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

Series on Testing & Assessment
No. 166

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OECD Environment, Health and Safety Publications

Series on Testing and Assessment

No. 166

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

IOMC INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate

ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT

Paris 2012

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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.

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

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

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FOREWORD

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

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

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

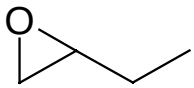
The collection of SIAPs has been divided in six parts, following a chronological order, to keep individual parts to a manageable size. For each part of the document, the corresponding SIDS Initial Assessment Meeting (SIAM) number and the year of the meeting have been indicated below.

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

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

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-88-7
Chemical Name	1,2-epoxybutane
Structural Formula	C_4H_8O 

RECOMMENDATIONS

For use in closed systems the substance is currently of low priority for further work.

For other uses the substance is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,2-Epoxybutane caused acute toxic effects in mammals: LD_{50} rat (oral) 900 mg/kg body weight, LC_{50} rat (inhalative, 4 h) > 6,300 < 20,000 mg/m^3, LD_{50} rabbit (dermal) 1,757 (1,255 - 2,546) mg/kg body weight.

It was irritating to the eyes. Irritating effects to the skin were severe (corrosion) if evaporation was minimised due to occlusive application, but there was no effect by semi-occlusive application. 1,2-Epoxybutane was not sensitising in a guinea pig maximisation test. In 90-day inhalation studies with rats and mice 1,2-epoxybutane mainly caused nasal lesions (NOAEC 600 and 150 mg/m^3, respectively). Systemic effects occurred at higher concentrations (rat 2400 mg/m^3: decreased mean body weight gain; mice 2400 mg/m^3: e.g. renal tubular necrosis).

1,2-Epoxybutane was genotoxic *in vitro*. However, it caused neither chromosomal aberrations in bone marrow nor dominant-lethal mutations in germ cells of rats.

There is clear evidence for 1,2-epoxybutane being a locally acting carcinogen in male rats (inhalation of 600 mg/m^3 caused no tumours and 1,200 mg/m^3 caused neoplasms of the nasal cavity and the lung of male rats) and there is equivocal evidence for a carcinogenic activity in female rats. There was no evidence for carcinogenic activity in male or female mice. However, the mortality of females was increased in this study due to an infection and this raises difficulties in the interpretation of the result. Regarding the overall database on genotoxicity and structural relationship to epoxyethane and -propane, epoxybutane seems to be a genotoxic compound, showing a carcinogenic activity at the site of application only at high concentrations. However, irritating properties of the compound may cause cell proliferation and contribute thereby to tumor induction.

With respect to reproductive toxicity the 90 day studies with rat and mice did not reveal adverse effects on the reproductive organs up to 2400 mg/kg body weight. Additionally, the lack of an effect from pre-gestational exposure in the developmental toxicity study and a negative dominant-lethal test may indicate that 1,2-epoxybutane does not reach male and female germ cells in effective concentrations.

No developmental toxicity or teratogenicity was detected in rats after inhalation of up to 3,000 mg/m^3 throughout gestation. From the rabbit study no conclusions can be drawn due to high mortality in the high dose group.

Environment

1,2-Epoxybutane has a water solubility of 59 g/l, a vapor pressure of 227 hPa and a log Kow of 0.68.

According to Mackay I air is the main target compartment for 1,2-epoxybutane (89 %), while 11 % partitions to water. The substance has no considerable potential for bio- and geoaccumulation (log P_{ow} = 0.68). The half-life for photochemical degradation in air is calculated to 7.6 days. 1,2-Epoxybutane is classified as readily biodegradable, failing the 10d-window criterion. In sewage treatment plants the substance will be eliminated by stripping and biodegradation. Hydrolysis and photolysis are slowly under environmental conditions.

The following aquatic effects concentrations are available:

Leuciscus idus: LC_{50} (96 h) = 100 - 215 mg/l, *Daphnia magna*: EC_{50} (48h) = 69.8 mg/l, *Scenedesmus subspicatus*: ErC_{50} (72 h) > 500 mg/l, *Pseudomonas putida:* EC_{50} (17 h) = 4,840 mg/l. All values are related to nominal concentrations. Due to the volatility of the substance the real effect values may be lower. QSAR estimations give effect values of 20 mg/l for fish and 32 mg/l for daphnia and show that the effect values are indeed lower than those found in the test but not by orders of magnitude. Based on the measured and predicted effect data the substance can be classified as moderately toxic. A PNEC of 20 µg/l can be derived based on the predicted effect value for fish using an assessment factor of 1000. No data are available on terrestrial organisms.

