuploidy but an increased incidence of polyploid cells was observed in *in vitro* test systems indicating interaction with proteins or enzymes involved in mitosis. The *in vivo* micronucleus assay according to OECD TG 474 revealed no damage to the chromosomes or the mitotic apparatus of mouse bone marrow cells. Overall, available data showed no effects in gene and chromosome mutation assays, but revealed some evidence of polyploidy- inducing effects *in vitro*.

In a combined repeated dose toxicity study with the reproductive/developmental toxicity screening test (OECD TG 422, data on repeated dose toxicity see above) no effects were recorded on mating and fertility at 15 mg/kg bw/day. Doses of $\geq$ 50 mg/kg bw/day, which also induced general toxicity in males and females, prolonged the gestation

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.

period and/or affected delivery, with death of pregnant rats. The NOAEL for general toxicity, maternal toxicity, parturition and development of progeny is 15 mg/kg bw/day. The NOAEL for male reproductive performance and fertility is 75 mg/kg bw/day. The reproductive effects are not suitable for the differentiation between effects on female fertility and developmental effects. No data are available on carcinogenicity.

Environment

2-Mercaptoethanol is miscible with water. The substance has a vapour pressure of ca. 2 hPa at 25 °C, and a measured log Kow of –0.056 at 25 °C. The distribution modelling using Mackay, Level I, indicates water to be the almost exclusive (99.7 %) target compartment at 25°C. The calculated Henrys Law Constant of $1.29 * 10^{-2}$ Pa*m³/mol indicates a low to moderate potential for volatilization from aqueous solution. The substance has a low potential for bio- and geoaccumulation. 2-Mercaptoethanol is not readily biodegradable according to OECD criteria. There is evidence for abiotic degradation in water. The half-life was influenced by the pH and temperature. At a constant temperature of 20 °C and pH 8.5 the half-life was 4 h, at a pH of 7.5 the half-life increased to 10 h, at a pH of 6.5 to > 100 h. The reaction of hydroxyl radicals with 2-mercaptoethanol in aqueous solution is insignificant. The substance is photodegraded by reaction with hydroxyl radicals ($0.5 * 10^6$ molecule/cm³) in the atmosphere with an estimated half-life of 8.4 h. No information on direct photodegradation is available.

The following effect values are available from the short-term tests on aquatic species with fish, invertebrates and algae:

Leuciscus idus LC_{50} (96 h) = 37 mg/l
Daphnia magna EC_{50} (48 h) = 0.4 mg/l
Desmodesmus subspicatus E_rC_{50} (72 h) = 19 mg/l. (E_bC_{50} = 7.0 mg/l after 72 h)

For microorganisms (*Pseudomonas putida*) an EC_{50} (17 h) = 125 mg/l was determined.

A $PNEC_{aqua}$ = 0.4 µg/l can be calculated based on the lowest toxicity value (EC_{50} = 0.4 mg/l) for aquatic invertebrates (*Daphnia*) with the assessment factor of 1,000.

Exposure

In the EU there are three known producers of 2-mercaptoethanol. The production volume in the EU in the year 2003 was about 10,000 to 15,000 tonnes/year. Further producers of 2-mercaptoethanol are known in China (4), Mexico (1) Japan (1) and in the US (1) but no data on production volumes are available.

By far the largest use of 2-mercaptoethanol (≥ 90 %) is the use under controlled conditions as an intermediate in the synthesis of organo-tin thermal stabilizers for plastics (polyvinyl chloride). After two steps of reactions 2-mercaptoethanol is entirely consumed.

App. 10 % of the total 2-mercaptoethanol production volume is either used as regulator in polymerization processes consumed by reacting with the polymer chain or as chain transfer agent and used as lab chemical (e.g. reduction agent in immune biochemistry). 2-Mercaptoethanol is also used as an intermediate for the synthesis of pickling agents for seed and as textile auxiliaries. Less than 1 % is transferred to the sodium salt and used as additive in low percentages at an early stage of the leather production process (de-hairing). This de-hairing process is performed at a pH > 9. After this first leather manufacturing step the waste is collected and separately totally oxidized to sulphate, sulphur and sulphite by catalytic aeration treatment. 2-Mercaptoethanol, sodium salt does not reach the aquatic environment via the industrial effluents – as it is either consumed as intended during the de-hairing process or abiotic degraded under the alkaline conditions. (Di)Sulphides are formed by reaction with the keratinic materials or by abiotic degradation. The sulphides are totally oxidized during the final step of the de-hairing process or during the pre-treatment step of the sewage formed.

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.

During production, transport and processing of 2-mercaptoethanol releases into the environment may occur accidentally. Significantly less than 25 kg are emitted in 2000 to the atmosphere from production and processing sites at BASF AG and no 2-mercaptoethanol loaded sewage was formed. Exposure of operators/workers can be as far as possible avoided due to a manufacturing process in closed system and due to efficient personal protective equipment. During cleaning and maintenance procedures formed sewage is collected and disposed by combustion. Further exposure information from other production sites and processing sites is not available.

It can be summarized that the European Product registers provide no evidence for the presence of 2-mercaptoethanol in consumer products. All entries of 2-mercaptoethanol containing products are found in the categories of industrial uses apart from one finding in the category "health, education and welfare". The known and recommended uses according to all 2-mercaptoethanol producers are listed above. At BASF the requirements of the chemical weapon convention are voluntary fulfilled for 2-mercaptoethanol. All customers are obliged to declare the uses of 2-mercaptoethanol and are assessed for their reputability. Reputability assessments also take place at all producers. The CWC regulation applies to all customers in Germany, Europe and outside of Europe and along the chain of downstream users. No industrial use entries of 2-mercaptoethanol products in the product registers are raising questions and doubts at the producers.

2-Mercaptoethanol was tabulated among 30 different thiols (mainly methanthiol and 3-mercaptopropionates) detected in reducing, intertidal sediments from Biscayne Bay (Florida, USA), the concentration ranges between 0.5 - 20 µM. Thiols arise as a result of biotic and abiotic reactions.

At all possible scenarios exposure is limited by the very strong, disagreeable odor similar to hydrogen sulfide (odour threshold ≤ 2 mg/m³).

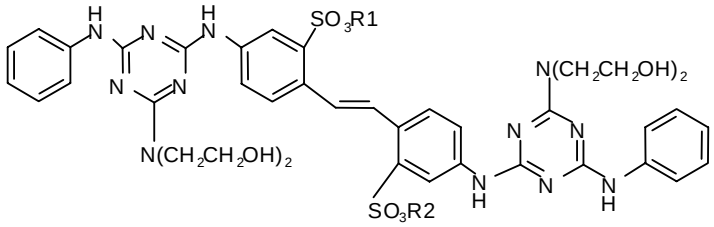
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. 2-Mercaptoethanol possesses properties indicating a hazard for the human health (irritating to the skin and corrosive to the eye, sensitisation, some evidence on polyploidy inducing effects *in vitro*, toxic after acute and repeated exposure, developmental and reproductive toxicity in the range of maternal general toxicity). Based on the data presented by the Sponsor country (relating to production by one producer and the use pattern in several OECD countries), the chemical is therefore strictly controlled in occupational settings, and any repeated or prolonged exposure of workers is practically excluded. Warning of possible exposure is given by the quality of odour and the odour threshold (0.4 - 2 mg/m³). Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

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 and 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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos. and Chemical Names	70942-01-7 Potassium sodium 4,4'-bis[6-anilino-4-[bis(2-hydroxyethyl)amino]-1,3,5-triazin-2-yl] amino]stilbene-2,2'-disulphonate (C.I. Fluorescent Brightener 28/113) 71230-67-6 Dipotassium salt 4,4'-bis[6-anilino-4-[bis(2-hydroxyethyl)amino]-1,3,5-triazin-2-yl] amino]stilbene-2,2'-disulphonate 4193-55-9 Disodium salt 4,4'-bis[6-anilino-4-[bis(2-hydroxyethyl)amino]-1,3,5-triazin-2-yl] amino]stilbene-2,2'-disulphonate 4404-43-7 Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis[5-[[4-[bis(2-hydroxyethyl)amino]-6-(phenylamino)-1,3,5-triazin-2-yl]amino]-
Structural Formulas	 70942-01-7: R1 = K; R2 = Na 71230-67-6: R1 = R2 = K 4193-55-9: R1 = R2 = Na 4404-43-7: R1 = R2 = H

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rational

C.I. Fluorescent Brightener 28/113 is a technical product which is manufactured as the potassium/sodium salt (CAS No. 70942-01-7), dipotassium salt (CAS No 71230-67-6), disodium salt (CAS No. 4193-55-9), and free acid (CAS No. 4404-43-7). All these types of C.I. Fluorescent Brightener 28/113 are based on the identical organic disulfonates which determines the ecological and the toxicological properties. Additionally there are a number of very similar fluorescent whitening agents with only minor differences of the structure and very similar physical and chemical properties. Data from these substances have been used to bridge possible data gaps in the section “Human health”: (C.I. Fluorescent Brighteners 24, 220, 225, and the Fluorescent Brightener 4,4´-bis[4-anilino -6-[(2-hydroxyethyl)methyl-amino]-s-triazin-2-yl)amino]2,2´-stilbenedisulphonate = CAS No. 12224-02-1, 16470-24-9, 24019-80-5, and 13863-31-5, respectively).

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.

Human Health

The results of absorption/elimination/metabolism studies indicate virtually no absorption from the gut of the Fluorescent Brightener with CAS 13863-31-5 (chemical name see above) a chemically similar compound to C.I. Fluorescent Brightener 28/113. For this compound the faeces were the main elimination route. It is not metabolized in the gut. The excretion rate is solely dependent on the passage time through the gut.

The oral LD_{50} of C.I. Fluorescent Brightener 28/113 for rats is > 15 000 mg/kg bw. The acute inhalation toxicity study showed a reversible and sporadic reduction of general health after 4 hours exposure to > 1225 mg/m³ of rats. No pathological changes were seen in these animals. The 4h-LC_{50} value was > 1895 mg/m³ air.

No indication for skin irritation was seen in several rabbit studies (24-hour semi-occlusive or occlusive applications of 500 mg) or in the available human data. Slight signs of eye irritation were recorded in one of three studies.

The C.I. Fluorescent Brightener 28/113 is considered not to be a skin sensitizer in a guinea pig maximization assay according to Directive 84/449/EEC, B.6. Acute toxicity (skin sensitization).

Dermal application (90 weeks) on male mice (3 times/week, 50 µl, 7.8 %) revealed no toxicity. Two 2 years oral feeding studies in rats with the C.I. Fluorescent Brightener 28/113 were performed. The NOEL for male rats was 54.1 mg/kg bw and day in one study (only slight reduction of body weight), the NOAEL for female rats was ≥ 779 mg/kg bw and day, the NOAEL for male rats was ≥ 542.80 mg/kg bw/day. In the second study the NOAEL for female rats was ≥ 10 000 ppm (app. 500 - 1000 mg/kg bw /day). The NOEL for male rats was < 100 ppm because of an increased relative liver weight (up to 35 % at 10 000 ppm) in male rats considered as adaptive effect. The NOAEL for male rats is considered to be ≥ 10 000 ppm, however, this is a borderline case.

C.I. Fluorescent Brightener 28/113 is considered to be non-mutagenic as determined in vivo in a dominant lethal test with mice or in vitro up to 5000 µg/plate in *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and the *Escherichia coli* strain WP2 uvrA according to OECD TG 471. An in vitro cytogenetic study (chromosomal aberrations and sister chromatid exchanges) in Chinese hamster cells with a structurally very similar Fluorescent Brighteners (C.I. Fluorescent brighteners 24, and 225 = CAS No. 12224-02-1, and 24019-80-5) showed that these substances did not exhibit a potential to induce chromosomal aberrations nor sister chromatid exchanges. Another report describing the results of several tests in structurally very similar Fluorescent Brighteners (C.I. Fluorescent Brighteners 24, and 225 were tested) without giving experimental details (Ames Test in TA 100 TA 98; rec assay in *Bacillus subtilis*; Chromosomal aberrations in hamster lung fibroblasts and human embryo fibroblast; SCE in hamster lung fibroblasts and human embryo fibroblasts; chromosomal aberrations in rat bone marrow in vivo) confirmed the findings. Additionally no indication of mutagenic potential was found in the carcinogenicity studies conducted with these substances.

No indication for a carcinogenic potential of the C.I. Fluorescent Brightener 28/113 was seen, neither after dermal administration (3 times/week, up to 50 µl, 7.8 %) to mice on irradiated skin, nor after chronic oral administration (up to 10 000 ppm) to rats respectively.

A study available as secondary citation only described C.I. Fluorescent Brightener 28/113 as having no effect on reproduction and teratogenicity. In addition, well documented lack of effects on reproduction in rats and rabbits were reported for the chemically related optical brightener C.I. Fluorescent Brightener 220 (CAS 16470-24-9). These reports support the notion for C.I. Fluorescent Brightener 28/113 to have no effects on fertility, developmental and teratogenic properties.

Environment

C.I. Fluorescent Brightener 28/113 (K/Na- and Na_2-salts) is a yellowish solid without odour, with a melting point of 322 °C (K/Na-salt), 260 °C (Na_2-salt), and 290 °C (free acid). According to the structure of the substance and to decomposition starting at 351 °C, boiling point and vapor pressure are not measurable. The substance is soluble in

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.

water with 27.1 g/l (K/Na-salt, at 20 °C [OECD TG 105]), 50 g/l (Na_2-salt, at 20 °C), and 80 g/l (free acid, at 25 °C). The bulk density of the Na_2-salt is 340 kg/m³. A log K_{OW} of 3.23 is estimated for the undissociated form of the free acid and a log K_{OW} of limited value of 0.65 for the salts of C.I. Fluorescent Brightener 28/113.

The calculated half-life of the C.I. Fluorescent Brightener 28/113 in air due to indirect photodegradation is $t_{1/2}$ = 1.2 hours.

C.I. Fluorescent Brightener 28/113 is not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups.

The calculation of the distribution of C.I. Fluorescent Brightener 28/113 between the environmental compartments according to the Mackay fugacity model level 1 and of the Henry's Law Constant are not practicable with the EPIWIN estimation program. From the physico-chemical properties it can be concluded that the sole target compartment for C.I. Fluorescent Brightener 28/113 is water. However, as a high adsorption to soil was calculated, it has to be assumed that the substance will strongly adsorb also to the sediment and soil compartments.

For C.I. Fluorescent Brightener 28/113 (free acid) biodegradation < 10 % during 28 days was determined in a Closed Bottle test [method similar to OECD TG 301D]. However, the elimination of the substances from waste water was shown by a Zahn-Wellens test according to OECD TG 302B. The elimination by adsorption was 83.6 % after 24 hours. In an OECD Confirmatory test (later modified to OECD TG 303A) two compounds containing C.I. Fluorescent Brightener 28/113 (Na_2-salt) showed a mean degradation rate of 11 % during 28 days and 56 % during 31 days, respectively. Based on these results, C.I. Fluorescent Brightener 28/113 can be classified as not readily biodegradable but elimination by adsorption is significant.

The calculated bioconcentration factor of 3 indicates no significant bioaccumulation potential in aquatic organisms via the water phase. Bioaccumulation from the sediment in benthic organisms due to the high adsorption potential of C.I. Fluorescent Brightener 28/113 cannot be excluded.

No experimental data on geoaccumulation is available. The calculated K_{OC} value of 8.1 x 10^9 for the salts and of 1.4 x 10^9 for the free acid of C.I. Fluorescent Brightener 28/113 indicates a very high sorption potential of the test substance onto the organic phase of soil or sediment.

Concerning the acute toxicity towards aquatic species valid studies for the three trophic levels are available. The lowest valid results for each aquatic trophic level are the following (n = nominal):

Danio rerio (fish):	96 h-LC_{50} = 5382 mg/l (n)	[OECD TG 203]
Daphnia magna (aq. invertebrate):	48 h-EC_{50} > 100 mg/l (n)	[Directive 92/69/EEC, C.2]
Selenastrum capricornutum) (algae):	72 h-E_rC_{50} > 22 mg/l (n)	[Directive 92/69/EEC, C.3]
Selenastrum capricornutum) (algae):	72 h-E_bC_{50} > 22 mg/l (n)	[Directive 92/69/EEC, C.3)
Activated sludge (bacteria):	3h-EC_{50} > 10 000 mg/l (n)	[OECD TG 209)]

No tests are available on chronic toxicity and on toxicity of C.I. Fluorescent Brightener 28/113 on sediment organisms.

For terrestrial organisms reliable experimental data are available with earthworms. A 14 d-LC_{50} of > 5000 mg/kg soil dry weight (n) was determined with the OECD TG 207.

Based on the acute aquatic toxicity data on three trophic levels (fish, *Daphnia*, algae), a Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000 (EU Technical Guidance Document) applied to the lowest concentration tested of 22 mg/l towards algae, as no EC_{50} value could be determined at this level and the LC_{50} for *Daphnia* and fish was found at higher concentrations. This leads to a **$PNEC_{aqua}$ of > 22 µg/l.**

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.

Exposure

In Germany there is only one manufacturer, which produces 1000 - 5000 tonnes/a of C.I. Fluorescent Brightener 28/113. In Western Europe there are about 5 producers, and presumably one in each of the following countries: USA, Japan, Russia, Poland, India, China, and Indonesia. Worldwide, 10 - 20 producers manufacture about 5000 - 10 000 tonnes/a of the active ingredient of C.I. Fluorescent Brightener 28/113.

C.I. Fluorescent Brightener 28/113 is exclusively used as a whitening agent in the paper and textile industry. It can also be used for brightening of polyamides.

C.I. Fluorescent Brightener 28/113 is confidentially listed in the Swedish Product Register as an industrial product in 2004. C.I. Fluorescent Brightener 28/113 and its salts are also listed in preparations in Sweden, Denmark, and Norway, but they are not reported to occur in consumer preparations in the Nordic countries in 2003 and in the Swiss Product Register in 2006. They are not listed in the Finnish Product Register Disodium salt 4,4'-bis[6-anilino-4-[bis(2-hydroxyethyl)amino]-1,3,5-triazin-2-yl]amino]- stilbene-2,2'-disulphonate is listed with 4 industrial products in the Swiss Product Register.
From the manufacturing site of the Sponsor country virtually no C.I. Fluorescent Brightener 28/113 was emitted into the environment in 2000. Workplace air sampling shows that there is no exposure of workers at this site.

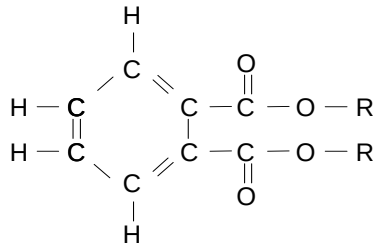
Releases into the hydrosphere may occur during processing of textiles and paper as well as during paper recycling and washing of treated textiles during cleaning processes. C.I. Fluorescent Brightener 28/113 is effectively eliminated predominantly by adsorption onto sludge from wastewater streams during secondary and tertiary wastewater treatment.

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

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	71888-89-6
Chemical Name	1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich (diisoheptyl phthalate ester)
Structural Formula	$C_{22}H_{34}O_4$ (based on di-C7 alkyl groups) Diisoheptyl phthalate ester has the following basic structure with R = C_6H_{13} to C_8H_{17} (primarily C_7H_{15}), where R is an alkyl group that can have various methyl branching patterns (the linear portion of the alkyl group can be referred to as the backbone of this moiety):  DIHP consists of at least 80% of methyl hexyl phthalate. Therefore the backbone (i.e. the longest linear C- chain) is predominantly C6. The methyl group branching can be found on different C positions of the hexyl backbone chain.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

DIHP has a low order of acute toxicity (oral LD_{50} greater than 10 mg/kg bw; dermal LD_{50} greater than 3.16 g/kg bw), is mildly irritating to the skin and eyes, is neither a skin nor a respiratory sensitiser, and is not mutagenic.