Exposure

In the European Union there is only one known producer of 1,2-epoxybutane. The production volume of this chemical in BASF Aktiengesellschaft Ludwigshafen was 5,000-10,000 t in 1999. The total production volume is mainly used at the production site as an intermediate (non-disperse use) for synthesis in closed systems of fuel additives, non-ionic surfactants, defoamers and various other products. Monitoring data showed no emission into the air during production and processing. There is no information on emission of 1,2-epoxybutane into the hydrosphere. In the USA the substance is used as a stabilizer in hydrocarbon solvents. Therefore emissions into the environment cannot be excluded during formulation and use of the solvents.

NATURE OF FURTHER WORK RECOMMENDED

For use in closed systems no further work is recommended.

For other uses there is a need for an exposure assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-22-2
Chemical Name	Glyoxal
Structural Formula	HC(=O)-C(=O)H

RECOMMENDATIONS

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

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

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute toxicity of glyoxal ranged from low to harmful in animal experiments performed with different species, depending on the active ingredient concentration of the tested product. Glyoxal 40% has a moderate toxicity by the oral route, a low toxicity by the dermal route and a moderate toxicity by inhalation. Glyoxal causes slight to definite skin irritations depending on the exposure duration. Irritations up to necrotic changes have been described on the rabbit eye. It acts as a sensitizer to the skin of guinea pigs and humans.

In a subacute inhalation study on rats for 29 days, a 40% glyoxal aerosol concentration of 10 and 2 mg/m^3 results in a minimum squamous metaplasia of the epiglottal epithelium in the larynx. A NOEL of 0.4 mg/m^3 is given for local effects and of > 10 mg/m^3 for the systemic toxicity. In a 28 day oral study in rats, a NOEL of 100 mg/kg bw/d (40% glyoxal) was determined. A dose related decrease of the water, food consumption and body weight were noted at 300 mg/kg and 1000 mg/kg. Variations of some haematological and blood parameters occurred at these doses. No macrocopic and microscopic pathological findings were seen that were considered to be compound related. In a 90d feeding study in rats, glyoxal in daily doses of ca. 30 to 250 mg/kg bw/d is tolerated without clinical, macroscopic and histopathological changes. A temporary reduced body weight gain and an increase of the relative liver and kidney weights, without any histopathological correlation, have been observed only in the males of the highest dose group. The NOEL is ca. 125 mg/kg bw/d related to 40% glyoxal. In 90-d drinking water studies with male rats with daily doses of ca. 140, 290 and 370 mg/kg bw/d, a decreased food and water intake as well as retarded body weight gain was found in the highest dose group. The glyoxalase activities in the liver, kidney and erythrocytes are increased, while the aspartate aminotransferase activity, the alanine aminotransferase and lactate dehydrogenase activities as well as the albumin and total protein value are also determined in the low dose group. The LOEL lies at 107 mg/kg bw/d related to pure glyoxal. Overall, a NOEL of 100 mg/kg bw/d related to 40% glyoxal (40 mg/kg bw/d related to active ingredient) can be retained for repeated dose toxicity.

Glyoxal is shown to be mutagenic in *in vitro* genotoxicity studies in prokaryotes and eukaryotes. *In vivo*, glyoxal is proven to be negative in the micronucleus test on the mouse after oral administration. On Drosophilia melanogaster, glyoxal is proven to be negative in the sex-linked recessive-lethal test, in the dominant-lethal test and in the studies on the reciprocal translocation and on the loss of sex

chromosomes. Chromosome aberrations in the duodenum, testes and spleen are described in an older, only insufficiently documented study after subcutaneous administration to rats. After oral administration to the rat, a significant increase of the unscheduled DNA synthesis is found in the pyloric mucosa, but not in primary hepatocytes, as well as an increase of DNA single-strand breaks in the liver and in the pyloric mucosa. These findings indicate that glyoxal reacts at the point of entry (the stomach) and immediately downstream (the liver), but not in more remote organs.

No dose-dependant effects were found on reproductive organs in repeated dose studies up to a dose of approx. 300 mg/kg bw/d (related to the active ingredient). Furthermore, a NOAEL of 125 mg/kg bw/d (related to the active ingredient) could be derived for prenatal development toxicity and of 25 mg/kg bw/d for maternal toxicity.

No carcinogenic effect is detected in mice after dermal application of glyoxal over the entire life span. Glyoxal possesses no tumor initiating effect after the dermal administration to mice After oral administration, glyoxal exhibits local tumor promoting properties in the mucosa of the forestomach of the rat (tissue not existing in other species or man). In a liver promotion model on the rat, no indications were found for a promoting effect of glyoxal through systemic action. Finally, glyoxal is a metabolite of ethylene glycol and there are two negative carcinogenic studies on ethylene glycol (rats and mice).

Environment

Glyoxal is not volatile and is not expected to accumulate in biota or soil/sediment. It is clearly readily biodegradable.

In short-term tests with fish, daphnids and algae the following results were found: *Pimephales promelas*: 96 h-LC50 = 215 mg/l; *Daphnia magna*: 48h-EC50 = 404 mg/l; *Scenedesmus subspicatus*: 96h-EC50 > 500 mg/l. With an assessment factor of 1000 a PNECaqua of 215 µg/l can be calculated from the LC50 for fish (The results refer to the 40% aqueous solution). For the active ingredient, the results are *Pimephales promelas*: 96 h-LC50 = 86 mg/l; *Daphnia magna*: 48h-EC50 = 161 mg/l; *Scenedesmus subspicatus*: 96h-EC50 > 200 mg/l; PNEC = 86 µg/l).

Exposure

The worldwide production volume of glyoxal is estimated to be approx. 120000 to 170000 t/a. Glyoxal is commercialized as a 40% aqueous solution. Glyoxal is mainly used as a chemical intermediate and also for a small part as an active ingredient in disinfectant products in preparation with other components (formaldehyde, glutaraldehyde, quaternary ammonium).

NATURE OF FURTHER WORK RECOMMENDED

Human health: Taking into account the skin irritation, the skin sensitising properties and the genotoxic potential and, based on the use pattern of glyoxal, a detailed risk assessment would be necessary. Especially the risks based on the exposure from open uses (e.g. as a disinfectant) should be evaluated.

Environment: No further work is necessary

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-98-2
Chemical Name	1-Methoxypropan-2-ol
Structural Formula	$CH_3OCH_2CHOHCH_3$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Propylene Glycol Methyl Ether (PGME) exhibits low acute toxicity by the oral**,** dermal, and inhalation routes. The oral LD 50 ranges from 1,840 mg/kg in rabbits, 4,600 mg/kg in dogs, to >5,000 mg/kg in rats. Dermal LD 50 values were 13-14 gm/kg in rabbits. Inhalation LC 50 values were generally above 6,000 ppm for rats, mice, and guinea pigs. PGME is not a skin sensitizer or skin irritant, and was only slightly irritating to the eye. In repeated dose studies (11 days to six months) NOAELs of 300 ppm and higher have been observed in inhalation studies using rats, mice, rabbits, guinea pigs, and monkeys. Effects observed included sedation, hepatic changes, and decrease in body weight gain. NOAELs (oral) of 459.5 mg/kg and 919 mg/kg were observed in rat studies lasting 13 and 5 weeks, respectively. Observations included central nervous system (CNS) effects, enlarged livers and weight loss. In reproductive toxicity testing, effects observed at 3000 ppm appear to be related to decreased maternal body weights and secondary to general toxicity and nutritional stress. Decreased maternal body weights were also noted at 1000 ppm. The NOAELs observed in the two-generation study were 300 ppm for adults and 1,000 ppm for offspring. Studies in rats, mice, and rabbits showed that PGME was not teratogenic (two inhalation and three gavage studies with teratogenicity NOAELs of 3000 ppm and 800 to 2000 mg/kg, respectively). Commercial PGME is a mixture of two isomers (α and β). The β-isomer is metabolized to 2-methoxyproprionic acid; a known animal teratogen. Although commercially available PGME contains less than 0.5% of the β-isomer, for consistency with the earlier studies, the PGME tested in the animal studies described here was altered to contain approximately 2% of the β-isomer. The weight of the evidence indicates that PGME is not genotoxic. In a 2-year bioassay, there were no statistically significant increases in tumors in rats and mice. In humans, volunteers' eyes were slightly irritated at doses greater than 100 ppm for 1-2 hours; doses of 750 ppm were strongly irritating; and CNS depression was observed at 1,000 ppm. At 300 ppm, mild eye and nasal irritation occurred within 5 minutes and became intolerable after 1 hour. Human exposures to concentrations of PGME greater than 150 ppm are expected to be self-limiting due to irritation effects.