No repeated dose toxicity studies are available for DIHP. However a two-generation reproductive toxicity study has been conducted in rats (1000, 4500, or 8000 ppm in the diet for 70 days, prior to mating and through mating, gestation, and lactation periods) which can be used to evaluate this endpoint. No treatment related changes were observed in body weights, clinical observations or food consumption. The target organs were the testis, liver and the kidneys. There were no organ weight or pathological changes in rats of either sex at the 1000 ppm level. Therefore, this level has been selected as the NOAEL for the systemic toxicity and equates to an overall average dose to the males of 64 mg/kg bw/day. The average doses to the females were approximately 84 mg/kg bw/day during the premating period, 64 mg/kg bw/day during the mating period, and 162 mg/kg bw/day during lactation.

Reproductive effects in this two-generation study included decreased reproductive performance and fertility for both sexes in the F_1 generation at the highest dose level. Decreased mean sperm production rates and decreased testicular sperm concentration were observed in F_1 males, but this finding may have been an experimental artifact rather than a treatment related effect except in the high dose group. Several other effects such as: reduced anogenital distance, delays in balanopreputial separation, testicular abnormalities, changes in external genitalia, and retention of thoracic nipples were also noted at the highest dose level. Similar effects were also seen in the F_2 generation. Additional

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.

effects included reductions in body weights along with decreased gonadal and spleen weights, and increased kidney, liver, and pituitary weights. There were also dose-related increases in the liver weights and correlating hepatocellular histopathology changes that are indicative of peroxisomal proliferation. The NOAEL for parental systemic toxicity in the F_0 and F_1 generations was 1000 ppm in the diet (in the range of 50 to 162 mg/kg bw/day) based on peroxisomal proliferation in the liver. The overall NOAEL for reproductive effects in males and females was 1000 ppm in the F_2 generation (in the range of 64 to 162 mg/kg bw/day for gestation - lactation periods).

A developmental study conducted on DIHP in rats using oral gavage at doses of 0, 100, 300, and 750 mg/kg bw/day on gestation days 6-20 showed a statistically significant decrease in mean body weight of the 750-mg/kg bw/day dams and increase in liver weights. Changes included an increase in the mean number of resorptions per litter and resorptions per implantation site with a concomitant decrease in live fetuses and live fetuses per implantation site. Fetal weight was significantly reduced and there was an increase in the incidence of fetuses with external, visceral and skeletal malformations compared to controls (9.8 vs. 1.0%). The developmental NOAEL was established at 300 mg/kg bw/day and the maternal NOAEL at 750 mg/kg bw/day. In assays to assess estrogenic activity (screening tests for competitive binding and gene expression using the estrogen receptor *in vitro*, and vaginal cornification and uterotrophic assays assessing estrogenic activities *in vivo*), DIHP showed no positive results.

DIHP was not tested for carcinogenicity.

Environment

Additional data from other similar phthalate ester (PE) substances (analogues) are used in this submission to support diisoheptyl phthalate ester (DIHP) and/or provide additional weight of evidence for select endpoints. The use of read-across data for single substances and within categories or "families" of substances has been used previously within HPV programs. Data from analogue PEs are used to augment the current database for DIHP on the basis that these substances exhibit common physicochemical, ecotoxicological and environmental fate properties.

Furthermore it has been shown that for environmental hazard assessment, it is possible to consider the use of analogue data from among PEs having a backbone alkyl chain length longer than 5 carbons. Indeed, the water solubility of these PEs is so low and no toxicity in fish, invertebrates, and algae is exhibited at their limit of solubility. And also, in general, their data can be applied across the range of increasing/decreasing alkyl side-chain carbon (C) numbers. The validity of applying read-across data for select aquatic toxicity endpoints as is done in this submission, is supported from a review of all directly comparable data for DIHP and the analogues.

To define select biological endpoints, measured analogue data are used from 5 PEs, namely 1,2-Benzenedicarboxylic acid, diheptyl ester or di-nC7 PE linear (CAS RN 3648-21-3), 1,2-Benzenedicarboxylic acid, heptyl undecyl ester, branched and linear or di-C7-11 PE (CAS RN 111381-90-9), 1,2-Benzenedicarboxylic acid, diisooctyl ester or di-C8 PE (CAS RN 27554-26-3), 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester or DEHP (CAS RN 117-81-7), 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich or DINP (CAS RN 68515-48-0).

Diisoheptyl phthalate (DIHP) is a liquid at 25°C with a reported vapor pressure of 9.3×10^{-7} hPa (25°C), water solubility of 0.017 mg/l (22°C), log Kow of 6.9 (25°C), melting point of -45°C, boiling point of 393°C (1,013 hPa), and density of 0.99 g/cm^3 (20°C).

Results of distribution modelling suggest that DIHP will partition primarily to the soil compartment (approximately 98%), with a small amount partitioning to sediment (approximately 2%). Volatilisation to air will not contribute to the loss of DIHP from terrestrial or aqueous habitats because it has a very low vapour pressure. Results of modelling confirm that only a negligible amount of DIHP is calculated to partition to air (<1.0%). However, the small fraction that may partition to air has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals. The DIHP half-life from hydroxyl radical attack is calculated as 7.2 hours (0.6 days based on a 12-hour day as this reaction occurs primarily during daylight hours). Aqueous photolysis and hydrolysis will not contribute to the transformation of DIHP in aquatic environments because it is either poorly or not susceptible to these reactions.

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.

DIHP was shown to be readily biodegradable, based on a 28-day biodegradation study with a test substance concentration of 50 mg/L that resulted in approximately 80% biodegradation. DIHP is expected to sorb to organic matter in soil, sediment, and wastewater solids based on a log K_{oc} of 4.5.

The acute and chronic aquatic toxicity of DIHP has been evaluated using various species covering the three trophic levels. For select endpoints for which DIHP data were not available, which includes the alga endpoint, analogue data from similar substances were used including di-C8 PE and DINP. All studies were conducted by either developing water accommodated fraction (WAF) exposure solutions that were prepared at loading levels (100 or 10 mg/L) above the water solubility of DIHP or testing at concentrations (1 mg/L) using dispersants. On the basis of testing results with DIHP and/or analogues, it can be concluded that DIHP does not produce acute or chronic toxicity at or below its maximum attainable water solubility, which has been measured as 0.017 mg/L.

DIHP showed no effects on seed germination and growth at a concentration of 1000 mg/kg soil. Additionally, DIHP is not expected to be inhibitory to soil microorganisms, based on a respiration study using an analogue phthalate ester (DINP), at test substance/soil loadings as high as 10000 mg/kg soil. DIHP is not expected to exhibit effects to wastewater microorganisms, based on a study using an analogue phthalate ester (DEHP) at a test substance loading of 2000 mg/L that showed no inhibition to respiration in an activated sludge sample.

In the sediment, results obtained with an analogue phthalate ester that contains C7 alkyl groups (di-C7-11PE), showed no effect on survival and growth to two freshwater sediment species at a test substance loading of 3000 mg/kg sediment, suggesting that DIHP is not toxic to benthic organisms.

The potential for DIHP to bioaccumulate in fish is estimated to be low to moderate (BCF from 0.9 to 840), based on OECD Guideline and non-standard testing, on two analogues, di-nC7 PE and DEHP.

Exposure

DIHP production volume is between 20 000 and 200 000 tonnes per annum worldwide, with production sites in both Europe and in the USA.

DIHP is mainly used as an additive (plasticiser) to impart flexibility to polyvinylchloride (PVC) resins, which are largely used in the manufacture of flooring products. Furthermore, DIHP is not used in applications such as medical devices or toys for ethical and technical reasons.

DIHP released from its manufacture, which can occur when cleaning manufacturing systems, enters wastewater treatment facilities where it can be biodegraded or sorbed to sewage sludge.

The majority of PEs found in the environment likely comes from the slow release of these chemicals from polymer products as a result of weathering processes. Indeed, once PEs are produced and used in various products, emissions may occur during the end-use of these products. However, since most PEs are contained within a polymer matrix, emissions are retarded during the life of the polymer product.

Exposure to DIHP in the occupational setting has not been extensively measured but is expected to be low. Area monitoring and personal sampling data have been collected for airborne exposure to two other phthalate esters, e.g. butylbenzyl phthalate (BBP) and DINP, at two flooring manufacturers. The data show that at typical customer sites, measured airborne levels ranged from 0.01 to 1 mg/m^3. As a very conservative basis, assuming exposure at 1 mg/m^3 for 8 hours and 10 m^3 inhaled during a working day, and complete absorption of inhaled materials, this equates to an internal dose of 10 mg. Assuming that the typical worker weights 70 kg, this equates to a dose expressed on a body weight basis of 0.14 mg/kg/day.

There have not been any quantitative estimates of DIHP exposure in the general population, but it is expected to be low. There are recent estimates of exposures to a number of other phthalates within the US population based on a biomonitoring method developed by the United States Centers for Disease Control (U.S. CDC). Human exposures calculated from these estimates indicated that for DEHP, the phthalate ester most widely used in commerce, the

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.

median exposures were less than 1 µg/kg/day. As production levels of DIHP are below those of DEHP, it would be reasonable to assume that exposures to DIHP would not exceed those of DEHP.

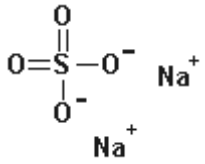
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (reproductive toxicity). Given its use pattern, the chemical is a candidate for further work. Member countries are invited to perform an exposure assessment for workers and consumers and if necessary a risk assessment.

Environment: This chemical is currently of low priority for further work due to its low hazard potential in the environment.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7757-82-6
Chemical Name	Sodium sulfate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Sulfate (and sodium) ions are important constituents of the mammalian body and of natural foodstuffs and there is a considerable daily turnover of both ions (several grams/day expressed as sodium sulfate). Near-complete absorption of dietary sulfates may occur at low concentration, depending on the counter-ion, but absorption capacity can be saturated at higher artificial dosages resulting in cathartic effects. Absorption through skin can probably be ignored since sodium sulfate is fully ionised in solution. One source suggests that very high levels of sulfate in urine may occur due to absorption from dust inhalation. At dietary levels, excretion is mainly in the urine. Sulfates are found in all body cells, with highest concentrations in connective tissues, bone and cartilage. Sulfates play a role in several important metabolic pathways, including those involved in detoxification processes.

The acute toxicity (LD_{50}) of sodium sulfate has not been reliably established but is probably far in excess of 5000 mg/kg. In an inhalation study with an aerosol, no adverse effects were found at 10 mg/m^3. Also human data indicate a very low acute toxicity of sodium sulfate. Human clinical experience indicates that very high oral doses of sodium sulfate, 300 mg/kg bw up to 20 grams for an adult, are well tolerated, except from (intentionally) causing severe diarrhoea. WHO/FAO did not set an ADI for sodium sulfate. There is no data on acute dermal toxicity, but this is probably of no concern because of total ionisation in solution.

Sodium sulfate is not irritating to the skin and slightly irritating to the eyes. Respiratory irritation has never been reported. Based on wide practical experience with sodium sulfate, in combination with the natural occurrence of sulfate in the body, sensitising effects are highly unlikely.

No suitable dermal and inhalation repeated-dose toxicity studies are available. Valid oral repeated dose toxicity studies with 21, 28 and 35 day studies in hens and pigs are available. Toxicity was confined to changes in bodyweight, water and feed intake and diarrhoea. These changes occurred only at very high doses of sodium sulfate. In ruminants, high concentrations of sulfate in food may result in the formation of toxic amounts of sulfites by bacterial reduction the rumen, leading to poly-encephalomalacia. The available data do not allow the derivation of a NOAEL. Based on available consumer data, a daily dose of around 25 mg/kg/day is well tolerated by humans.

There are no data on *in vitro* and *in vivo* genotoxicity, apart from a negative Ames test. There is no valid oral carcinogenicity study. Limited data from experimental studies support the notion that a substance that is abundantly present in and essential to the body is unlikely to be carcinogenic.

Limited data of poor validity did not provide an indication of toxicity to reproduction.

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.

There are considerable data gaps and the data that are available are not all of standard quality or from animals commonly used for toxicity testing. Nevertheless the weight of evidence, combined with previous assessments of both the sodium ion and sulfic ions lead to the conclusion that the identified data gaps need not necessarily be filled.

Environment

Sodium sulphate is a solid inorganic salt well soluble in water (161-190 g/l at 20 ^{o}C) with a melting point of 884 ^{o}C and density of 2.7 g/cm^{3}. In water solutions it is fully dissociated to sodium and sulfate ions.

In water sodium sulfate completely dissociates into sodium and sulfate ions. The ions cannot hydrolyse. In anaerobic environments sulfate is biologically reduced to (hydrogen) sulphide by sulfate reducing bacteria, or incorporated into living organisms as source of sulphur, and thereby included in the sulphur cycle. Sodium sulfate is not reactive in aqueous solution at room temperature. Sodium sulfate will completely dissolve, ionise and distribute across the entire planetary "aquasphere". Some sulfates may eventually be deposited, the majority of sulfates participate in the sulphur cycle in which natural and industrial sodium sulfate are not distinguishable

The BCF of sodium sulfate is very low and therefore significant bioconcentration is not expected. Sodium and sulfate ions are essential to all living organisms and their intracellular and extracellular concentrations are actively regulated. However some plants (e.g. corn and *Kochia Scoparia*), are capable of accumulating sulfate to concentrations that are potentially toxic to ruminants.

Algae were shown to be the most sensitive to sodium sulfate; EC_{50} 120h = 1,900 mg/l. For invertebrates *(Daphnia magna)* the EC_{50} 48h = 4,580 mg/l and fish appeared to be the least sensitive with a LC_{50} 96h = 7,960 mg/l for *Pimephales promelas*. Activated sludge showed a very low sensitivity to sodium sulfate. There was no effect up to 8 g/l. Sodium sulfate is not very toxic to terrestrial plants. *Picea banksiana* was the most sensitive species, an effect was seen at 1.4 g/l. Sediment dwelling organisms were not very sensitive either, with an LC_{50} 96h = 660 mg/l for *Trycorythus sp*. Overall it can be concluded that sodium sulfate has no acute adverse effect on aquatic and sediment dwelling organisms. Toxicity to terrestrial plants is also low.

No data were found for long term toxicity. The acute studies all show a toxicity of sodium sulfate higher than 100 mg/l, no bioaccumulation is expected, therefore it can be considered that no further chronic studies are required.

Exposure

Production: production of sodium sulfate is 4.6 million tonnes/year (1999), of which approximately 50% a by-product of the chemical industry and the remainder is extracted from natural deposits.
Use: The main uses are manufacturing of glass and detergents. Other users are from a wide range of industries, including dyeing technology, electrochemical metal treatment, (animal) feeds, pharmaceuticals, textile, semi-conductors, intermediates, agriculture.
Release: Releases to water come from natural sources as well as from detergents and nearly all industrial sources listed above.
Occupational exposure: Exposure to sodium sulfate-containing dusts or aerosols is possible
Consumer products: Exposure to sodium sulfate occurs via drinking water and through naturally occurring or added amounts in foodstuffs. The maximum acceptable concentration for drinking water is 200 – 500 mg/l sulfate, and is based on taste rather than toxicity.

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

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-79-5
Chemical Name	1,3-Butadiene, 2-Methyl- (Isoprene)
Structural Formula	C_5H_8 (CH_2=C(CH_3)-CH=CH_2)

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,3-Butadiene, 2-methyl- (isoprene) is formed endogenously at the rate of 1.9 umol/kg per hour in both rats and mice and at the rate of 0.15 umol/kg per hour in humans. Isoprene is metabolized by microsomal cytochrome P-450 dependent monooxygenases to two monoepoxide metabolites, i.e., 3,4-epoxy-3-methyl-1-butene (EPOX-1) and 3,4-epoxy-2-methyl-1-butene (EPOX-2). These metabolites may then be hydrolyzed, conjugated with glutathione, or further oxidized to the isoprene diepoxide, i.e., 2-methyl-1,2:3,4-diepoxybutane. The intrinsic rates of formation of monoepoxides in human, rat and mouse liver microsomes are roughly similar, when epoxide hydrolase is inhibited, whereas the amount of monoepoxides at the end of incubation can be two to 15 times higher in mouse liver microsomes than in rat and human liver microsomes, respectively. A physiological toxicokinetic model has been developed for inhaled isoprene in mice, rats and humans, taking into account published or assumed kinetic parameters. On the basis of this model, at human exposure conditions (up to 50 ppm [140 mg/m^3]), rates of metabolism are about 14 times faster in mice and about eight times faster in rats than in humans. As the epoxide metabolites are likely responsible for the toxic effects of isoprene, this may explain why the mouse is more susceptible to isoprene toxicity than the rat.

Isoprene has a low potential for acute toxicity. In rats and mice, the oral LD_{50} of isoprene is in the range of 2,043 to 2,210 mg/kg. The 4-hour rat LC_{50} is 64,620 ppm (180,037 mg/m^3) and the 2-hour mouse LC_{50} is 56,363 ppm (157,033 mg/m^3). In humans, isoprene vapors are irritating to the eyes, nose and throat. Liquid isoprene is irritating to the eyes and skin. Data from a 13-week repeated dose study conducted in mice and rats found degeneration of the olfactory epithelium in male mice only at the highest concentration, i.e., 7,000 ppm (19,503 mg/m^3), but not at lower concentrations. IARC reports that in isoprene rubber production workers, subtrophic and atrophic processes in the upper respiratory tract, catarrhal inflammation, and degeneration of the olfactory tract were observed. Prevalence and degree were correlated with increasing length of service.

Repeated dose studies demonstrate clear species differences between rats and mice in susceptibility to isoprene. In a 2-week repeated dose inhalation study, the NOAEL for rats was 7,000 ppm (19,503 mg/m^3), the highest dose tested. However, in this same study, exposure of mice to isoprene produced changes in hematological parameters(decreased hematocrit, hemoglobin, erythrocytes), body and organ weights (increased liver weights, decreased thymus, spleen and testes weights) and also produced microscopic lesions in certain tissues (testes, thymus, liver, nasal cavity, forestomach) at levels as low as 438 ppm (1,220 mg/m^3). Thus, 438 ppm was the LOAEL for mice. Similarly, in the 13-week repeated dose inhalation study, the NOAEL for rats was 7,000 ppm (19,503 mg/m^3). In mice, however, hematological effects indicative of a nonresponsive macrocytic anemia and histopathological changes (forestomach, olfactory epithelium, liver) were observed at exposures of 700 ppm (1,950 mg/m^3) and higher. The NOAEL for mice in the 13- week repeated dose study was 220 ppm (613 mg/m^3). Isoprene was tested for mutagenicity in a series of *in vivo* and *in vitro* studies. Isoprene was not genotoxic in any of the *in vitro* assays conducted. However, when exposed by inhalation, isoprene was clearly genotoxic to mouse bone marrow *in vivo*.

Two-year inhalation carcinogenicity studies were conducted with isoprene in B6C3F1 mice and F344 rats. There is

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.

clear evidence of carcinogenicity of isoprene in mice. Isoprene produced exposure-related increases in the incidence of malignant neoplasms in the liver, lung, Harderian gland and forestomach of mice, as well as increases in the number of hemangiosarcomas and histiocytic sarcomas. In rats, there were no significant increases in the incidence of malignant tumors. Isoprene exposures in rats were associated with increases in the rates of benign tumors in the testes and kidney (male) and mammary gland (male and female). Although single incidences of several rare brain neoplasms were observed in female rats, the fact that they were of several distinct cell types makes it difficult to determine if they are truly exposure related. Based on the carcinogenicity studies conducted in mice and rats, the NTP listed isoprene as reasonably anticipated to be a human carcinogen and IARC has classified it as 2B; possibly carcinogenic to humans.

Isoprene did not produce any maternal or developmental toxicity in rats following exposure to concentrations as high as 7000 ppm. However, both maternal and developmental toxicity were evident in mice. In mice, both maternal weight gain and uterine weight were significantly reduced at the highest dose (i.e., 7000 ppm). Significant reductions in fetal bodyweights were observed at the 280 ppm dose level for female fetuses and at the 1400 ppm level for male fetuses. Thus, in this study, 1400 ppm was the NOAEL for maternal toxicity. A NOAEL for developmental toxicity could not be determined as effects were observed at the lowest exposure concentration tested, i.e., 280 ppm.