Environment

PGME is not persistent in the environment and is not expected to bioaccumulate in food webs. The half-life of PGME in air is estimated to be 3.1 hours due to direct reactions with photochemically generated hydroxyl radicals. PGME is readily biodegraded under aerobic conditions. Although environmental monitoring data are not available for PGME, fugacity-based modeling indicates that PGME is likely to partition to water compartments in the environment (surface water, groundwater) with small to negligible amounts remaining in other environmental compartments (air, soil, sediment, and fish). Acute toxicity testing in fish, invertebrates, and algae indicate a very low order of toxicity with effect concentration exceeding 1,000 mg/L. Using an assessment factor of 100 for the fish

96 hour LC 50 of 20,800 mg/L, a PNEC of 208 mg/L was derived.

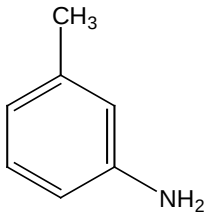
Exposure

Approximately 100,000 to 500,000 tons of PGME are produced worldwide each year. Within the US, approximately 145 million pounds of PGME were produced in 1999 (Appendix A). According to the Chemical Economics Handbook (SRI International), in the USA, a production volume of 165 million pounds of PGME is estimated for 2000. In 1995, approximately 420 million pounds (190,000 metric tons) were produced worldwide with an estimated annual growth rate of 0.7% - 2.0% according to producer specification. Commercially available PGME contains less than 0.5% of the β-isomer as is required by European Union labeling regulations. PGME is used in the manufacture of propylene glycol methyl ether acetate, as well as in a wide variety of industrial and commercial products, including paints, varnishes, inks, and cleaners. In the US, PGME is used as follows: 34% propylene glycol methyl ether acetate (PMA) production; 30% surface coatings; 23% cleaners; 7% adhesives/electronics; and 6% inks. Exposures to PGME are likely to occur for workers and consumers. Inhalation exposures to relatively high concentrations of PGME are believed to be self-limiting due to the irritant effects of the chemical. Use of protective gloves to minimize absorption is recommended when prolonged dermal exposures to PGME are anticipated.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-44-1
Chemical Name	m-Toluidine
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Although the metabolites, 2-amino-4-methylphenol and 4-amino-2-methylphenol were identified in the rat urine with a small amount of the parent compound, there is not sufficient information on metabolism and toxicokinetics. Acute toxicity of m-toluidine is low because the oral LD50 values in rat, mouse and rabbit are from 450 to 1,430 mg/kg. This chemical is slightly irritating to skin and moderately irritating to eyes. There is no information available on skin sensitisation.

In accordance with an OECD combined repeat dose and reproductive/developmental toxicity screening test [TG 422], m-toluidine was given to Crj: CD (SD) male and female rats by gavage at doses of 0, 30, 100, 300 mg/kg/day for at least 41 days. The critical effect at 100 and 300 mg/kg is a hemolytic anemia, revealed by reduction of erythrocyte counts and hemoglobin concentration, and histological changes such as pigment deposit and extramedullary hematopoiesis in liver and spleen. Other toxicity is renal tubular epithelium lesions accompanied with pigment deposit in kidney. As there is suggestive evidence of hemolytic anemia such as marginal pigment deposit and extramedullary hematopoiesis in spleen at the lowest dose of 30 mg/kg, probably caused by methemoglobin formation, LOAEL for repeat dose toxicity was 30mg/kg/day.

In the above screening test [OECD TG 422], m-toluidine was given from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. As implantation losses were found in all animals at 300 mg/kg and two of ten at 100 mg/kg but not at 30 mg/kg, NOAEL for reproductive toxicity is 30 mg/kg/day. The death of all pups or more than half the number of pups observed at 30 and 100 mg/kg/day is considered as the result of maternal toxicity because there is clear evidence of the lack of the nursing activity, probably due to anemia, and all live offsprings of 30 and 100 mg/kg had normally developed up to 4 days. Therefore the NOAEL for developmental toxicity is considered to be 100 mg/kg/day.

Bacterial genotoxicity studies show negative results in *S. typhimurium* and *E. coli* with and without metabolic activation. In chromosomal aberration test conducted in cultured Chinese hamster lung

(CHL/IU) cells by OECD TG 473, clastogenicity was not observed but significant increase of polyploidy (0.9 to 1.25 %) was found at the highest concentration. However, this result was considered not to be positive because it was within historical control and generally accepted criteria of significance (5 %). Two kinds of *in vivo* studies, sister chromatid exchange and inhibition of DNA-synthesis, also show negative results. Therefore m-toluidine is considered not to be genotoxic. Tumors were not observed in dietary study of male rats at 9,400ppmand male and female mice at 14,700 and 20,400 ppm, respectively. However, the carcinogenicity in rodents is inconclusive because the experimental conditions were insufficient compared to a current carcinogenicity testing protocol.