Isoprene did not produce any significant effects on reproductive endpoints in rats. However, significant effects on reproductive endpoints were observed in male mice exposed to isoprene at concentrations of 700 ppm (1,950 mg/m^3) and higher. These effects included testicular atrophy as well as decreases in epididymal weight, sperm head count, sperm concentration, and sperm motility. In female mice exposed to 7,000 ppm (19,503 mg/m^3), the average estrous cycle length was significantly longer than that of the control group. Thus, in this study, 70 ppm (195 mg/m^3) is the NOAEL for reproductive effects in male mice and 700 ppm (1,950 mg/m^3) is the NOAEL for female mice.

Environment

Isoprene is a liquid at 25° C with a reported melting point of –145.9° C, a boiling point of 34.0° C, and vapour pressure of 733.3 hPa (25° C). Isoprene has a water solubility of 642 mg/l (25° C), a log K_{ow} of 2.42, and a density of 0.681 g/cm^3 (25° C).

In the air, isoprene has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals with a calculated degradation half-life of 1.2 hours depending on hydroxyl radical concentration. Aqueous photolysis and hydrolysis will not contribute to the transformation of isoprene in aquatic environments because it is either poorly or not susceptible to these reactions.

Results of Mackay Level I distribution modeling at steady state show that isoprene will partition primarily to the air compartment (99.9%), with a negligible amount partitioning to water (0.06%) and soil (0.02%). Level III modeling predicted greatest distribution (99.96%) to the primary compartment of release; when equal releases were assumed, the predicted distribution was: water (88%), soil (9.0%), air (3.1%), and sediment (0.21%).

Isoprene biodegraded to 61 % after 28 days in an OECD 301F study, but was not readily biodegradable because the replicate data exceeded the allowable range (53 to 75%). In an OECD 301D study, isoprene biodegraded to an extent of 2 and 58% in duplicate samples after 28 days, and showed no inhibitory effect in a supplementary study. The supplementary study resulted in 64% biodegradation on day 7, using the acclimated inoculum from the initial study. These data show that isoprene can exhibit high extents of biodegradation once acclimation has occurred. Bioaccumulation of isoprene is unlikely based on a low potential to bioconcentrate. The measured BCF is reported as 5 to approximately 20. The calculated BCF is 15.

Acute aquatic toxicity values for a fish and invertebrate are 7.4 (96hr-LC_{50}) and 5.8 (48hr-EC_{50}) mg/L, respectively. For algae, the 72- and 96-hr EC_{50} is 15 mg/L for biomass and >35 mg/L for growth rate. The algae 72- and 96-hr NOEC is 1.7 and 6.0 mg/L for biomass and growth rate, respectively.

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.

Exposure

Isoprene is a petrochemical that is used as a chemical intermediate to manufacture primarily polymers, which occurs in closed production systems. Greater than 95% of high-purity isoprene is used as a monomer to manufacture elastomers such as polyisoprene, styrenic thermoplastic elastomer block copolymers (styrene-isoprene-styrene [SIS]), and butyl rubber. The remaining amount of isoprene is used to manufacture specialty chemicals, intermediates and derivatives which are then used in the production of vitamins, pharmaceuticals, flavorings and perfumes, and epoxy hardeners. The European Union has evaluated isoprene in the framework of Food Contact Material (CS/PM/3351/21640).

Total world isoprene consumption was reported as over 700,000 metric tons in 2004. Most isoprene production is consumed in the country of origin. Isoprene world consumption in 2000 was 579,000 metric tons, of which approximately 96% was consumed in the country of manufacture. In the United States, isoprene production in 1995 was approximately 619 million lb (281,000 metric tons).

Potential occupational exposure to isoprene through inhalation and dermal contact could occur at workplaces where isoprene or synthetic rubber is produced or used. A WEEL (Workplace Environmental Exposure Limit) of 2 ppm was established by AIHA in 2004. The WEEL was 50 ppm prior to the 2004 revision. Isoprene concentration in 426 workplace air samples (4-hr or greater) taken at 3 major isoprene or isoprene polymer producers in the United States from 1993 to 1998 showed that 81% were below 0.5 ppm, 91% were below 1 ppm, and 99% were below 10 ppm.

There are no direct sales to consumers. However, isoprene is used in production of polymers used in paint resins, tyres, footwear, moduled goods, adhesives, motor oil viscosity improvers. Isoprene monomer residual concentration was not detectable in isoprene-derived polymer samples at an analytical sensitivity of 0.1 ppm in work conducted prior to June 1998. Subsequent work in latter 1998, with an increased analytical sensitivity of 0.02 ppm, that evaluated polyisoprene samples demonstrated that 17 out of 19 samples had no detectable isoprene monomer residual, while 2 samples contained between 0.04 and 0.02 ppm. Consequently, potential for consumer exposure will be negligible.

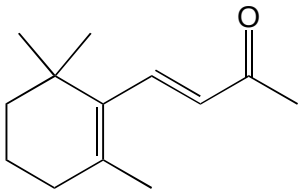
The greatest potential for exposure to isoprene in the environment is in the air compartment because of its high vapor pressure. Partitioning to air from aquatic and terrestrial compartments would occur rapidly due to isoprene physico-chemical characteristics. As such, isoprene has an overall low potential for exposure in environmental compartments other than air. However, its persistence in air is short lived as a result of degradation processes, which suggests that exposure to isoprene will be limited in the environment.

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

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (irritation, genotoxic, reproductive and developmental toxicity, carcinogenic) and the environment (fish, invertebrates, algae). Based on data presented by the Sponsor country, relating to production in one country which accounts for approximately 40% of global production and relating to the use pattern in one country, under normal manufacturing, formulation, industrial and consumer use of polymerized isoprene containing products, 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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-77-6
Chemical Name	β-Ionone [(E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one]
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

From animal experiments it can be concluded that β-ionone is absorbed after oral exposure. Metabolism takes place mainly in the liver. Metabolites, which were identified in the urine of exposed rabbits, are 3-oxo-β-ionone, 3-oxo-β-ionol, dihydro-3-oxo-β-ionol and 3-hydroxy-β-ionol. β-Ionone was found to be an inducer of CYP 1A and 2B isozymes in the liver of rodents.

β-Ionone has only low acute toxicity after oral ingestion. A gavage study conducted with a mixture of 60 % α-Ionone and 40 % β-ionone revealed a LD_{50} of 4590 mg/kg bw. Clinical signs of toxicity were depression and tremors.

In studies conducted according to OECD test guidelines and under GLP conditions, β-ionone was not irritating to the skin of rabbits after semiocclusive application for 4 hours and only slightly irritating to the eyes. After a 24-hours exposure under occlusive conditions, a slight irritation of the skin was observed in rabbits. A limited human patch test did not reveal a potential for skin irritation when a not further specified mixture of α- and β-ionone was applied undiluted to the skin of volunteers.

A limited Guinea pig maximization test found no evidence that β-ionone is a dermal sensitizer. According to secondary sources, ionone (a not further specified mixture of α- and β-ionone) was negative in an open epicutaneous test with Guinea pigs as well as in a human maximization test with a product containing 97.5 % α-ionone and 2.5 % β-ionone.

The administration of β-ionone over a period of 90 days according to OECD TG 408 at dietary concentrations of 100, 1000 and 10 000 ppm (7 and 8 mg/kg bw/day, 72 and 83 mg/kg bw/day or 720 and 801 mg/kg bw/day for males and females) to rats led to signs of general systemic toxicity at the high and mid dose. Target organs were liver, kidneys and thyroid glands. The liver findings in both sexes and the increased kidney weights in high dose females were indicative of adaptive and most likely reversible processes with the aim to increase the metabolizing and/or excretory capacity of these organs. The findings in males with respect to kidneys as well as kidney relevant parameters should be seen in the light of high amounts of alpha2u-globulin in these animals. The occurrence of alpha2u-globulin was confirmed by immunohistochemical examination. The accumulation of this protein appears to be a unique feature of male rats and is not known to occur in other species, including man. No signs of neurotoxicity were observed during functional observational battery as well as measurement of motor activity performed towards the end of the administration period.

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.

Thus, the no-observed-effect-level (NOEL) under the conditions of the present study was 100 ppm for both sexes (about 7 and 8 mg/kg bw/day for males and females) based on adaptive liver effects in both sexes and minor urine findings in males at 1000 ppm which correspond to a dosage of 72 and 83 mg/kg bw/day for males and females (no-observed-adverse-effect-level, NOAEL). The lowest-observed-adverse-effect-level (LOAEL) was found at 10 000 ppm (720 and 801 mg/kg bw/day for males and females) due to liver, kidney and thyroid findings in both sexes.

β-Ionone gave no indication of a mutagenic effect in bacteria or a clastogenic potential in an *in vivo* mouse micronucleus test. Therefore, there is no indication of a genotoxic potential *in vivo*.

No studies that would be considered adequate for the evaluation of carcinogenic potential were available. A short-term screening experiment investigating a tumor-promoting potential on mouse skin did not indicate such an effect at a low test concentration.

In a well-conducted 90 days study in rats according to OECD TG 408 with administration of the test substance in the diet, β-ionone did not have the potential to damage the reproductive organs at least up to the highest tested concentration of 10,000 ppm (720 and 801 mg/kg bw/day for males and females).

Based on the results of a GLP and guideline conforming developmental toxicity study (OECD TG 414) with gavage application of β-ionone, the no observed adverse effect level (NOAEL) for maternal toxicity was 100 mg/kg bw/day. The NOAEL for prenatal developmental toxicity could be fixed at the highest tested dose (400 mg/kg bw/day). The test substance had no influence on gestational parameters and induced no adverse signs of developmental toxicity and in particular no indications of teratogenic effects up to and including the highest dose level were observed.

Environment

The colorless to yellowish liquid β-ionone has a water solubility of about 0.169 g/l and a vapor pressure of about 0.009 hPa at 25 °C. The measured log K_{OW} of 4.0 at 25 °C, the calculated log K_{OC} of 2.80 - 3.34 and the calculated BCF of 501 indicate a potential for bio- and geoaccumulation. According to distribution modeling using Mackay Level I, water (34 %), soil (27 %), sediment (27 %) and air (12 %) are the main targets for the compound. β-Ionone is with > 70 % (within 28 days, 10-day-window criteria fulfilled) readily biodegradable according to OECD criteria. In the atmosphere, it will be rapidly photodegraded by reactions with OH radicals (calculated $t_{1/2}$: 1.6 hours) and ozone (calculated $t_{1/2}$: 18 minutes).

Results on acute aquatic toxicity are available for fish (*Pimephales promelas*; LC_{50} (96 hours): 5.1 mg/l), invertebrates (*Daphnia magna*; EC_{50} (48 hours): 3.7 mg/l) and algae (*Scenedesmus subspicatus*; $E\mu C_{50}$ (72 hours): 22.2 mg/l; EbC_{50} (72 hours): 21.2 mg/l). Based on these acute toxicity studies, β-ionone is considered as toxic to aquatic organisms. No results on prolonged or chronic toxicity to aquatic organisms are available. According to the EU risk assessment procedure, a $PNEC_{aqua}$ of 3.7 µg/l was obtained by applying an assessment factor of 1000 on the lowest $L(E)C_{50}$ value, the result of the test with *Daphnia magna*.

Exposure

In the year 2003 the world production of industrial β-ionone was between 4000 and 8000 tonnes/a and in Europe between 1000 and 5000 tonnes/a. In the Sponsor country the production volume of the sole producer is between 1000 and 3000 tonnes/a. The production in USA and Asia was < 1000 tonnes/a and < 2000 tonnes/a, respectively.

In the Sponsor country about 70 % of the manufactured industrial β-ionone is used as intermediate internally for complete consumption in chemical processes for the synthesis of fine chemicals (e.g. vitamins, aroma chemicals). About 30 % of β-ionone are distributed to industrial clients which are using the substance as intermediate for chemical syntheses or directly as flavoring compound and/or aroma additive in e.g. food.

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.

Exposure to β-Ionone occurs via food, cosmetics and some house wares like cleaning agents (flavoring compound, aroma additive). In cosmetics usual concentrations are up to 0.3 % and in food maximum amounts added ranging from 0.5 – 10 ppm. β-ionone occurs also naturally in food (some plants e.g. corn) and plant extracts used for example in perfumes. Typical use concentrations in final products are 0.03 % (soap), 0.003 % (detergent), 0.016 % (creams, lotions) and 0.3 % (perfume). β-Ionone is listed in the Danish, Norwegian and Swedish product register and not listed in the Swiss product register. For Denmark and Norway the use in consumer preparations (Denmark: cleaning / washing agent) is stated.

The substance naturally occurs as a biogenic volatile organic compound and shows a ubiquitous occurrence in the air due to emissions from plants or surface waters. For instance, β-Ionone was found in concentrations ranging from 0.002 µg/l up to 1.2 µg/l in waters of lakes and rivers mainly due to biotransformation processes in phytoplankton. Further, it was measured in red wine with 0.72 µg/l and was described as a volatile compound in beef flavor. It was also identified in several fruits as well as in drinking water- and in wastewater samples. The odor threshold is indicated with 0.007 ppb or 56 ng/m³ based on vapor.

In the Sponsor country (Germany) worker protection is adequate and includes the use of appropriate technical equipment during substance handling and the use of protective equipment, etc.

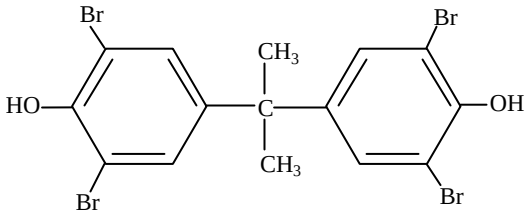
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The only hazards identified are slight irritation to the eyes and changes in the liver, kidneys and thyroid after repeated oral exposure, which were either of minor severity or were considered to be a species-specific effect in male rats. Given the main use as a chemical intermediate and the low content of the substance in consumer products in the Sponsor country, the 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: β-Ionone possesses properties indicating a hazard for the environment. Based on the data presented by the Sponsor country (relating to production by one producer which accounts for approx. 10 – 40 % of global production and relating to the use in several OECD countries), exposure to the environment from human production and use of β-ionone 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.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-94-7
Chemical Name	2,2',6,6'-Tetrabromo-4,4'-isopropylidene diphenol (Tetrabromobisphenol-A; TBBPA)
Structural Formula	

SUMMARY OF THE CONCLUSIONS OF THE SIAR

Human Health

The available data indicate that TBBPA is absorbed in humans (as shown by levels of 0.3-12 µg/kg in whole blood of exposed persons). There is also evidence that once absorbed, TBBPA and/or its metabolites can be excreted in humans via breast milk (0.01-11 µg/kg lipid from 3 studies).

In experimental animals, toxicokinetic data are available in the rat only. Following oral exposure, 100 % of the administered dose of TBBPA is absorbed from the gastro-intestinal tract. The toxicokinetics following inhalation and dermal exposure have not been investigated. TBBPA is largely non-respirable (4% particles <15 µm) and therefore a relatively small proportion of particles may be expected to enter deeply into the lung following inhalation. The majority of the particles will deposit in the nasopharyngeal region of the respiratory tract and then be swallowed, while the remainder are likely to be exhaled. Regarding dermal exposure, the low water solubility, the high *n*-octanol/water partition coefficient (5.9), and the high molecular weight (>500) of TBBPA suggest that dermal absorption is likely to be low.

Information is available on distribution, metabolism and excretion following exposure via the oral route only. TBBPA is metabolised by glucuronide conjugation and to a lesser extent sulphate conjugation (accounting for around 30% of the administered dose). Excretion of TBBPA and its metabolites is predominantly in the faeces (around 95% of the administered dose) with minimal excretion in urine (<1%) at 72 hours after dosing. There is little information on the distribution/fate of TBBPA (and/or its metabolites) between being absorbed and appearing in the faeces 72 hours post-dosing, as from 4 hours after administration onwards the general systemic distribution of TBBPA and /or its metabolites appears to be very low.

No information is available on the effects of single exposure to TBBPA in humans. Available animal data indicate LC50 (1 hour), oral LD50 and dermal LD50 values in excess of 1.3 mg/l, 50 g/kg and 10 g/kg, respectively. No toxicologically significant signs of systemic toxicity were evident following exposure via any route. Thus, it can be concluded that TBBPA is of low acute toxicity by all routes of exposure.

The weight of evidence from animal studies indicates that TBBPA is not a skin, eye or respiratory tract irritant. It is not a skin or respiratory sensitiser.

Only one repeat dose inhalation study is available. Exposure of rats to concentrations of up to 18 mg/l for 4 h/d for 14 days produced no compound related, toxicologically significant systemic effects. In a 90-day rat study conducted in accordance with GLP and OECD guidelines no toxicologically significant effects were seen following oral exposure to 100, 300 or 1000 mg/kg TBBPA; therefore the NOAEL is = 1000 mg/kg/d. A decrease in serum T4

levels was observed in all treated males on days 33 and 90 and on day 33 only in all treated females. However, there was no dose response relationship associated with the finding and it did not persist in females; there were no statistically significant changes in serum levels of TSH or T3 in animals of either sex; and macroscopic and microscopic examination revealed no treatment-related changes in the liver, thyroid, parathyroid or pituitary gland. In the absence of changes in other parameters of thyroid homeostasis in a species (the rat) that is very sensitive to perturbations in thyroid hormone levels, these decreases are not considered to be adverse. The same decreases in T4 levels were seen in the 100 and 1000 mg/kg groups of the F0 and F1 generations in the 2-generation rat study (see below). However, again, given that there was little impact on other parameters associated with a disruption of thyroid homeostasis in the rat, it is deemed that the decreases observed are not toxicologically significant. In the only conventional repeated dermal exposure study, in which rabbits were dosed with up to 2500 mg/kg, no toxicologically significant compound related effects were observed.

TBBPA has demonstrated consistently negative results in a range of *in vitro* tests using bacterial strains (Ames test) and yeast both in the presence and absence of metabolic activation. In a well-conducted chromosomal aberration study using human peripheral lymphocytes and in an unconventional *in vitro* recombination assay, TBBPA tested negative. No *in vivo* data are available but in view of the negative profile *in vitro* and given that there are no structural indications that TBBPA would be genotoxic, there are no concerns for this endpoint.

There are no human or animal data available to inform on the carcinogenic potential of TBBPA. However, there is no evidence from the available *in vitro* mutagenicity data and no indications from repeated exposure studies (for example, no target organ toxicity or proliferative changes) to raise any concerns for carcinogenicity.

Information available from a 2-generation reproductive toxicity study in rats indicates that TBBPA has no toxicologically significant effects on fertility or reproductive performance at doses of 10, 100 or 1000 mg/kg, therefore the NOAEL is =1000 mg/kg/d.

The effects of TBBPA on development have been investigated in a pilot range finding study and two standard developmental toxicity studies. No evidence of developmental toxicity was seen at doses up to 2500 mg/kg/d in these studies, therefore the NOAEL is = 2500 mg/kg/d.

In addition, 2 well-conducted developmental neurotoxicity studies have been conducted in the rat and a post-natal developmental neurotoxicity study in the mouse. The rat studies involved exposure of dams during pregnancy and lactation periods. The first study was part of the 2-generation oral gavage study and included behaviour and learning/memory tests, specialised neurohistopathology and morphometric examination of the brain. This study provided no convincing evidence of an adverse effect on neurodevelopment at dose levels up to 1000 mg/kg/d. A statistically significant decrease in the thickness of the parietal cortex was observed in F2 pups of the 1000 mg/kg group on PND 11, however, the same effect was not present in these pups on PND 60. Also, no microscopic changes were reported in these animals on either PND 11 or PND 60. Therefore, the decreased thickness of the parietal cortex is regarded as a transient or chance finding that is unlikely to be toxicologically significant.

The second study included behaviour and learning/memory tests, neurohistochemistry, but no specialised neurohistology. Pregnant rats were administered 0, 50 or 250 mg/kg/d TBBPA by gavage in peanut oil from gestation day 7 to postnatal day 17 and a neurobehavioural assessment was carried out on weanling rats. The study showed limited evidence of changes in the habituation behaviour of female offspring and learning and memory in male offspring in the 250 mg/kg/d group. However, it is not possible to draw definitive conclusions from this study because the size of the reported changes was very small and there was not a convincingly consistent pattern of changes in investigations conducted at different time points. Also, the evidence of developmental neurotoxicity is weakened by the absence of consistent changes in the two genders, the lack of histopathological investigations that could provide corroborative findings, and the lack of any similar findings in the first study at dose levels of 100 and 1000 mg/kg/d.

In the mouse study, a single exposure to 10-day old neonates, to a relatively low oral gavage dose, had no effect on behaviour, learning or memory.

In a non-standard study, an effect on the kidneys (polycystic lesions associated with the dilatation of the tubules) of newborn rats dosed from day 4 up to day 21 after birth by gavage with 200 and 600 but not 40 mg/kg TBBPA was

reported. However, no similar effect was observed in 5-week old rats administered by gavage 2000 and 6000 mg/kg TBBPA for 18 days and in a comprehensive GLP- and OECD-compliant rat 2-generation study with gavage doses of up to 1000 mg/kg/d. These findings indicate that newborn rats are more susceptible to the nephrotoxic effects of TBBPA than young and adult rats. However, it is considered that this effect is likely to be the consequence of the direct gavage administration of very high doses of TBBPA to such young animals.

Overall, the data do not provide strong evidence of the potential for TBBPA to act as a developmental toxicant or neurotoxicant.

Environment

The substance is a white crystalline powder with a melting point of 181-182^{o}C and a very low vapour pressure of $<1.19\times10^{-5}$ Pa at 20^{o}C. The substance does not have a distinct boiling point as it decomposes at 200-300^{o}C. The substance is a weak acid (pKa_1 = 7.5 and pKa_2 = 8.5) and the water solubility varies with pH (0.148 mg/l at pH 5, 1.26 mg/l at pH 7 and 2.34 mg/l at pH 9; all at 25^{o}C), reflecting the increased solubility of the dissociated forms over the undissociated acid. The n-octanol water partition coefficient (log Kow) has been measured as 5.9. Similar to water solubility, the log Kow would be expected to vary with pH of the solution.

The substance is not readily biodegradable but has been shown to undergo primary biodegradation, but only limited mineralisation, under aerobic conditions in soils (18-64% primary degradation in 64 days) and sediments (36-55% primary degradation in 56 days). In addition, the substance has been shown to undergo primary degradation under anaerobic conditions in soils (10-56% degradation in 64 days) and contaminated sediments (85% degradation in 10 days). More recent studies have shown 18-22% mineralization of TBBPA over six months' incubation in soil, suggesting a mineralization half-life of > 6 months. Bisphenol-A has been identified as a degradation product of TBBPA under anaerobic conditions. The substance is also expected to degrade in the atmosphere by reaction with hydroxyl radicals and a rate constant for this reaction of around 2.96×10^{-12} cm^3 $molecule^{-1}$ s^{-1} has been estimated (atmospheric half-life of 130 hours).

The low vapour pressure, water solubility and high log Kow value indicates that the substance has a high potential for adsorption onto soil, sediment or suspended sediment. Laboratory studies indicate that the substance has a moderate potential for bioaccumulation in aquatic species (the fish BCF is around 1,234 l/kg based on ^{14}C-residues or around 485 l/kg based on parent compound measurements).

The environmental effects database meets the requirements of the SIDS data package. In addition, results from several post SIDS tests are also available. Based on the available data for fish, invertebrates and algae, the substance appears to have a high toxicity in short-term tests, with the lowest acute values being a 96h-LC_{50} of 0.54 mg/l for fathead minnow (*Pimephales promelas*), a 48h-EC_{50} of 0.96 mg/l for *Daphnia magna*, a 72h-EC_{50} of >5.6 mg/l for the freshwater algae *Pseudokirchneriella subcapitata* and a 72h-EC_{50} of 0.09-0.89 mg/l for the marine alga *Skeletonema costatum*.

In longer-term toxicity tests, NOEC/EC_{10} values of 0.16 mg/l for fish over 35 days, 0.3 mg/l for *Daphnia magna* over 21 days, ≥5.6 mg/l for the freshwater algae *Pseudokirchneriella subcapitata* over 72 hours, <0.066 mg/l for *Chironomus tentans* over 14 days, 0.017 mg/l for *Mytilus edulis* over 70 days and 0.0127 mg/l for *Acartia tonsa* over 5 days have been determined. Based on the *Acartia tonsa* data a PNEC for surface water of 1.3 µg/l was derived using an assessment factor of 10.

A number of studies have investigated the effects of tetrabromobisphenol-A on the endocrine system in aquatic organisms. The results obtained in these studies show considerable variability, and appear to be dependent on the test system used. Overall, in terms of population effects, the available studies with fish have generally shown that tetrabromobisphenol-A has little or no adverse effect on parameters such as survival, growth and reproduction that can be assigned specifically to effects on the endocrine system. For amphibians, although possible thyroid-mediated effects of tetrabromobisphenol-A are evident in some *in vitro* assays, the results of a recent, well conducted, *in vivo* assay suggest that the effects seen *in vivo* may be a result of a toxic side effect rather than direct effects on thyroid function.

Longer-term toxicity data for sediment and soil organisms are also available. The lowest NOECs found in studies using sediment are a 28-day NOEC of 125 mg/kg dry weight with *Chironomus riparius*, a 28-day NOEC of 250 mg/kg dry weight with *Hyalella azteca* and a 28-day NOEC of 90 mg/kg dry weight with *Lumbriculus variegatus.* Based on these data, a PNEC of 2.7 mg/kg wet weight is derived for sediment using an assessment factor of 10, after normalising the data to a standard organic carbon content (5%) and converting from dry weight to wet weight values.

The lowest NOECs found in studies using soil are a 56-day NOEC of 0.29 mg/kg dry weight with *Eisenia fetida*, a 21 day NOEC of 16 mg/kg dry weight with *Cucumis sativa* and a 28 day NOEC of 300 mg/kg dry weight for soil microorganisms. Based on these data, a PNEC of 0.012 mg/kg wet weight is derived for soil using an assessment factor of 10, after normalising the data to a standard organic carbon content (2%) and converting from dry weight to wet weight values.

For microorganisms, no effects were seen in a 3-hour activated sludge respiration inhibition test at a concentration of 15 mg/l. A $PNEC_{microorganisms}$ for waste water treatment plants of $\geq$1.5 mg/l can be derived from this value using an assessment factor of 10.

Exposure

The substance is imported into the EU and is used as both a reactive flame retardant (where it is chemically bonded into the polymeric material), and additive flame retardant in plastics. The main uses as a reactive flame retardant are in epoxy and polycarbonate resins. The main use as an additive flame retardant is in acrylonitrile-butadiene-styrene (ABS) resins. In addition, tetrabromobisphenol-A is used as an intermediate in the production of other reactive and additive flame retardants.

The current total amount of TBBPA produced worldwide is estimated at 150,000 tonnes/year. TBBPA is produced by the bromination of bisphenol-A in the presence of a solvent. The production process is largely conducted in closed systems. TBBPA is produced in the USA, Israel and Japan. There is currently thought to be no production of TBBPA or its derivatives in the EU. In relation to TBBPA uses, occupational exposure to TBBPA can occur in a number of ways, for example, during the addition of TBBPA powder to mixes of polymer compounds, during the production of laminates for printed circuit boards, during recycling of computers and electrical equipment, during the assembly of printed circuit boards, during the recycling of plastic housings and to employees in offices containing electronic equipment.

Consumption of TBBPA in the EU was around 13,800 tonnes/year in the late 1990s, but there has been a decline in demand since then as product manufacture has shifted away from the use of this compound, and more recent figures are around 6,500-7,500 tonnes/year. TBBPA is used in a range of consumer goods as a flame retardant. However, since the free residual monomer is likely to be less than 1,000 ppm, consumer exposure to TBBPA is likely to be insignificant.

Emissions to the environment can occur both to the atmosphere (as vapour and as dust) and waste water. Sources of release include flame retardant production sites, epoxy and polycarbonate resin production sites and polymer processing sites. In addition, emissions to the environment could also occur from finished articles (e.g. plastic components) during their use and at disposal.

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.

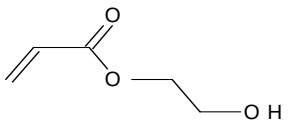
Note: No human health hazard of concern has been identified in an assessment performed in the European Union in the context of the EU Existing Substances Regulation (793/93/EEC).

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (high toxicity to fish, aquatic invertebrates and soil and sediment organisms). Member countries are invited to perform an exposure assessment, and if necessary

a risk assessment for the environment.

NOTE: An EU risk assessment in the context of the Existing Substances Regulation has been conducted and is available. This indicates that a possible risk to surface water, sediment and soil may exist from the use of this substance.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	818-61-1
Chemical Name	Hydroxyethyl Acrylate (Acrylic Acid, Monoester with Ethylene glycol, HEA)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The metabolism and excretion of HEA has been examined in male Fischer 344 rats using oral, intraperitoneal, and dermal and inhalation routes of exposure. Results indicated rapid metabolism via hydrolysis of the ester functionality, similar to many other acrylic acid esters. Rapid metabolism to CO_2 and urinary metabolites was observed for hydroxyethyl acrylate and was not route-dependent. The half-lives of elimination of radioactivity were approximately 14 hours for urine and 17 hours for CO_2. The half-life of elimination of radioactivity from plasma was approximately 26 hours.

Studies on the acute toxicity of hydroxyethyl acrylate indicate oral LD_{50} values of 540 – 1070 mg/kg bw. Clinical signs (following administration of 10% aqueous solution) included hypoactivity, rough fur, labored breathing, muscle weakness, GI tract hemorrhage in animals that died. Neat material may have burned the tissues of the mouth, throat, and GI tract. Acute dermal toxicity studies showed LD_{50} values of 154 (rabbits, undiluted material) and >1000 mg/kg bw (rats, vehicle olive oil). At high concentrations, the following were noted: decreased eyelid tone, decreased corneal reflex, loss of righting reflex, and muscle coordination. The acute inhalation data indicate that exposures of rats to 333 to 394 ppm for 4 or 8 hours caused irritation and were in the threshold area for lethality. Nearly 100% lethality was observed for rats at exposures of 500 ppm and above.

Hydroxyethyl acrylate is severely irritating to the skin. Upon eye contact, hydroxyethyl acrylate caused severe irritation with irreversible corneal injury. Skin sensitization studies in animals and humans indicate that hydroxyethyl acrylate is a sensitizer and may cross-react with other acrylates in some exposed individuals.

Repeated exposures to vapors of hydroxyethyl acrylate to rats via inhalation (7 hr/day, 5 days/week for four weeks) caused severe nasal irritation, resulting in death due to respiratory failure at higher concentrations. Concentration-related local irritation (focal ulcerative rhinitis) was seen at sub-lethal exposures. The LOAEC for subchronic exposure, based on irritation, was 5 ppm (24 mg/m^3) for hydroxyethyl acrylate. The principal treatment-related effects observed following 18 months exposure of laboratory rats to 5 ppm of hydroxyethyl acrylate were also related to irritation of the respiratory tract, without significant evidence of systemic toxicity.

Hydroxyethyl acrylate was not mutagenic to *Salmonella typhimurium* (bacterial reverse mutation assay) *in vitro* with or without metabolic activation but was positive with metabolic activation when tested with two *E. coli* strains. No evidence of chromosomal damage was seen when as part of the 18-month chronic inhalation study, four rats/sex/group were killed after 12-months exposure and the bone marrow cells examined for chromosomal damage. Hydroxypropyl acrylate (an analog) was not mutagenic in an *in vivo* mouse micronucleus study. Overall, hydroxyethyl acrylate did not show evidence of mutagenic potential *in vivo* by the inhalation route of 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.

Histopathological examination of the reproductive organs of rats from the 18-month inhalation study revealed an increase relative to controls in a normally observed age-related lesion (fibrinoid degeneration in the vascular channels of the testes) and uterine inflammation (without any other associated histopathological effects). Neither effect was considered treatment-related or adverse to reproduction. Dietary administration of hydroxyethyl acrylate to rats or dogs did not result in treatment-related effects on testicular weight or histopathology of the testes or uterus.

In a well-conducted inhalation study exposing pregnant rats to hydroxyethyl acrylate from gestation day 6 to 20 to 0, 1, 5 or 10 ppm (0, 4.8, 24 or 48 mg/m^3) hydroxyethyl acrylate, maternal body weight gain was reduced at 10 ppm over the entire exposure period, and found to be statistically different from controls on days 6-13, but no embryo-fetal or developmental toxicity or teratogenicity was observed. Based on the available studies, hydroxyethyl acrylate does not show evidence for developmental toxicity.

No evidence of a carcinogenic effect was observed in a chronic toxicity/oncogenicity study conducted by the inhalation route of exposure.

Environment

The melting point is –60.2°C and the boiling point is 210°C. The vapor pressure is 0.06974 hPa at 25°C. The measured log Kow has been reported to be – 0.21. Hydroxyethyl acrylate is miscible in water at 25°C. The specific gravity is 1.101 g/cm^3 at 25°C.

Hydroxyethyl acrylate is photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 10 hours (calculated). The hydrolysis rate of hydroxyethyl acrylate at 25°C is pH dependent with no hydrolysis observed at a pH of 3; rapid hydrolysis at pH 11 with a half-life of 0.051 days; and a half-life of >270 days at pH 7. The hydrolysis half-life at 40°C and pH 7 or 9 is 39.6 days and 15 hours, respectively.

Distribution modeling using Mackay Level I indicates hydroxyethyl acrylate released into the environment partitions almost completely (99.9%) to the water phase. Fugacity model Level III with 100% of the hydroxyethyl acrylate release to air distribution is: <1% (air), 37% (water), 62.5% (soil) and <0.1% (sediment). Fugacity model Level III distribution with 100% of the hydroxyethyl acrylate release to water (assuming accidental release) is: <0.1% (air), 100% (water), <0.1% (soil) and <0.1% (sediment).

A low bioaccumulation potential is expected based on the partition coefficient and other physical/chemical parameters (BCF of 0.41, calculated). Hydroxyethyl acrylate is readily biodegradable.

Hydroxyethyl acrylate is acutely toxic to aquatic organisms. The 96-hour LC_{50} for fathead minnow was. 4.8 mg/L (measured), the 48-hour EC_{50} for *Daphnia magna* was 0.78 mg/L (nominal) and the 96-hour EC_{50} values for biomass and growth rate of algae (*Selenastrum capricornutum*) were 4.12 and 8.26 mg/L (nominal), respectively.

Exposure

In 2001, the worldwide production volume of hydroxyethyl acrylate was estimated to be 15,000 tonnes. Of that, the US production volume was approximately 10,000 tonnes. Hydroxyethyl acrylate is produced and used mainly in closed systems. Its principle use is either as a co-monomer in the manufacture of polymers or as a chemical reactant in the manufacture of chemical intermediates. The polymers and chemical intermediates made with hydroxyethyl acrylate find applications in automotive top coatings, architectural coatings, photocure resins, and adhesives.

Results from workplace measurements at a US production site indicated that hydroxyethyl acrylate did not exceed an occupational exposure limit of 1 ppm in 140 samples collected over 20 years. Worker exposure is limited by the use of enclosed processing systems, industrial hygiene controls and personal protective measures such as goggles, gloves, protective clothing and organic respirator, if necessary. Hydroxyethyl acrylate has a characteristic acrylic odor, which

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.

can provide a measure of warning of the presence of hydroxyethyl acrylate vapors. End-use consumer products contain only trace levels of acrylic acid and esters (as a result of polymerization). Therefore, consumer exposure to acrylate monomers is not anticipated.

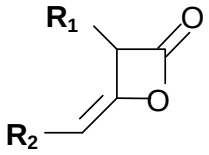
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (severe eye irritation with corneal injury which may result in permanent impairment of vision, even blindness, skin and upper respiratory tract irritation, skin sensitization, and acute toxicity from inhalation exposure). Based on exposure data presented by the Sponsor Country (relating to production in one country which accounts for 67% of global production and relating to the use pattern in the Sponsor country), this chemical is currently of low priority for further work. Countries may wish to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical possesses properties indicating a hazard for the environment (fish, invertebrate, and algae). However, the chemical is of low priority for further work for the environment because of its ready biodegradability and the limited potential for bioaccumulation.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	84989-41-3* *CAS No 68390-56-7 is used in the USA
Chemical Name	2-Oxetanone, 3-C_{12-16}-alkyl-4-C_{13-17}-alkylidene (Alkyl Ketene Dimer, AKD)
Structural Formula	 $R_1 = C_{12-16}$, $R_2 = C_{12-16}$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There are no specific toxicokinetic data for alkyl ketene dimer (AKD). Due to the high lipophilicity and the effects in rat feeding studies, intestinal absorption and distribution in the body is anticipated. Cross reading from a newly developed alkyl ketene dimer demonstrated that dermal absorption is very low. AKD is of low toxicity after a single exposure (LD_{50} oral, rat >40 000 mg/kg bw). It is neither irritating to skin and eyes nor a skin sensitiser, as concluded from experimental animal and human studies. AKD was not genotoxic *in vitro* (three Ames tests and a mammalian cell chromosomal aberration test). There are no other data regarding the carcinogenic potential of AKD. In an OECD TG 422 screening test, repeated oral gavage of 100, 350 and 1000 mg/kg bw/day to rats resulted in inflammation of several organs, including female reproductive organs. As a result of ovary inflammations, an increase in pre-implantation losses (the number of implantation sites compared to corpora lutea was reduced) was observed at all doses; this effect is secondary to the general organ inflammation and therefore not a specific reproductive effect. No effects on male reproductive organs and pup development were observed. In a 90-day feeding study in rats inflammation of several organs (typically lymph nodes, liver, heart, kidney, pancreas and lung) were observed at concentrations of 650 ppm and 6500 ppm (which was the highest dose tested) in the feed; at a concentration of 65 ppm in the feed no adverse effects were observed. The LOAEL was 63.4 and 69.6 mg/kg bw/day and the NOAEL was 6.3 and 6.8 mg/kg bw/day for males and females, respectively (estimated from dietary concentrations of 650 and 65 ppm, respectively). The observed inflammation is considered a generic response in the rats to higher molecular weight hydrocarbons, and is not considered to be a response specific to AKD.

Environment

Alkyl ketene dimer (AKD) is a waxy solid material with a low melting point. i.e., between 43.6 °C and 56.4 °C, and decomposes above 200° Celsius without boiling. It has a very low solubility in water, predicted to be 5.6×10^{-7} to 4.8×10^{-11} mg/l. Its predicted Log Kow of 11 – 15 suggests a high bioaccumulation potential. Its vapour pressure is predicted to be very low, 5.85×10^{-13} – 6.12×10^{-10} hPa. Distribution modelling using Mackay Level I indicates that AKD will partition to sediment and soil (49.54% to soil and 50.10% to sediment) and the estimated Koc of 1.51×10^{7} - 2×10^{9} indicates that AKD will adsorb strongly to soil and sediments. Its Henry's law constant is predicted to be 46 – 648 indicating that AKD could partition from water into the atmosphere but in practice this is unlikely to be

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.

an important route of transport in the environment due to its low water solubility.

AKD is predicted to photodegrade rapidly in air with a half life for indirect photolysis of 3.7 hours. Studies on the hydrolysis of commercial AKD preparations show that AKD hydrolyses readily under neutral and alkaline conditions but only slowly under acid conditions. Half lives of between 23 – 140 hours have been calculated for AKD emulsion at 30˚C, pH 8, under the conditions of a paper mill. There is no information available on the hydrolysis half lives in the aquatic environment. Based on the available data, AKD is expected to hydrolyse readily under neutral and alkaline conditions in the environment and is assumed to be stable to hydrolysis at acidic pHs in the environment, pH 5-7. AKD has been shown to be readily biodegradable when tested in the presence of small amounts of emulsifier, used to increase bioavailability of the substance to micro-organisms, with >94% biodegradation in 28 days.

Alkyl ketene dimer showed no toxicity in acute toxicity tests on the fish *Danio rerio*, the aquatic invertebrate Daphnia magna and the algae *Selenastrum capricornutum*. The E/LC50s were all above the water solubility limit. In a 21 day reproduction test with *Daphnia magna*, conducted on a dispersion of AKD, no effects on either reproduction or growth were observed at the highest concentration tested (mean measured concentration of 0.8 mg/l). This indicates that the NOEC is greater than the water solubility limit. There is no data available on toxicity to sediment dwelling organisms. AKD is not inhibitory to activated sludge microorganisms, in an activated sludge respiration inhibition test the 30 minute EC20 was > 1000 mg/l.

AKD is of low acute toxicity to plants and earthworms. The 14d EC50 (emergence) and 28d EC50 (vegetative growth) for oat (*Avena sativa*), sunflower (*Helianthus annuus*) and mung bean (*Phaseolus aureus*) were all > 1000 mg/kg soil. The 14 day LC50 for the earthworm *Eisenia foetida* is >1000 mg/kg.

Exposure

Alkyl ketene dimers are produced in a Best Available Technology [BAT] closed process in Belgium, China, France, Finland, Germany, Italy, Japan, Sweden, United Kingdom and United States of America. The total production volume amount is between 10 000 and 50 000 tonnes per annum. AKD is normally transported and used as a dispersion containing between 5 and 25% AKD.

Alkyl Ketene Dimer [AKD] is used exclusively as a process chemical by the paper industry to add some hydrophobic character to the surface of the cellulose fibres. This is traditionally known within the industry as “sizing”. Typical examples of paper products manufactured with AKD are office paper, liquid packaging board and folding-box board. The amount used is between 0.05 and 0.3% by weight of the end product.

Releases into the environment may occur during the production and processing of AKD. AKD itself is unlikely to be detected in paper as it either reacts with the cellulose to form a covalent bond or with the water present in the paper making system to form the dialkyl ketone. Releases of AKD itself are therefore not anticipated from paper recycling. Release of AKD to wastewater treatment plants could potentially occur from production, formulation and paper making sites.

A survey completed by the GPA consortium demonstrated that, for the five production sites covered by the survey, 29 people (2 of whom were female) worked continuously with the product and another 20 people (no females) worked intermittently, i.e., up to 50% of their time. The recommended personal protection equipment [PPE] included gloves, goggles and overalls in the manufacturing, maintenance and disposal/waste management areas.

Consumer exposure to AKD is negligible because it is only used in the manufacture of paper and board. Paper made with AKD can be used in the manufacture of packaging materials intended to come into contact with food. However, the AKD itself will not be detected in the paper as it will have either reacted with the cellulose fibre to form a covalent bond or with the water present in the paper making system to form the dialkyl ketone. AKD has many national approvals for use in food contact packaging materials, e.g., in America, France, Germany, Italy and The Netherlands.

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.

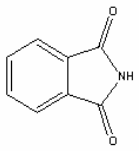
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (inflammation of several organs following repeated oral exposure, and secondary to this, pre-implantation loss). 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 high Log Kow of AKD suggests it has a high bioaccumulation potential. However, the concern that AKD could cause long term effects in the environment is reduced by the data which indicate that AKD is readily biodegradable by micro-organisms when tested in the presence of a 1.5% concentration of emulsifier and hydrolyses under neutral and alkaline conditions. AKD shows low acute toxicity to aquatic organisms, plants and earthworm and low chronic toxicity to Daphnia and algae. It is therefore of low priority for further work due to its low hazard potential.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	85-41-6
Chemical Name	Phthalimide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Comprehensive data on toxicokinetic, metabolism, or distribution are not available. In a limited animal study placental transfer of phthalimide is demonstrated.

The acute toxicity of phthalimide has been well characterized and is generally low. Reduced appetite, reduced activity and slight lethargy for one to three days are the only effects observed in animals dosed with 7940 mg/kg bw by the oral or dermal route.

In animal experiments phthalimide is slightly irritating to the skin or the eye. Observed effects are reversible within 2 to 3 days.

Phthalimide is of low repeated dose toxicity. In a sub-acute inhalation study in rats the NOAEL for males is estimated to be 523 mg/m^3 (highest dose tested), and in females the NOAEL is 154 mg/m^3 based on the significant lower lung to body weight ratio in the 523 mg/m^3 dose group, although no histopathological alteration of the lung was observed at any dose. Oral repeated dose toxicity was investigated in a recent guideline study (OECD TG 422). No compound related effects were observed in male rats dosed with up to 1000 mg/kg bw/day (highest dose tested). In one female rat given 1000 mg/kg bw/day food consumption and body weight were decreased, and histopathological examination revealed peritoneal fatty changes in the liver, renal epithelial fatty changes, and atrophy in the thymus. Consequently, the NOEL for oral repeated dose toxicity is considered to be 500 mg/kg bw/day for females and 1000 mg/kg bw/day for males (highest dose tested).

Phthalimide is not active in a variety of mutagenicity tests *in vitro*. It is not mutagenic in "bacterial reverse mutation test" (OECD TG 471, and 472) in the presence and absence of metabolic activation system (S9-mix). It does not induce mutations in the mouse lymphoma assay. In the chromosomal aberration test (OECD TG 473) no polyploidy is observed at any concentration in the absence and presence of metabolic activation. Weak clastogenic effects are observed in the presence of metabolic activation at high concentrations where cytotoxicity is seen in parallel. Genotoxicity studies *in vivo* are not available. Overall phthalimide is considered to be not genotoxic *in vitro* and based on the available data it is anticipated that it will not be genotoxic *in vivo*.

In the previously described "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (OECD TG 422) the NOEL for reproductive and developmental toxicity is 250 mg/kg bw/day, based on the observation that pups in the 500 and 1000 mg/kg bw/day groups showed slightly reduced body weights or lower body-weight gains in the lactation period at day 4, and that 8 pups were dead or cannibalized and the surviving 9 pups showed body weight loss in one female dosed with 1000 mg/kg bw/day with abnormal histopathological

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.

findings.

No evidence for embryonic/fetal lethality or teratogenicity was seen after oral application to hamsters as well as in two oral studies in rabbits both being limited by an insufficient study design: either low number of animals tested and only external malformations evaluated or only a single dose tested.

Environment

Phthalimide forms white crystalline leaflets with a melting point of 238 °C. For the boiling point it was reported both sublimation and a measured value of > 350 °C at 1013hPa (OECD TG 103). The measured density is 1.455 at 25 °C, the measured vapor pressure is 0.00056 Pa at 25 °C (OECD TG 104), the measured log K_{ow} 1.15. The measured solubility in water is 370 mg/l at 25 °C. The flash point is 214 °C, the auto flammability (ignition temperature) 530 °C. Phthalimide is a weak acid with a pK_a of 8.3.

In the atmosphere phthalimide is degraded by photochemically produced OH radicals. The half-life is calculated to be ca. 2.6 days. Removal of phthalimide in rain water and soil was influenced by light. Phthalimide is expected to hydrolyze in the hydrosphere to phthalic acid and ammonia with phthalamic acid being an intermediate. According to a test performed according to OECD TG 111, hydrolysis is faster in basic solution with a half-life of 1.1 h at pH 9; $t_{1/2}$ at pH 7 is 57 h, and at pH 4 is 115 days. Phthalimide is readily biodegradable with a biodegradation rate of 92 % after 14 days [OECD TG 301C]. In a Zahn-Wellens test 96.2 % phthalimide were degraded within 5 days, and in a test using acclimated activated sludge 63-88 % were degraded within 24 h.

According to the Mackay fugacity model level I, the favourite target compartments of phthalimide are water with 99.8 %, followed by sediment and soil with both 0.1 %. The calculated Henry's law constant 1.03×10^{-3} - 0.22×10^{-3} Pa m^3/mol at 25 °C, proves a very low potential for volatilisation from surface waters.

The calculated BCF of 1.53 and the experimental bioconcentration factors of 4.6-8.5 at 1.0 mg/l and 4.7-22 at 0.1 mg/l phthalimide, respectively, measured in the fish *Cyprinus carpio* [method similar to OECD TG 305], indicate no significant bioaccumulation potential.

No experimental data on geoaccumulation is available. The calculated K_{oc} values of 10.75-10.84 indicate a low sorption potential of phthalimide onto the organic phase of soil or sediments.

Concerning the acute toxicity of phthalimide towards aquatic species, experimental results for the three trophic levels are available. The lowest valid results of phthalimide for each aquatic trophic level are the following (n = nominal concentration, e = mean measured concentration):

Salmo gairdneri (fish)	96 h-LC_{50} = 51 mg/l (n)
Daphnia magna (aq.invertebrate):	48 h-EC_{50} = 21 mg/l (e)
Selenastrum capricornutum (algae):	72 h-E_bC_{50} = 33 mg/l (e)
	72 h-E_rC_{50} = 161 mg/l (e)
Pseudomonas putida (bacteria):	16 h-EC_0 = 260 mg/l (e)

Results on chronic toxicity towards *Daphnia* and algae are available as well:

Daphnia magna (aq.invertebrate):	21 d-NOEC = 7.6 mg/l (e)
Selenastrum capricornutum (algae):	72 h-$NOEC_b$ = 0.6 mg/l (e)
	72 h-$NOEC_r$ = 10.7 mg/l (e)

No standard tests on toxicity towards terrestrial plants are available. Phthalimide and phthalimide potassium salt were shown to increase vigour of plants *Fragaria ananassa* and *Datura metel* respectively. The derivative of phthalimide, phthalimide potassium salt was additionally reported not to be toxic towards *Datura metel*. Other available results:

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.

Lactuca sativa (plant):	3 d-EC_{50} = 34 mg/l (n)	[endpoint germination]
Bufo bufo japonicus (amphibian):	24 h-$LC_0 \geq$ 42 mg/l (n)	[toad tadpole toxicity]

Exposure

Phthalimide is obtained by heating phthalic anhydride with ammonia. The resulting product is often not isolated but directly converted. In 1998, the global production capacity of isolated phthalimide is estimated to be more than 8,000 tonnes/a, located in the EU. Another approximately 18,000 tonnes/a worldwide is converted directly to anthranilic acid (capacities in tonnes/a): Germany 10,000, UK 2,000, Japan 500, USA 6,000, India 120, and China <300. In Germany, there is one production site for isolated phthalimide with an estimated manufacturing capacity of 2,500 tonnes/a. In Japan, the manufacturing volume is 1000-2000 tonnes/a.

Phthalimide is exclusively used as an intermediate in the production of

- agricultural pesticides
- pigments and dyes
- pharmaceuticals and
- rubber processing chemicals

The only producer of isolated phthalimide in Germany manufactures and processes phthalimide in closed systems. The exhausts from manufacturing and processing are connected to particulate filters and air washing units. Virtually no phthalimide is emitted into the atmosphere. Waste from the manufacturing process is incinerated in incinerators for hazardous wastes. The wastewater from manufacturing and processing is led to a producer-owned industrial wastewater treatment plant at each site. Neither phthalimide nor its hydrolysis product phthalic acid were detected in the effluents of the wastewater treatment plants. To protect workers from exposure, several precautionary and protective measures are taken, e.g. during sampling, repair and maintenance. In the Sponsor country (Japan), similar measures are applied to protect the environment and the workers (e.g. phthalimide was not detectable in the effluents of the wastewater treatment plant of the production plant).

Phthalimide is an intermediate in dithalimfos (O,O-diethyl phthalimidophosphonothioate) and folpet (*N*-(trichloromethylthio)phthalimide) degradation but is shown to be rapidly degraded under environmental conditions.
A direct use of phthalimide is not known. Phthalimide is listed confidentially in the Danish and Finnish Product Registers in 2001 (last year of record). It is not listed in the Swedish and Norwegian Product Registers. The main use category is “use in closed system”. The Swiss product register does not list a consumer product containing phthalimide. In Japan; phthalimide has not been detected in 151 agricultural products (limit of detection: 0.01 ppm). Exposure of consumers to phthalimide is considered to be negligible.

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.

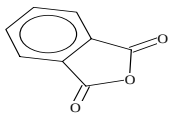
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (some indications for reproductive toxicity at high doses). Based on data presented by the Sponsor country and by the main producer in Germany (relating to production by 2 producers in 2 countries which accounts for 44-56 % of global production and relating to the use pattern in several 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 is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (aquatic toxicity). These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure level. They should nevertheless be noted by chemical safety professionals and users.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	85-44-9
Chemical Name	Phthalic anhydride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

On contact with water, phthalic anhydride is rapidly hydrolyzed to phthalic acid. Unconjugated phthalic acid was found in the urine of humans exposed to phthalic anhydride by the inhalation route, demonstrating systemic absorption and elimination via the urine and the existence of phthalic acid as a hydrolysis product *in vivo*.

The oral LD_{50} in rats was 1530 mg/kg bw. Clinical signs at doses equal or higher than 500 mg/kg bw included sedation, imbalance, and bloodshot eyes. There were no reliable animal acute toxicity studies available for the inhalation and dermal routes of exposure.

In poorly documented human case reports, which provide no reliable information on exposure levels, headache, dizziness, nausea, epigastric burning and a feeling of suffocation were described after acute occupational exposure to phthalic anhydride dust or vapor.

In rabbits, phthalic anhydride was slightly irritating to the skin (OECD TG 404), and irritating to the eyes. In humans, effects on the eye after occupational exposure are described (including conjunctivitis, lacrimation, corneal ulceration, necrosis, and photophobia). For humans, phthalic anhydride in the form of vapor, fumes, or dust is a primary irritant to mucous membranes and the upper respiratory tract. Initial exposure produces coughing, sneezing, burning sensations in the nose and throat, and increased mucous secretion. Repeated or continued exposures may result in general inflammation of the respiratory tract, nasal ulceration and bleeding, atrophy of the mucous membranes (reversible), loss of smell, hoarseness, bronchitis, urticaria, and symptoms of allergic hypersensitivity.

Phthalic anhydride demonstrated skin sensitizing properties in animals, with positive results being observed in guinea pig tests according to OECD TG 406 and in local lymph node assays similar to OECD TG 429. Evidence that phthalic anhydride has respiratory sensitization potential has been demonstrated in an experimental guinea pig model. In humans, there are a number of reports providing information on the respiratory sensitization potential of phthalic anhydride after occupational exposure. Workers were reported to suffer from work-related rhinitis, chronic productive bronchitis, and work-associated asthma. Phthalic anhydride sensitization is generally associated with either an asthma-rhinitis-conjunctivitis syndrome or with a delayed reaction and influenza-like symptoms and with increased IgG and/or phthalic anhydride specific IgE levels in the blood. Reports on skin reactions in humans are rare.

Phthalic anhydride has been shown to have low repeated dose toxicity by the oral route in rats. The evidence of toxicity in a chronic rat study is limited to adverse effects on body-weight gain at the dose level of 1000 mg/kg bw/day. The NOAEL was at 500 mg/kg bw/day. It is noted that no hematology and clinical biochemistry examinations were performed in this study. A NOAEL could not be established in a chronic feeding study in mice

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.

because of pathological effects seen down to the lowest tested dose level (LOAELs: 12 019 ppm level in female mice = approximately 1717 mg/kg bw/day, and 16 346 ppm in male mice = approximately 2340 mg/kg bw/day; increased incidences of lung and kidney lymphocytosis in the males and females, and dose-related adrenal atrophy and mineralization of the thalamus in males. The LOAELs are time-weighted averages because a dose reduction in males from 25 000 to 12 500 ppm (= approximately 1785 mg/kg bw/day) and for females from 12 500 to 6250 ppm (= approximately 890 mg/kg bw/day) was necessary after 32 weeks of exposure due to reduced weight gains). There were no valid repeated dose studies available using the dermal or respiratory routes of exposure.

Phthalic anhydride was not mutagenic in the Ames test with and without metabolic activation (OECD TG 471). Chromosomal aberrations were induced in mammalian cells *in vitro* at the highest phthalic anhydride concentrations (10 mM) only in the absence of S9 mix with concomitant marked cytotoxicity and compound precipitate. *In vivo* studies are not available. Overall, it can be concluded that phthalic anhydride is genotoxic *in vitro* at extremely high, cytotoxic concentrations, and only in the absence of a metabolic activation system. This genotoxic effect is not expected to be relevant under *in vivo* conditions, where phthalic anhydride is rapidly hydrolyzed to the non-genotoxic phthalic acid.

No evidence of carcinogenicity was seen in rats after exposure to approximately 1000 mg/kg bw/day of phthalic anhydride, or in male and female mice after exposure to 4670, and 3430 mg/kg bw/day, respectively, in comprehensive chronic (105-week) feeding studies.

There was no fertility study with phthalic anhydride available. No evidence of toxicity to reproductive organs was observed in comprehensive carcinogenicity studies in rats and mice, as no treatment-related changes were observed for any reproductive organ investigated during macroscopic and microscopic examination (NOAEL, rat: 1000 mg/kg bw/day; NOAEL (time-weighted average), mouse: 3430 (f), 4670 (m) mg/kg bw/day). Following i.p. injection which is a route of exposure with unknown relevance for the normal human situation, of doses in the lethal range, developmental toxicity was found in mice in a poorly reported study. However, the chemical is quickly hydrolyzed to phthalic acid after oral, dermal or inhalation exposure. Phthalic acid was investigated in a developmental toxicity feeding study in rats and gave no evidence of embryotoxicity, or fetotoxicity at a non-maternally toxic dose level (1.25 % in feed = approximately 1000 mg/kg bw/day = NOAEL for maternal toxicity). Significant decreases in the weight of male fetuses and in the numbers of ossified centers of the caudal vertebrae were, however, found in the 5.0 % group, where maternal toxicity was also observed (NOAEL, developmental toxicity: 2.5 % in feed = approximately 1700 mg/kg bw/day). Based on the data of phthalic acid, the hydrolysis product of phthalic anhydride, it is concluded that, in the absence of maternal toxicity, phthalic anhydride is not a developmental toxicant.

Environment

Phthalic anhydride forms white flakes or needles with a melting point of about 132 °C. The boiling point is 284.5 °C at 1013 hPa. The density is 1.527 g/cm^3 at 20 °C, the vapor pressure 0.0006 hPa at 26.6 °C, the log K_{OW} = 1.6. The flash point is about 152 °C, and the auto flammability (ignition temperature) is 580 °C. Phthalic anhydride hydrolyzes in water at pH 6.8 - 7.24 with half-lives of 0.5 - 1 min at 25 °C, forming phthalic acid that has dissociation constants of about 2.8 and 5.4. Any phthalic anhydride emitted into the air or into the terrestrial compartment would be rapidly hydrolyzed by humidity in the air or in the soil, respectively.

In the atmosphere phthalic anhydride is degraded by photochemically produced OH radicals. The half-life is calculated to be about 21 days. For phthalic acid a half-life of 13 days is estimated. Removal of phthalic acid in sea water was proved to be influenced by light. Phthalic anhydride is readily biodegradable. In an aquatic ready test system (aerobic) conducted according to OECD TG 301D, > 70 % biodegradation was reported after 30 days for phthalic anhydride as well as for its degradation product, phthalic acid.

Due to the rapid hydrolysis of phthalic anhydride in water, the distribution of the hydrolysis product phthalic acid is calculated. According to the Mackay fugacity model level I, the favorite target compartment of phthalic acid is water with 99.9 %. The calculated Henry's law constants (2.21×10^{-7} Pa m^3/mol at 25 °C for phthalic acid, and 0.64 Pa m³/mol at 25 C for phthalic anhydride) prove a low potential for volatilization from surface waters.

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.

The bioconcentration factors (BCF) of 3.4 for phthalic anhydride and 3.2 for phthalic acid, calculated from the octanol-water partition coefficients, indicate that there is a low potential for bioaccumulation of phthalic anhydride and phthalic acid in aquatic organisms. Tests with ^{14}C-phthalic acid in plants indicate a low potential of phthalic anhydride and phthalic acid for bioaccumulation in plants.

Experimentally obtained adsorption coefficients (K_{oc}) revealed a low sorption potential of phthalic acid. The experimentally achieved K_{oc} values were in the range of 2 to 31 depending on soil properties. In addition, K_{oc} values were calculated with PCKOCWIN v. 1.66 (K_{OC} = 11 for phthalic anhydride, and K_{oc} = 73 for phthalic acid). These results indicate a low sorption potential of phthalic anhydride and phthalic acid onto the organic phase of soil or sediments.

Concerning the toxicity of phthalic anhydride and its hydrolysis product phthalic acid to aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The result for algae refers both to growth rate and biomass. The tests were performed according to standard procedures or similar methods. The lowest effect values from the aquatic toxicity tests are (n = nominal concentration):

Cyprinus carpio	:	48 h-LC_{50}	>500 mg/l (n) (phthalic acid)
Danio rerio	:	7 d-LC_{50}	= 560 mg/l (n)
Oncorhynchus mykiss (*S. gairdneri*)	:	60 d-NOEC	= 10 mg/l (n)
Daphnia magna	:	24 h-EC_{50}	= 140 mg/l (n) (phthalic acid)
Desmodesmus subspicatus	:	72 h-EC_{50}	≥ 100 mg/l (n) (phthalic acid)
Desmodesmus subspicatus	:	72 h-NOEC	≥ 100 mg/l (n) (phthalic acid).

Since chronic toxicity tests are available for fish and algae with phthalic anhydride and phthalic acid, respectively, an assessment factor of 50 can be applied using the lowest available effect concentration (NOEC = 10 mg/l) which was obtained for *Oncorhynchus mykiss* (*S. gairdneri*). Calculation yielded a $PNEC_{aqua}$ of 200 µg/l.

Exposure

Phthalic anhydride is produced by oxidation of o-xylene or naphthalene. In 2000, the world wide production volume of phthalic anhydride is estimated to be about 3 232 000 tonnes, with the following regional distribution (tonnes): Western Europe 770 000; Eastern Europe 171 000; USA 485 000; Mexico, South and Central America 249 000; Japan 302 000; Middle East 75 000; other Asia 1 156 000; and others 24 000.

Phthalic anhydride is an important intermediate in the chemical industry. The major subsequent product groups are plasticizers (56 %), unsaturated polyester resins (17 %), and alkyd resins (17 %). Phthalic anhydride is also used as an intermediate in the production of pigments and dyes, agricultural, pharmaceutical, and several other chemical products. Phthalic anhydride containing materials are used in coatings applications for home appliances, automobiles, medical devices and furniture.

Phthalic anhydride is listed in the Swedish and Swiss Product Registers and in the SPIN Database (including consumer products).

The most probable human exposure to phthalic anhydride is through dermal contact or inhalation during manufacture or use. In the Sponsor country, exposure is controlled in occupational settings. Consumers may be exposed to phthalic anhydride from the use of plastics, furniture, glues, coatings and home products from which phthalic anhydride may leach. Consumers may be exposed to (non-synthetic) phthalic anhydride from natural flavor and oak smoke. Oak smoke and its aqueous preparations are used in the production of several smoked foods and alcoholic beverages. Phthalic anhydride is reported to occur in the volatile flavor of baked potatoes, in spent chlorination liquor from sulphite bleaching, in a hazardous waste dump in Northern Spain, and in sediments of San Diego Bay after sediment pyrolysis. There is no study which unambiguously demonstrates that phthalic anhydride may occur in environmental waters or drinking water (phthalic anhydride may be formed as an artifact during gas chromatographic

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.

analysis). Phthalic anhydride is present in ambient air, fly ash, diesel exhaust, oak smoke, and pyrolysis products.

The Sponsor company manufactures phthalic anhydride in closed systems. During production virtually no phthalic anhydride is emitted into the atmosphere (< 25 kg/a) and into environmental waters.

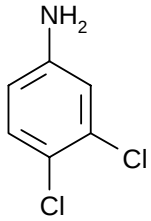
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (irritation of skin and respiratory system, serious eye damage, respiratory and skin sensitization). Based on data presented by the Sponsor country, adequate risk management measures are being applied for occupational settings. A potential for consumer exposure exists as a result of its use in plastics, furniture and home products. It is therefore recommended to perform an exposure assessment and, if then indicated, a risk assessment.

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-76-1
Chemical Name	3,4-Dichloroaniline
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Like other chloroanilines, the primary toxic effect of 3,4-dichloroaniline (3,4-DCA) is methaemoglobin formation. Acute intoxication is indicated by methaemoglobinemia (cyanosis), fatigue, dyspnoea, and muscle weakness.

In vitro studies on rat liver and kidney slices indicated that 3,4-DCA may have a hepatotoxic and nephrotoxic potential as other structurally related compounds observed after single in vivo applications.

3,4-DCA has demonstrated for rats moderate acute toxicity after oral application and after inhalation (LD50 values of 530 – 880 mg/kg bw and a LC50 of 3300 mg/m^3 (4 h) in a test according to OECD TG 403). Acute dermal toxicity demonstrated great species differences: In tests with rats the dermal LD50 was detected to exceed 1000 mg/kg bw (no mortalities and no toxic signs) whereas a test with male rabbits demonstrated a dermal LD50 of 300 mg/kg bw.

In a Draize test with rabbits according to OECD TG 404 3,4-DCA caused mild skin irritation. In two Draize eye tests with rabbits according OECD TG 405 moderate reversible irritation of conjunctivae, iris and cornea occurred, but corneal vascularization was observed 7-14 days after instillation of the substance into eyes.

In humans, cyanosis, methaemoglobinemia, eye and skin irritation were observed after prolonged occupational exposure to mixed chemicals including 3,4-DCA.

3,4-DCA has no local corrosive properties, but demonstrated skin sensitizing properties in a Magnusson Kligman test with guinea pigs according to OECD TG 406. Sensitization of humans is not reported.

In rats, mice, and rabbits repeated inhalation, oral or dermal exposure to 3,4-DCA or structurally related compounds resulted primarily in methaemoglobinemia and hemolytic anemia. Spleen weight increase, microscopically hemosiderosis in the spleen, liver, and/or kidneys and increased compensatory erythropoeisis were observed as main effects. From the 14-day inhalation study with 10, 45, or 200 mg/m^3 3,4-DCA to rats (OECD TG 412, 6 h/d, 5 d/week) a LOAEC of 10 mg/m^3 was derived based on significant increase of methaemoglobin levels. Similar effects were seen on male rabbits after daily application of 60 mg/kg bw to the dorsal skin on 10 days. 3,4-DCA did not induce gene mutations in all bacterial tests according to OECD TG 471.

In vitro tests were negative for gene mutations with CHO cells (OECD TG 476) and for chromosomal aberrations with human lymphocytes (OECD TG 473). Limited evidence for a mutagenic potential may be derived from a positive a mitotic spindle damage test with V79 cells. The clearly negative *in vivo* micronucleus tests according

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.

OECD TG 474 indicate that this potential is unlikely to be expressed *in vivo*.

No data on the cancerogenic potency of 3,4-DCA itself is available. From data on the structurally related compound 4-chloroaniline some concern may be derived that 3,4-DCA might have carcinogenic properties, too. However, the available metabolic data give no evidence for an in vivo dehalogenation of 3,4-DCA to 4-chloroaniline. Thus this suspicion is considered to be negligible.

The assessment of data from the available teratology gavage study with rats according to OECD TG 414 did not indicate any significant developmental toxicity (doses of 5, 25, or 125 mg/kg bw/d). Borderline developmental toxicity occurred at the clearly maternally toxic high dose level of 125 mg/kg bw/d in form of a slight but not statistically significant increase in resorptions and consequently post-implantation loss. Also a significant delay in ossification of a few skeletal elements was observed. Thus, the NOAEL for developmental toxicity is 25 mg/kg bw/d, whereas that for maternal toxicity is 5 mg/kg bw/d (reduced food consumption and average body weight gain).

There are no adequate data available on fertility impairment. Limited data from short term repeated dose toxicity studies on structurally related compounds such as 2-chloroaniline and 2,5-DCA did not reveal changes in male reproductive organs. However, 3,4-DCA is one of the metabolites which are formed in vivo from the herbicide diuron. In a 2-year study in dogs administration of up to 1250 mg/kg food (highest dose, equivalent to 62.5 mg/kg bw/d diuron) resulted in formation of 1.2% 3,4-DCA. No histopathological changes in gonads and uterus were reported at this dose of 62.5 mg/kg bw/d diuron (NOAEL) which represents an internal exposure to 3,4-DCA of 0.75 mg/kg bw. The weight of evidence indicates that there is no evidence of effects on fertility; therefore, no further testing is necessary.

Environment

3,4-DCA has a Koc of 334 l/kg calculated from a log Pow of 2.7, a water solubility of 580 mg/l and a vapor pressure of 0.184 Pa at 20°C. Based on a Henry`s law constant of 0.05 Pa m^3mol^{-1}, only a low volatilization from the hydrosphere is to be expected. According to the Mackay fugacity model level I calculation, the favorite target compartment of DCA is water with 91.38 %, followed by soil with 3.62 %, sediment 3.38% and air 1.62%.

3,4-DCA is not readily and not inherently biodegradable. In surface waters, the substance is removed by photolysis and by chemisorption onto the organic matter of sediments.

In agricultural soils, DCA is formed by biodegradation of the plant protection agents. Within some days, DCA forms covalent bounds with soil organic matter. The reaction product is extremely slowly biodegraded and accumulates when the agents are periodically applied.

For 3,4-DCA short- and long term tests with fish, daphnids and algae are available. Daphnids are the most sensitive species in short term tests. For *Daphnia magna* a 48 h-LC50 of 0.23 mg/l and a 96 h LC50 of 0.16 mg/l could be found. The most sensitive species in long-term tests are *Brachydanio rerio* and *Poecilia reticulata* with 42d-NOECs of 2 µg/l. A PNEC of 0.2 µg/l was determined on the available data basis using an AF of 10. For the sediment one long-term test with *Lumbriculus variegatus* with a NOEC of 5 mg/kg dw for the endpoint total number of worms is available. With an assessment factor of 100, a PNECsediment of 0.05 mg/kg is calculated.

For the terrestrial compartment long-term data are available for plants, micro-organisms and invertebrates. The most sensitive species appears to be the micro-organisms with a 28 d-NOEC of 100 mg/kg for inhibition of nitrification. As long-term tests are available for species from three trophic levels an assessment factor of 10 can be used on the NOEC for the species showing the most sensitive endpoint, giving a PNECsoil of 10 mg/kg.

Exposure

In the European Union, in the period 1996 – 1998 13,500 – 15,500 t/a 3,4-DCA were produced, from this 3,700 – 4,600 t were exported. 3,4-Dichloroaniline (DCA) is produced by hydrogenation of 1,2-dichloro-4-nitrobenzene. More than 99% of the production volume are processed by phosgenation to the 3,4-dichlorophenylisocyanate. At the

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.

present for 3,4-DCA there is only one producer in the EU. 3,4-DCA is exclusively used as an intermediate in the chemical industry primarily for the synthesis of 3,4-dichlorphenylisocyanate as intermediate for the production of herbicides. Only small amounts of 3,4-DCA are used for the synthesis of the bactericide trichlorocarbanilide and an azo dye.

Manufacture of 3,4-DCA from 3,4-dichloronitrobenzene takes place in a closed environment. Therefore provided the integrity of the system is maintained there should be no human exposure during manufacture, Exposure could occur however during maintenance, cleaning or repair work or by taking samples and analysing them. The down stream users of EU produced 3,4-DCA also appear to use closed systems for manufacture of the products derived from 3,4-DCA.

The exposure of the general public is likely to be very low, since 3,4-DCA exposure will only occur via degradation of products that have 3,4-DCA as part of their structure.

During production 3,4-DCA it released via waste water into the hydrosphere. Further releases into the hydrosphere are expected from processing of the isocyanate compound to the pesticides diuron, linuron, and propanil.

A direct use of 3,4-DCA by consumers does not exist. There might be the possibility of a very low exposure of 3,4-DCA due its metabolic formation from diuron containing products. The herbicide diuron and paint formulations with this substance do not contain 3,4-DCA.

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

Human Health: The chemical possesses properties indicating a hazard for human health (skin and eye irritation, sensitization, methaemoglobinemia, developmental toxicity at maternally toxic doses). 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.

Note: A risk assessment performed in the European Union in the context of the EU Existing Substances Regulation reveals concern for several toxicological endpoints. A finalized risk reduction strategy for workers concluded, that the legislation for workers protection currently in force in the EU is considered to give an adequate framework to limit the risk of the substance to the extent needed.

Environment: The chemical possesses properties indicating a hazard for 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.

Note: This substance has been assessed in the European Union Risk Assessment program under Regulation EEC/793/93. A finalized risk reduction strategy for the environment concluded, that there is no longer a risk identified in the risk assessment from production and processing in the EU.
An environmental pollution of 3,4-dichloroaniline from the use of diuron as antifouling agent and as algicide in the construction sector has to be expected. These releases could not been taken into account in the risk characterization, as neither sufficient exposure relevant information nor an appropriate exposure model are available. Diuron is more toxic than 3,4-DCA and probably occurs in higher concentrations, thus the 3,4-DCA exposure from these applications should be covered by a diuron assessment.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	97-85-8
Chemical Name	Isobutyl isobutyrate
Structural Formula	CH_3-CH(CH_3)-CH_2-O-C(=O)-CH(CH_3)-CH_3

SUMMARY CONCLUSIONS OF THE SIAR

Analogue justification

Data from isobutanol toxicity studies have been included in the human health section. Data from isobutanol are useful when assessing the hazards associated with the systemic toxicity of isobutyl isobutyrate exposure due to the rapid and complete metabolism of isobutyl isobutyrate to isobutanol and isobutyric acid in vivo. Isobutanol is then further metabolized to isobutyric acid. Therefore, exposure to isobutyl isobutyrate via dermal, inhalation, and water or dietary administration is expected to result in the rapid appearance of isobutanol and isobutyric acid in the systemic circulation. Since exposure to either isobutyl isobutyrate or isobutanol results in systemic exposure to isobutanol and isobutyric acid, systemic toxicity data from studies that administer isobutanol directly are useful in identifying hazards associated with isobutyl isobutyrate exposure. Data from studies conducted with isobutyric acid were not included, since there were none available. The toxicokinetics of the metabolic reaction is documented and explained below.

The acute aquatic toxicity database of isobutyl isobutyrate was supported using data from a structural analog, compound, 2-ethylhexyl acetate (CAS# 103-09-3), alleviating the need for additional testing on isobutyl isobutyrate. Data from structurally similar compounds may be used to address the aquatic toxicity of isobutyl isobutyrate.

Human Health

Metabolism/toxicokinetic studies have been conducted with isobutyl isobutyrate using intravenous injections. Isobutyl isobutyrate levels peaked immediately after injection and rapidly decreased thereafter. The calculated T1/2 by one-compartment modeling was 11.1 seconds. Isobutyl isobutyrate is metabolized extremely rapidly in vivo to isobutanol and isobutyric acid. Isobutanol is then further oxidized to isobutyric acid.

The oral LD_{50} in rats is >6400 mg/kg bw. Dermal LD_{50} in male rabbits was >10 ml/kg bw. Inhalation LC_{66} values for vapor exposures were 5423 ppm (31.94 mg/L) in rats (6 hours of exposure). Exposures to 658 ppm caused no deaths in 6 hours. Isobutyl isobutyrate is a slight skin irritant. Data for eye irritation and skin sensitisation are not available.

An 18-week oral gavage study in rats at dose levels of 0,10,100, and 1,000 mg/kg/bw/day with isobutyl isobutyrate reported an increase in relative spleen weights following a slight decrease in terminal body weights in the male animals treated with 1,000 mg/kg/bw/day. The lack of histopathological findings in the spleen and the lack of effect in the female animals resulted in the NOAEL being 1,000 mg/kg/bw/day. Studies with isobutanol generally corroborate this value although acute signs of toxicity were noted immediately after oral dosing with isobutanol. The use of different vehicles (corn oil with isobutyl isobutyrate and distilled water with isobutanol) affects the rate of absorption of these related materials and explains the presence or absence of clinical signs immediately after oral exposures. An *in vitro* mutagenicity study in bacteria indicates that isobutyl isobutyrate is not a genotoxicant. In addition, isobutanol was negative in an *in vivo* mouse micronucleus study. An inhalation two-generation reproductive toxicity study conducted with Isobutanol (up to 2500 ppm; 7.58 mg/L) did not cause any parental systemic, reproductive, or neonatal toxicity when administered for two generations via whole-body exposure. No adverse developmental effects were noted in rats or rabbits exposed up to 10mg/L Isobutanol during gestation.

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

The available physicochemical data are adequate to describe the properties of isobutyl isobutyrate. Isobutyl isobutyrate has a melting point of -80.7 ^{o}C, boiling point of 148.6 ^{o}C and vapor pressure of 5.8 hPa at 25^{0}C, a water solubility of 520 mg/L at 20^{0}C and a calculated log K_{ow} of 2.68. The photochemical removal of isobutyl isobutyrate as mediated by hydroxyl radicals occurs with a calculated half-life of 1.947 days. Isobutyl isobutyrate is readily biodegradable under aerobic conditions, based on data for isopropyl- and isobutyl-acetate. Isobutyl isobutyrate volatilizes easily from moving rivers, but volatilizes only moderately from quiescent lakes and other surface water bodies (calculated volatilization half-lives of 1.67 hours from a river and 4.955days from a lake). Isobutyl isobutyrate is not persistent in the environment and is not likely to bioaccumulate in food webs. Using a calculated log K_{ow} of 2.68, the BCF is 23.1. Based on Level III distribution modeling (assuming equal releases to water, air, and soil) it is estimated that the majority of isobutyl isobutyrate released to the environment will partition into water (34.4%) and soil (52.7%), with a smaller amount in air (12.6%). The stability of isobutyl isobutyrate in water is pH dependent, at neutral pHs (7) the $T_{1/2}$ = 9.2 years at 25^{0}C and at higher pHs (8) the $T_{1/2}$ is shortened to 337 days.

Except for a study with the aquatic invertebrate, *Daphnia magna*, aquatic toxicity data are not available for isobutyl isobutyrate. Data for the structurally similar 2-ethylhexyl acetate (CAS# 103-09-3) were used to supplement the data for isobutyl isobutyrate. For fish, two studies with rainbow trout (*Oncorhynchus mykiss*) and 2-ethylhexyl acetate are available. Acute 96-h LC_{50}s of 8.27 and >4.2 mg/L were reported for 2-ethylhexyl acetate, respectively. Data are available with isobutyl isobutyrate and the invertebrate *Daphnia magna* with 48-h EC50 values of 55.8 to 59.3 mg/L reported. In addition, a daphnid study with 2-ethylhexyl acetate reported a 48-h EC_{50} of 22.9 mg/L. Data are available with 2-ethylhexyl acetate and the green alga *Selenastrum capricornutum* with a 72-h EC_{50} value of >21.9 mg/L and a 72-h NOEC of 10.3 mg/L reported. ECOSAR values for isobutyl isobutyrate were calculated to be 9.455 mg/L for fish, 27.556 mg/L for daphnids, and 0.771 mg/L for green algae. ECOSAR values for 2-ethylhexyl acetate were calculated to be 3.057 mg/L for fish, 3.571 mg/L for daphnids, and 0.260 mg/L for green algae. Data for 2-ethylhexyl acetate can be used to estimate the acute toxicity of isobutyl isobutyrate to fish and algae.

Exposure

Isobutyl isobutyrate occurs naturally in fruits and essential oils. Environmental concentrations of isobutyl isobutyrate may also occur from waste streams during manufacture or through solvent use in lacquers and thinners. Workplace exposure may occur via inhalation or dermal contact. Exposure during manufacture is limited by the enclosed nature of the process and by bulk handling and good manufacturing practices. Industrial and occasional consumer exposure can occur both dermally and via inhalation during application of lacquer and thinner formulations containing isobutyl isobutyrate. General population exposure can occur through inhalation of ambient air that may contain low concentrations resulting from industrial or commercial releases. General population exposure also occur through ingestion of foods containing isobutyl isobutyrate either naturally or as a synthetic flavorant (21 CFR § 121.1164).

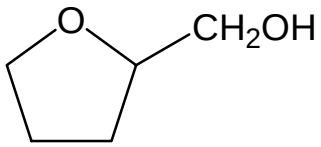
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

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

Environment: The chemical possesses properties indicating a hazard for the environment (fish and algae). However, the chemical is of low priority for further work due to ready biodegradability and limited potential for bioaccumulation.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	97-99-4
Chemical Name	2-Furanmethanol, tetrahydro-
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics, metabolism or distribution.

In an acute oral toxicity study [OECD TG 423] of 2-furanmethanol, tetrahydro- in rats, no changes in survival rate, body weight gain or necropsy findings were observed at 2000 mg/kg bw. At this dose, decreased locomotor activity and hypotonia were observed.

This chemical was a moderate eye irritant in rabbits but did not irritate the rabbit skin. Review sources suggest that it might be a moderate skin and eye irritant in humans.

There is no available information on sensitization.

In a repeated oral dose toxicity study [Japanese TG equivalent to OECD TG 407], Crj:CD(SD)IGS rats were administered by gavage at 0 (vehicle: distilled water), 10, 40, 150 or 600 mg/kg bw/day for 28 days. The initial numbers of rats were 10/sex at 0 and 600 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 600 mg/kg bw/day were kept without further treatment for another 14 days (recovery period). Increased locomotor activity followed by decreased locomotor activity and adoption of a prone position in males and females, and lowered grip strength of the hindlimb in males were found at 600 mg/kg bw/day. Increased locomotor activity was observed in females at 150 mg/kg bw/day. At 600 mg/kg bw/day, animals showed decreased body weight gain in males, reduced food consumption in males and females, and decreased urinary pH in males. . At this dose, hematological examinations revealed decreases in the mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocyte count and platelet count, and prolonged prothrombin time in males and females and decreases in the reticulocyte count in males and hemoglobin concentration in females. Blood biochemical examinations revealed decreases in the levels of alkaline phosphates (ALP), total protein, albumin, total bilirubin and calcium in males and females, and lactate dehydrogenase (LDH), triglyceride, blood urea nitrogen (BUN) and sodium in males at 600 mg/kg bw/day. At 150 mg/kg bw/day, a decrease in total protein was observed in males. Decreases in the relative weights of the thymus in males and females and pituitary in females, and an increase in the relative weights of the kidney in females were found at 600 mg/kg bw/day. At 150 mg/kg bw/day, a decrease in the relative weight of the pituitary was noted in females. Histopathological examinations revealed atrophy of the thymus in males and females, and atrophy of the red pulp with decreased extramedullary hematopoiesis and inflammation of the capsule of the spleen in males at 600 mg/kg bw/day. Necrosis of seminiferous tubular epithelium of the testes was observed at 150 and 600 mg/kg bw/day. Examination of the spermatogenic cycle showed a decrease in the ratio of the spermatid to Sertoli cell counts at 600 mg/kg bw/day. Histopathological examinations of the testes revealed a tendency for increase in the severity of changes at the end of

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.

the 14-day recovery period. Based on these findings, the NOAELs for repeated dose toxicity were 40 mg/kg bw/day in males and females.

In a reverse gene mutation assay [OECD TG 471], this chemical was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA1537, TA98 or *Escherichia coli* WP2 *uvr*A/ pKM101 with or without an exogenous metabolic activation. In a chromosomal aberration test [OECD TG 473], this chemical did not cause structural chromosomal aberration or polyploidy with or without an exogenous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells.

There is no available information on carcinogenicity.

In a preliminary reproductive toxicity study [OECD TG 421], Crj:CD(SD)IGS rats (12 animals/sex/dose) were administered by gavage at 0 (vehicle: distilled water), 15, 50, 150 or 500 mg/kg bw/day. Males were dosed for a total of 47 days beginning 14 days before mating. Females were dosed for a total of 42-52 days beginning 14 days before mating to day 4 of lactation throughout the mating and gestation period. Males showed decreased body weight gain at 500 mg/kg bw/day. At 150 mg/kg bw/day and higher, an increased locomotor activity in males and females, and decreased body weight gain in females were observed. At 500 mg/kg bw/day, decreased relative weights of the thymus, testes and epididymides, atrophy of the seminiferous tubule with hyperplasia of the interstitial cell in the testes, and decreased intraluminal sperms with cell debris in the epididymides were noted in males. Prolonged estrous cycles were observed at 500 mg/kg bw/day. At this dose, no females delivered their offspring and examination of the uterus of dams revealed early embryonic resorptions. Prolonged gestation length, decreased gestation index, and lowered delivery index, live birth index, numbers of pups born and live pups on postnatal days (PNDs) 0 and 4, and viability on PND 4 were observed at 150 mg/kg bw/day. No increase in the incidence of morphological abnormalities was found in pups of rats given this chemical. Based on these findings, the NOAEL for reproductive/developmental toxicity was 50 mg/kg bw/day.

Decreased testes weight, low sperm activity and/or testicular atrophy were caused in Beagle dogs fed a diet containing 1000 ppm 2-furanmethanol, tetrahydro- and higher for 90 days.

Rats (eight animals/group) were orally given this chemical at 0, 10, 50, 100, 500 or 1000 mg/kg bw/day on days 6 to 15 of pregnancy. Decreases in maternal body weight gain and food consumption were observed at 500 and 1000 mg/kg bw/day. A 100% incidence of early resorptions at 500 and 1000 mg/kg bw/day and decreased fetal weight at 100 mg/kg bw/day were found. The NOAELs for maternal and developmental toxicity were considered to be 100 and 50 mg/kg bw/day, respectively.

Environment

2-Furanmethanol, tetrahydro- is a colorless and flammable liquid with a water solubility of more than 250 g/L at 20 °C, a melting point of less than – 120 °C, a boiling point of 177.7 °C at 1013 hPa, a vapor pressure of 1.86 hPa at 25 °C and a relative density of 1.0544 at 20/20 °C. Based on the measured log Kow value of -0.11 bio- or geoaccumulation of this chemical is unlikely. Environmental distribution using Mackey level III suggests that when this chemical is released into the environment, it distributes mainly into water and soil. A calculated Henry's Law constant of 4.09^{-9} atm-m^3/mole indicates that only a limited extent of volatilisation from water may occur. 2-Furanmethanol, tetrahydro- is readily biodegradable (10-day window fulfilled) but abiotic degradation is not expected in water. In the atmosphere this chemical is indirectly photodegraded by reaction with OH radicals with a half-life of 0.5 days.

Ecotoxicity data for this substance was available in aquatic species from three trophic levels. In the algal growth inhibition test (OECD TG 201, *Pseudokirchneriella subcapitata*, open system), both the (0-72 h) ErC_{50} and the (0-72 h) EbC_{50} were > 98.9 mg/L. For daphnids, a 48 h EC_{50} of > 91.7 mg/L was reported (OECD TG 202, *Daphnia magna*, semi-static). For fish (OECD TG 203, *Oryzias latipes*, semi-static) a 96 h LC_{50} > 101 mg/L is available.

Regarding chronic toxicity to algae, the (0-72 h) NOEC by growth rate and biomass methods was 98.9 mg/L (OECD TG 201, *Pseudokirchneriella subcapitata*, open system). For daphnids, a 21 d EC_{50} of > 95.1 mg/L for reproduction

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.

and a 21 d NOEC of 95.1 mg/L for reproduction are available (OECD TG 211, *Daphnia magna*, semi-static).

Exposure

2-Furanmethanol, tetrahydro- is manufactured by a single manufacture in Japan with an annual production volume of approximately 30 tonnes. Worldwide production capacity outside Japan is not known. The major uses of this chemical are: solvents for various products and uses (fats, waxes, resins, dyes, vegetable oils, cleaners, paints, inks and others: ca 50 to 70% in total) and intermediate in industrial applications (ca. 30 to 50%). Human exposure to this chemical is expected in both occupational settings and consumer sites since some of the applications include open and direct uses (solvents for paints and nail cleaning agents). Such exposure can occur through inhalation and dermal routes. Exposure into the environment may also occur primary through evaporation during the production and down stream user sites.

The routes of occupational exposure are inhalation of vapor and dermal contact to liquid. As a volatile liquid and used as a solvent for various products, workers at production and user sites of this chemical may be exposed.

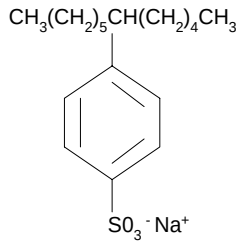
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses a hazard for human health (repeated dose toxicity, irritation, reproductive/developmental toxicity). Exposure to general public is expected through dermal contact and inhalation. This chemical is produced in a closed system 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, a risk assessment for workers and consumers are recommended.

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

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	1322-98-1 Decylbenzene sulfonic acid, sodium salt 25155-30-0 Dodecylbenzene sulfonic acid, sodium salt 26248-24-8 Tridecylbenzene sulfonic acid, sodium salt 27636-75-5 Undecylbenzene sulfonic acid, sodium salt 68081-81-2 C_{10-16} Monoalkylbenzene sulfonic acid, sodium salt 68411-30-3 C_{10-13} Alkylbenzene sulfonic acid, sodium salt 69669-44-9 C_{10-14} Alkyl deriv benzene sulfonic acid, sodium salt 85117-50-6 C_{10-14} Monoalkylbenzene sulfonic acid, sodium salt 90194-45-9 C_{10-13} Alkyl deriv benzene sulfonic acid, sodium salt 127184-52-5 4-C_{10-13}-sec Alkyl deriv. benzene sulfonic acid, sodium salt
Category Name	Linear Alkylbenzene Sulfonate (LAS)
Structural Formula	This structure of a C_{12}-LAS is representative of the category. 

SUMMARY CONCLUSIONS OF THE SIAR

Category Identification/ Justification

The LAS molecule contains an aromatic ring sulfonated at the para position and attached to a linear alkyl chain at any position except the terminal carbons. The alkyl carbon chain typically has 10 to 14 carbon atoms and the linearity of the alkyl chains ranges from 87 to 98%. While commercial LAS consists of more than 20 individual components, the ratio of the various homologs and isomers, representing different alkyl chain lengths and aromatic ring positions along the linear alkyl chain, is relatively constant in currently produced products, with the weighted average carbon number of the alkyl chain based on production volume per region between 11.7-11.8. LAS are supported as a category because of the close consistency of the mixtures, their commercial uses, fate, and health and environmental effects. LAS is the primary cleaning agent used in many laundry detergents and cleaners at concentrations up to 25 percent in consumer products, and up to 30 percent in commercial products, with the exception of one reported product at 45% percent in concentrated solid form that is mechanically dispensed into diluted solution for dishwashing.

Human Health

Substantial data exist for mammalian toxicity. The available data indicate that LAS exhibits slight acute toxicity. Oral LD_{50} values for rats range from 1,080 to 1,980 mg/kg bw. Oral LD_{50} values for mice are 2,160 and 2,250 mg/kg bw for males and females, respectively. The rat dermal LD_{50} value was greater than 2,000 mg/kg bw. The oral and dermal acute toxicity data for LAS generally indicate low hazard potential when all studies are considered together. Acute inhalation toxicity data indicate that LAS is moderately toxic, with mortality occurring at respirable particle concentrations of 310 mg/m^3 (MMAD = 2.5 microns).

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.

In a series of studies on rabbits, LAS was not irritating to the skin or eyes at low concentrations (0.5-2.5%), moderately irritating at 5%, and more severely irritating at higher (about 50%) concentrations. 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 a low volume eye test (LVET) using a 35% LAS solution, rabbits experienced moderate irritation that was completely reversible by day 35. (Note that the maximum concentration of LAS is 25 percent in consumer products and normally less than 30 percent in commercial products.) Accidental eye exposure in 231 manufacturing employee incidents and 284 consumer incidents established that eye irritation effects of exposure during manufacturing and use of products containing LAS and other surfactants are moderate, transient and reversible.

In 15 repeated dose studies with rats, mice, and monkeys exposed to LAS via oral and dermal routes, LOAELs ranged from 115 to 750 mg/kg bw/day. The corresponding NOAELs ranged from 40 to 250 mg/kg bw/day. Effects commonly observed included suppressed body weight gain, diarrhea, increases in relative liver weight, differences in enzymatic and serum-biochemical parameters, and mild degeneration and desquamation of the tubular epithelium in the kidneys.

In four well designed *in vitro* bacterial (*Salmonella*) mutagenicity studies, LAS shows no evidence of mutagenicity either with or without S9 metabolic activation. LAS showed no evidence of causing increased cell transformation in an *in vitro* cell transformation assay. In *in vivo* studies, no significant differences in chromosome aberrations were seen when mice were given either oral doses up to 800 mg/kg bw/day or dietary doses up to 1170 mg/kg bw/day. In a mouse micronucleus study, LAS did not induce a clastogenic effect. Rats given dietary doses up to 450 mg/kg bw/day also showed no significant differences in chromosome aberrations. Collectively, these data support that LAS is not genotoxic.

The highest dose tested in four carcinogenicity studies with rats was 300 mg/kg bw/day. In the most documented study, rats were administered up to 250 mg LAS/kg body weight/day in the diet for two years. Results of this study indicate no gross or histopathological evidence of a carcinogenic effect. No evidence of tumorigenesis was observed in any of the carcinogenicity studies. While the quality and focus of the studies precludes a definitive assessment, the results of the genetic toxicology and rodent bioassay studies collectively provide strong weight-of-evidence support that LAS is not genotoxic and is not a rodent carcinogen.

Similarly, no evidence of reproductive or fertility effects was observed in any of the three available reproductive toxicity studies in which rats were given dietary doses over three to four generations. NOAELs from these reproductive studies ranged from 70 to 350 mg/kg bw/day, which were the highest doses tested. In 17 developmental toxicity studies, effects such as embryo death or deformities, and litter loss were most often observed only at maternally toxic doses and were associated with the irritation effects of LAS on skin or 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 780 mg/kg bw/day in rats and at dermal doses of 500 mg/kg bw/day in mice and 90 mg/kg bw/day in rabbits.

All of the studies included in the dossier are considered reliable, but all with limitations. The results are consistent with each other and these data are used in a weight-of-evidence approach. Based on these considerations, the highest NOAEL value below the lowest LOAEL from all of the mammalian toxicity studies is the most appropriate. Therefore, the NOAEL is 85 mg/kg bw/day. This value comes from a rat drinking water, 9-month repeated dose toxicity study. The lowest LOAEL (115 mg/kg/day) was associated with increased weight of the cecum and slight degeneration of the renal tubules.

Environment

Pure LAS is a solid at ambient temperatures with a melting point of 198.5°C. The boiling point for LAS could not be determined experimentally due to decomposition beginning at 444°C. LAS has a low vapor pressure (calculated as 3-5 x 10^{-13} Pa). LAS is water soluble, with a critical micelle concentration (CMC) value of 0.1 g/L and forms a clear solution in water at concentrations up to 250 g/L. Although it is impossible to accurately measure an octanol-

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.

water partition coefficient for surface-active agents like LAS, an octanol-water partition coefficient of log 3.32 has been calculated for $C_{11.6}$ LAS. K_d values for LAS in activated sludge and sediment increased with increasing alkyl chain length of LAS homologues with K_d values for C_{12} LAS of 3210 L/kg in activated sludge and 330 L/kg in river sediment. In activated sludge, sorption and desorption equilibria for LAS were achieved very rapidly, and comparison of the extent of sorption and biodegradation shows that the absorbed fraction as well as the soluble fraction of LAS is available for biodegradation. Based on Fugacity III modeling results using the most relevant input parameters, more than 99 percent of the residual (non-biodegraded) fraction of LAS distributes to the soil. LAS does not undergo significant degradation by abiotic mechanisms under environmentally relevant conditions as photolyzable and hydrolyzable groups are absent from the chemical structure.

An extensive database of studies demonstrates rapid and complete (ultimate) biodegradation of LAS in many of the available aerobic biodegradation tests, including soil and the aqueous environment. In several tests, LAS has been shown to be readily biodegradable, and has passed the 10-day biodegradation window in mineralization tests for most ready tests. LAS is removed in biological wastewater treatment at percentages ranging from 77-82% for trickling filters up to 99%+ for activated sludge. The biodegradation kinetics of the longer alkyl chain lengths are generally faster, and their sorption coefficients larger. The primary degradation intermediates are sulfophenyl carboxylates (SPCs), which further degrade to CO_2, SO_4^{2-}, and water. LAS does not generally degrade under anaerobic conditions. The measured bioconcentration factors of pure homologues and isomers decrease with decreasing average alkyl chain lengths (from almost 1000 for 2-phenyl-C_{13} LAS to 2 for 6-phenyl-C_{10} LAS), all with rapid clearance. The calculated BCF for currently produced $C_{11.6}$ LAS is 87 and was 22 for filtered Mississippi River water (average alkyl chain length of surface water fingerprint = $C_{10.8}$).

Ecotoxicity data are extensively available for LAS, with several comprehensive reviews having been completed. The lowest reliable acute $LC_{50}/EC_{50}/ErC_{50}$ values based on a review of the aquatic toxicity data on commercially representative LAS ($C_{11.6}$-$C_{11.8}$) were 1.67, 1.62 and 29.0 mg/L for fish, *Daphnia magna*, and algae, respectively. Acute toxicity is greater for individual LAS homologues with longer alkyl chain lengths. LAS biodegradation intermediates are significantly less toxic than the parent LAS with L/EC_{50} values >1000 mg/L for fish and *D. magna*. Chronic freshwater toxicity studies following guideline exposures (28-30 days for fish, 21 days for invertebrates and 3-4 days for algae provided the following NOEC values: fish NOEC = 1 mg/L (two studies, two species); Daphnia, NOEC = 1.18-3.25 mg/L (six values, two studies, one with 5 diets); algae, NOEC = 0.4-18 mg/L (four studies, two species). In addition all of the available, reliable chronic single species aquatic toxicity data on LAS have been evaluated, including three freshwater species in which multiple studies were reported and nine freshwater species for which single studies were reported. Single NOEC values and geometric mean NOEC values (calculated for species with multiple results) were normalized to $C_{11.6}$ LAS. These NOEC values range from 0.25 to 6.1 mg/L for freshwater species, including fish, invertebrates, algae and higher plants. Geometric mean NOEC values for marine species ranged from 0.025 to 5.0 mg/L. Based on the model ecosystem studies, a NOEC of 0.27 mg/L (0.37 if normalized to $C_{11.6}$ LAS) was determined for the freshwater ecosystem. This value is based on model stream ecosystem studies of over 250 species, and is consistent with the single species chronic freshwater data.

NOEC values for sediment exposures were greater than or equal to 81 mg/kg dry matter based on studies in four species, including GLP studies in *L. variegates* (survival, reproduction and growth over 28 days) and *C. elegans* (egg production, 3 days). Field studies indicate no adverse effects of LAS in sludge-amended soil from LAS levels of 15 mg/kg dry matter in the soil (9 microbial functions/processes and abundance/diversity of microarthropods and earthworms, short-term and 4 years) or 31,300 mg/kg dry matter in sludge (function of microbial community, short-term and 1 year).

In laboratory studies in which young trees are exposed to artificial sea spray, LAS concentrations of 10 mg/L lead to increased foliar penetration of NaCl, a hypothesized mechanism of defoliation.

A health and environmental risk assessment is available (heraproject.com).

Exposure

Current LAS production is approximately 390,000 metric tons in the North America, 400,000 metric tonnes in

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.

Europe, and 85,000 metric tonnes in Japan. Global production was 2.6 million metric tonnes in 1995. In the production phase, manufacturing processes have been designed to maximize production yield and minimize potential releases. Worker exposure is possible during the detergent formulation stage by inhalation of powders or dermal contact of powders and liquids. Good manufacturing design practices (e.g., enclosed production in agglomeration processes, exhaust ventilation, dust collection) and personal protective equipment (e.g., protective clothing, eyewear, and gloves) in place at facilities that manufacture liquid and dry (granular/powder) materials are anticipated to mitigate worker exposure to LAS. Any LAS that is not incorporated into a product is captured by dust-handling equipment for recycling back into the production process. A limited amount of LAS 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. Incidental quantities of the dry (granular/powder) product (e.g., from floor sweepings) may be disposed in landfills.

Labeling of consumer products containing LAS and other surfactants include warnings of the potential for eye irritation and first aid instructions to rinse with water.

Data suggest that inhalation of LAS products during use will be low. Spray products containing LAS 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/m^3 range. Inhalation of detergent dusts during washing processes, modeled by HERA (2004), was 10-fold lower than inhalation of aerosols from cleaning product sprays. This estimate is based on a published study reporting an average of 0.27 µg dust per cup of product used for machine laundering. This is a conservative (protective) estimate as exposure from modern compact/granular detergent formulations produced in agglomeration processes, which produce larger particle sizes, would be expected to be much less. Based on these data, it is expected that exposures to respirable particles from inhalation are low.

Results of extensive environmental monitoring evaluations in the United States indicate that measured surface water concentrations were generally below 50 µg/L for river water samples collected under low dilution (worst case) conditions below treatment plant mixing zones. Values in the 2800 km reach of the Mississippi River from Minneapolis to New Orleans range from non-detect (<0.1 µg/L) to 28 µg/L (362 samples). LAS river water concentrations similar to those in the US were observed in monitoring studies conducted in Europe and Japan.

Measured LAS concentrations in river sediments were generally less than 1-2 mg/kg dry weight. Mississippi River sediments were <1 mg/kg dry matter with one exception. LAS levels in sediments of the receiving waters of the Tiber River (Italy) were 1.8 mg/kg dry matter. Higher LAS concentrations have been observed near untreated or poorly treated wastewater discharges, e.g. LAS in sediments of a small river (Rapid Creek, USA) below a trickling filter treatment plant averaged 190 mg/kg just below the outfall, 11.2 mg/kg less than 5 miles downstream and 5.3 mg/kg greater than 5 miles downstream

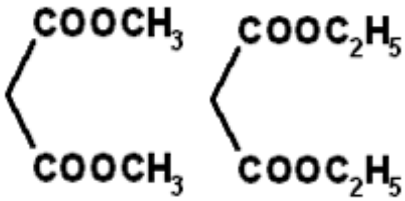
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals in the LAS category are currently of low priority for further work because of their low hazard potential except for skin and eye irritation and acute inhalation. Based on data presented by the Sponsor Country, exposure to respirable particles is anticipated to be low. Other countries may desire to investigate any exposure scenarios that were not presented by the Sponsor Country.

Environment: The chemicals in the LAS category possess properties indicating a hazard for the environment (fish, invertebrates and algae). However, they are of low priority for further work due to ready and/or rapid biodegradation and limited potential for bioaccumulation.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	108-59-8, 105-53-3
Chemical Names	Category of malonic acid diesters: Dimethylmalonate (DMM) and Diethylmalonate (DEM)
Structural Formulas	

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The production and use pattern of Diethylmalonate (DEM) and Dimethylmalonate (DMM) are comparable. The two chemicals have very similar physico-chemical properties and both esters are hydrolyzed via a two step reaction to malonic acid and the corresponding alcohol, methanol or ethanol. It is likely that unspecific esterases in the body catalyze the hydrolysis. The alcohols and malonic acid are physiological substances that are metabolized via physiological pathways. Ethanol (CAS No. 64-17-5) and methanol (CAS No. 67-56-1) were assessed at SIAM 19. For ethanol it was concluded that the chemical is currently of low priority for further work, because the hazardous properties of ethanol are manifest only at doses associated with consumption of alcoholic beverages. As it is impossible to reach these exposure levels as a consequence of the manufacture and use of malonates, it can be expected that malonic acid will be the metabolite that determines the toxicity of DEM. For methanol, SIAM 19 decided that this chemical is a candidate for further work. 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 DMM dose of more than 1000 mg/kg bw). As there were no indications of a methanol associated toxicity from a well performed repeated dose toxicity study with DMM in rodents (which are, however, known to be less sensitive to methanol toxicity than humans), and because methanol toxicity would not be expected up to doses as high as 1000 mg DMM/kg bw/day, it was concluded that methanol does not make a relevant contribution to the toxicity profile of DMM. A possible mode of action for systemic toxicity of DMM and DEM can only be deduced from the repeated dose study with DMM, indicating a reversible liver hypertrophy at the cellular level at high doses of 1000 mg/kg bw/day. This effect can be an indication of an induction of metabolism in the liver rather than a clear systemic toxicity.

Human Health

From the physical chemical properties of both substances it can be assumed that they are readily absorbed through mucous membranes and distributed into the water compartments. Absorption through skin in *in vitro* experiments in different species varied widely depending on the experimental conditions. *In vivo* skin absorption of undiluted [2-^{14}C]-DEM was highest in nude mice with 15 % absorption and lowest in pigs (2.5 %). In human skin grafted on nude mice and in hairless dogs absorption was 4 %. These experiments indicate relatively low skin absorption under non-occluded conditions. Both DMM and DEM are likely to be metabolized by esterases under cleavage of one or

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.

two ester bonds yielding the corresponding alcohols and malonic acid monoesters or malonic acid.

No acute inhalation study is available for DMM. In the dermal toxicity study in rats following OECD guideline TG 402 and GLP (limit test) the LD50 was > 2000 mg/kg bw. An acute oral toxicity study in rats revealed an LD_{50} > 2000 mg/kg bw. In both studies no test substance related effects were observed.

For DEM only limited literature data are available. No toxicity was observed after 8 h inhalation of concentrated vapors in rats. The dermal LD_{50} in rabbits was reported to be > 16 960 mg/kg bw, the oral LD_{50} in rats 15 794 mg/kg bw. Taken together the studies for both substances suggest that they are of low acute toxicity via the oral and dermal route and likely to be also of low toxicity after inhalation exposure.

DMM was not irritating to rabbit skin in a guideline study according to OECD TG 404 and GLP. For DEM no guideline study is available on skin irritation, but a slightly irritating effect was reported in the literature after 24 hours of occlusive exposure. Both substances showed slight to moderate eye irritating effects in rabbits that were completely reversible within the observation period. The studies were conducted according or similar to OECD TG 405 and under GLP.

DMM did not reveal any skin sensitizing effect in a Bühler test according to OECD TG 406 and GLP. Reports of maximization tests in human volunteers with both, DMM and DEM did not indicate any skin sensitizing properties.
One repeated dose study in rats by the oral route (gavage) according to OECD TG 422 and GLP is available for DMM. The only effect observed was a reversible hepatocellular hypertrophy in animals of the high dose group (1000 mg/kg bw/day). The NOAEL was 300 mg/kg bw per day. Only a limited dietary 90 day study in rats is available with DEM, which indicated no treatment related effect at dose levels of 36 and 41 mg/kg bw per day for male and female animals, respectively (only one dose level was tested). Although the information available for DEM is limited, it is considered sufficient because DEM is not likely to be more toxic than DMM. Overall, the toxicity of DMM and DEM after repeated dosing is considered to be low.

Both DMM and DEM were not mutagenic in the standard Ames assay in bacteria with and without metabolic activation. DMM did not show any clastogenic activity in the *in vitro* cytogenetic assay with peripheral human lymphocytes in the presence and absence of a metabolic activation system. All tests 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 mutagenic potential of the substances, both for gene mutations and chromosomal aberrations.

Based on the findings in a combined oral (gavage) repeated dose reproduction/developmental toxicity study in rats according to OECD TG 422 and GLP with DMM a NOAEL for parental toxicity of 300 mg/kg bw/day for males and females and a NOAEL for reproductive and developmental toxicity of 1000 mg/kg bw/day, the highest dose tested, can be derived. No reproductive/developmental toxicity study was available for DEM. Because it is impossible to reach blood levels of ethanol which are associated with reproductive/developmental toxicity as a consequence of the manufacture and normal use of DEM, it can be expected that malonic acid will be the metabolite that determines the toxicity of DEM. Taking also into account that DEM is not likely to be more toxic than DMM, which has shown no potential for reproductive and developmental toxicity, it is overall concluded that there is no indication for a relevant reproductive and/or developmental toxicity of DMM and DEM.

Environment

Both, dimethyl- and diethylmalonate are colorless organic liquids with an ester like odor. DMM has a melting point of –62 °C, a boiling point of 181.4 °C, a water solubility of about 142 g/l at 20 °C, a vapor pressure of 0.48 - 0.5 hPa at 20 °C and a measured log Kow of -0.05. DEM has a melting point of –48.7 to –51.1 °C, a boiling point of 199.3 °C, a water solubility of 20 g/l at 20 °C, a vapor pressure of 0.36 hPa at 25 °C and a measured log Kow of 0.96. Both substances are readily biodegradable (100 % (DMM) and 98 % (DEM) in a DOC-die away test) and undergo a two-step hydrolytic degradation in a first step to the monoester and in a second step to malonic acid and the corresponding alcohol, methanol or ethanol respectively. The half lives were shortest at pH 9, < 2.4 h (50 °C) for

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.

both substances, and increased to 5.7 h (50 °C) and 15.9 h (50 °C) for DMM and DEM respectively at pH 7 and 859 h (50 °C) for DMM at pH 4. At pH 4 and 50 °C DEM showed less than 10 % degradation within 5 days. For photodegradation via oxidation by OH-radicals half lives of about 31 days for DMM and 4.7 days for DEM in air were estimated. For DEM a 100% photolytic ozonisation after 40 min under UV-irradiation in water was reported. The generic fugacity model I indicates that both substances are preferably distributed in the water phase (98 % for DMM and 90 % for DEM) with a low amount distributing potentially into air (1.5 and 9.9 % respectively). The fugacity model III however, indicates that a considerable amount may be distributed to the soil if the substances are primarily released into air (36 % for DMM and DEM) or soil (38 % for DMM and 44.5 % for DEM). The measured octanol-water partition coefficients (log Kow -0.05 for DMM and 0.96 for DEM) indicate a low potential for bio- or geoaccumulation.

Acute toxicity data for 3 trophic levels of the aquatic environment are available for both substances.

Acute toxicity in mg/l:

	DMM	DEM
LC_{50} fish: 96 h, *Danio rerio*	21	-
LC_{50} fish: 96 h, *Pimephales promelas*	-	12 - 17
EC_{50} Daphnia: 48 h, *Daphnia magna*	> 728	179
Algae EC_{50}: 72h, *Desmodesmus subspicatus;* growth rate (biomass)	240(92)	> 667(424)

Based on the lowest LC_{50}-value for fish of 21 mg/l for DMM and 12 mg/l for DEM and an assessment factor of 1000 PNEC-values of 21 and 12 µg/l can be derived for DMM and DEM, respectively.

No growth inhibition of DEM to terrestrial plants in soil was observed up to concentrations of > 100 mg/kg soil and no toxicity to *Eisenia fetida* was observed at concentrations of DEM of 1000 mg/kg bw after 14 days of exposure.

Exposure

The worldwide production capacity of malonates with DMM and DEM as the most important products was estimated to be more than 20 000 t/a. The breakdown by country in 2000 was estimated as follows: Europe: 8000 t/a (Sponsor country: 8000 t/a by 1 Producer), Japan 4000 t/a, China 12 000 t/a, Korea 2000 t/a, and India 600 t/a. DMM and DEM are widely used in the chemical industry as intermediates for the synthesis of a variety of organic chemicals, for example to introduce an acetic moiety or a hydroxyester group into molecules. The end products of the different processes in which malonates are used as intermediates include pharmaceuticals, agrochemicals, vitamins, fragrances and dyes. It was estimated that about one third each of the volume of DMM is used in the production of agrochemicals, pharmaceuticals and industrial chemicals. For DEM the estimated breakdown is 30 % as an intermediate for the production of agrochemicals, 50 % pharma-intermediate, 20 % as intermediate for industrial chemicals. Because of the predominant production and use in chemical industry under controlled conditions, environmental exposure from production and use is considered low. DMM is a naturally occurring substance and has been detected in a number of fruits as a volatile aroma compound for example in pineapples, bananas and blackberries.

In production from the process description very low occupational exposure is anticipated. No data are available for the uses. As the majority of the products are used as intermediates in the chemical industry a controlled exposure situation is anticipated.

With regard to consumer exposure WHO (2000) evaluated the combined daily intake of 47 flavoring substances including DEM in Europe and the US. The annual production volume of these 47 substances was 200 metric tons in Europe and 1700 metric tons in the US. From this an estimate per capita daily intake of 28 mg in Europe and 300 mg in the US was derived. This intake was considered of no concern.

DMM is contained in the Swedish and Swiss Product Registers, but not in the SPIN Database. DEM is contained in the Swedish and Swiss Product Registers and in the SPIN Database.

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.

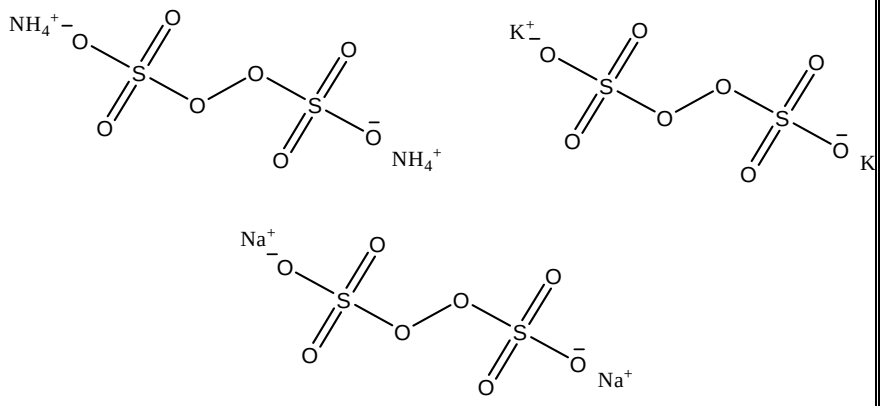
RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals of this category are currently of low priority for further work due to their low hazard profile.

Environment: The chemicals of this category possess properties indicating a hazard for the environment. Although 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. The chemicals are currently of low priority for further work.

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.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7727-54-0, 7727-21-1, 7775-27-1
Chemical Name	Ammonium persulfate, potassium persulfate, sodium persulfate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The persulfates category includes molecules with similar chemical structure and similar physical-chemical properties. The inorganic substances differ only by the cationic portion of the salt, which is not expected to influence the hazardous properties of the molecule. The anionic part is identical and, therefore, the three salts are expected to display the same environmental, ecotoxicological and toxicological behaviour based on the available data.

Human Health

Toxicokinetics and dynamics of the salts will be influenced mainly by the persulfate anion. This anion is likely to decompose to hydrogen peroxide and the sulfate ion. The hydrogen peroxide will be rapidly converted to oxygen and water by catalase and peroxidase enzymes.

The acute oral LD_{50} in rats, for the three salts, ranged from 495 mg/kg bw for the ammonium salt to 895 mg/kg bw for the sodium salt to 1130 mg/kg bw for the potassium salt. The acute dermal LD_{50} in rats and rabbits, for all three salts, was greater than 2000 mg/kg bw for the ammonium salt to greater than 10,000 mg/kg bw for the potassium and sodium salts. In acute inhalation studies in rats, the 4-hour LC_{50} was generally greater than the maximum attainable concentration (>5,100 mg/m^3 for sodium persulfate and >2,950 mg/m^3 for ammonium persulfate). Clinical signs in the inhalation studies included ocular and nasal discharge and respiratory distress.

Ammonium persulfate is slightly irritating to eyes and skin in rabbits. Older eye and skin irritation studies on the potassium and sodium salts produced little irritation in rabbits. Studies in humans indicate that aqueous solutions of 5% persulfate or higher can cause skin irritation. Persulfates also can be irritating to skin and the respiratory track of occupationally exposed individuals (hairdressers).

Results of animal skin sensitization tests (Buehler Test and Maximization Test) were negative when persulfate was applied topically and positive when persulfate was injected intradermally in induction and challenge phases in a non-

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.

standard Maximization Test. Numerous dermal challenge tests indicate that all three persulfates are dermal and respiratory sensitizers in humans occupationally exposed to persulfates in hairdressing salons and, in one case, in a production facility. In controlled clinical trials with non-occupationally exposed-subjects (NH_4 & Na salts), no sensitization reactions were observed.

In repeated-dose studies, local effects to the gastro-intestinal tract and the airways were reported. Administration of sodium persulfate to rats in the diet for 13 weeks resulted in a LOAEL of 3000 ppm (225 mg/kg bw/day) based on gastrointestinal lesions and reduced body weights. In a subchronic inhalation study in male and female rats, adverse effects at a high dose of 25 mg/m^3 ammonium persulfate aerosol consisted of inflammation of the trachea, bronchi, bronchioles, increased lung weight, decreased body weights, rales and increased respiratory rate. A NOAEL of 10.3 mg/m^3 was established. Pulmonary function tests of workers in a persulfate production plant (cation not identified) indicated that there were no short- or long-term effects on pulmonary function at levels in the plant (0.5 mg/m^3).

None of the three persulfates cause gene mutations or chromosomal effects *in vitro*. *In vivo* tests on sodium persulfate (micronucleus test and UDS test) were negative.

A 51 week dermal study in female SENCAR mice exposed to 0.2 ml of a 200 mg/ml solution of ammonium persulfate showed that ammonium persulfate is neither a tumor promoter nor a complete carcinogen when applied to the skin.

In a developmental/reproduction study with ammonium persulfate in rats (OECD TG 421), no effects on reproductive performance, fertility, fetal anomalies, fetal viability, spermatogenesis, spermatogenic cycle were reported up to 250 mg/kg-bw/day. Dose levels were chosen based on the acute lethality studies for the ammonium salt and on a 90-day repeat-dose study in rats with the sodium salt (high dose: 225 mg/kg-bw/day). In the developmental/reproduction study, animals were dosed prior to and during mating through gestation until lactation day 4. There was a transient depression in pup body weight at the 250 mg/kg dose level on lactation day 0 which resolved by day 4. This effect was not considered adverse. Based on the available data, the persulfates do not show evidence of reproductive or developmental toxicity. The NOAEL is 250 mg/kg bw/day.

Environment

Because they decompose below their melting and boiling points, persulfate decomposition temperatures are reported in their stead as 120, ~100, and >180ºC for the ammonium, potassium and sodium persulfates, respectively. The inorganic persulfates are soluble in water (≥ 60 g/L) and their vapour pressures are negligible.

The three persulfate salts will be distributed into the water compartment in the ionic form of the cation, (NH_4, Na or K) and persulfate anion. Aqueous persulfates are expected to degrade in the environment mainly via hydrolysis, but metal catalyzed decomposition, and reactions with organic chemicals in the soil or water also are possible.

Persulfates are not expected to adsorb to soil due to their dissociation properties, instability (hydrolysis) and high water solubility. They should behave as free ions or decompose into sulfate ions. In soils, upon decomposition, the cation could form more stable sulfate or bisulfate salts.

Persulfates are not expected to bioaccumulate in the soil or in aqueous solution. They will decompose into inorganic sulfate or bisulfate.

The LC_{50} values for acute toxicity to fish ranged between 76 and 323 mg/L for ammonium persulfate and from 163 to 771 mg/L for sodium persulfate. The acute toxicity EC_{50}-values for invertebrates were between 120 and 391 mg/L for ammonium persulfate and between 133 and 519 for sodium persulfate. In algae the EC_{50} for ammonium persulfate was 83.7 mg/L and for sodium persulfate 116 mg/L. For potassium persulfate, non-GLP data on fish and daphnia toxicity fell within the range of the other two category members.

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.

Exposure

For the year 2003 the global market for persulfate salts was estimated to be ca. 76,000 tonnes. The substances are used in polymerization reactions and printed circuit manufacturing. Persulfates also are used as oxidants in hair-bleaching products.

Occupational exposure occurs during manufacturing and during use as hair dyes. The dermal and inhalation routes will be the most important routes of exposure.

During end-use, consumers may be exposed to these substances (e.g., hair dyes may come into contact with the scalp and the hands).

There is potential for environmental exposure during production and processing; however, solid and liquid wastes will be treated to decompose the material or discharged properly as hazardous waste.

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

Human Health: The chemicals in this category possess properties indicating a hazard for human health (eye and skin irritation and skin and respiratory sensitisation). Based on data presented by the Sponsor country, adequate risk management measures (MSDS's and labelling) are being applied and therefore the chemicals in this category are currently of low priority for further work. Other countries may wish to consider their own risk management measures.

Environment: Some chemicals in this category possess properties indicating a hazard for the environment (acute toxicity for fish and algae). However, they are of low priority for further work due to rapid degradation and the absence of bioaccumulation.

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.