Environment

This chemical is mainly persistent in water and it will be transported to water compartment when released to other environmental compartments. The chemical is not readily biodegradable, and its bioaccumulation potential is low.

This chemical has been tested in a limited number of aquatic species. For algae, 72 h EC50 (biomass change in *Selenastrum capricornutum*) is 17.7 mg/L. For *Daphnia*, the lowest acute toxicity value is 0.73 mg/L (48 h EC50 for immobilization), and the lowest chronic value is 0.01 mg/L (21d NOEC for reproduction). For fish, only acute data were available, the lowest of which is 34 mg/L (96 h LC50, *Oryzias latipes*).

PNEC of 0.0001 mg/L for the aquatic organisms was calculated from the lowest chronic value (NOEC for *Daphnia;* 0.01 mg/L) using an assessment factor of 100. Toxicity of this chemical to aquatic organisms, specially against *Daphnia*, is high.

Exposure

The production volume of m-toluidine in Japan was less than 100 tonnes in 1990 - 1992, and imported volume was 97-285 tonnes/year in 1988-1992, however both the production volume and imported volume in Japan in 1998 was 0 ton. This chemical is used as intermediates for pigments, photography agents and others. This chemical is stable in neutral or alkaline solutions, and is classified as "not readily biodegradable". Direct photodegradation is expected. The half-life is estimated to be about 4 months. A generic fugacity model (Mackey level III) shows this chemical would be distributed mainly to water. In the monitoring study of the general environment in Japan in 1977, m-toluidine was detected from surface water and sediment, but in the monitoring study in 1999, it was not detected in water, sediment or air. According to a Japanese manufacturer, 400 kg/year (estimated) of m-toluidine are released with 1×10^{7} tonnes/year of effluent into bay. Local predicted environmental concentration (PEClocal) is 4.0×10^{-5} mg/l, employing the calculation model. The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. The concentration in drinking water is assumed to be less than 4.0×10^{-5} mg/l. Consumer exposure is negligible because m-toluidine is not contained in consumer products. As m-toluidine is mainly produced in a closed system, occupational exposures at production sites may occur by the inhalation and dermal route. Estimated human exposure for a worker who operates sampling (0.1 hr/day), drum filling (1.5 hr/day), and reaction vessel cleaning (2 day/year) without protective equipment is less than 0.21 mg/kg/day. By wearing chemical cartridge respirator during these operations, and ventilation systems during the filling process, exposure level is lower than the estimation.

NATURE OF FURTHER WORK RECOMMENDED

Local exposure assessment should be considered given the aquatic toxicity of the chemical.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-65-6
Chemical Name	1-Methoxy-2-propyl acetate
Structural Formula	$CH_3O\text{-}CH_2\text{-}CH(CH_3)\text{-}O\text{-}COCH_3$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

It is anticipated that rapid and extensive hydrolysis of 1-Methoxy-2-propyl acetate also known as 2-methoxy-1-methylethyl acetate (PMA) will occur *in vivo* following either oral, inhalation or dermal exposures to yield the corresponding glycol ether, propylene glycol monomethyl ether (PM). Thus, it is presumed that no substantial differences in the systemic toxicities of PM or PMA will exist. In particular, dermal testing with PMA in rats suggests that any effects arising from PMA would be overestimated by using PM toxicity data.
Acute toxicity of this chemical is low in rodents because LD_{50} values are greater than 5,000 mg/kg by oral or dermal routes and greater than 10,800mg/m^3 by inhalation.

This chemical is slightly irritating to the eye, but not to the skin. PMA is not skin-sensitising in guinea pigs.

In a oral rat study carried out according to the OECD combined repeated dose and reproductive/ developmental toxicity screening test [OECD TG 422], a dose of 1,000 mg/kg/day of PMA exerted some effects in only male rats. Blood examination revealed decreases in glucose and inorganic phosphorus and an increase in relative weight of the adrenals was also noted in males. However, such changes were not observed in females. Histopathological examination revealed none of the alteration of tissues at the highest dose group for both sexes. As such changes in males were considered not to be adverse effect, a NOAEL was considered to be 1,000 mg/kg bw/day for both sexes.

An inhalation study conducted for 6 hr/day, 5 day/week for 2 weeks using rats and mice at doses of 300, 1,000 or 3,000 ppm (1.62, 5.39 or 16.18 mg/L) demonstrated that haematology and clinical chemistry analyses revealed no treatment-related effect. However, the kidneys of all male rats and two of five females in the 3,000 ppm-exposure group appeared to be slightly reticulated at necropsy. The change noted in these animals was a slight increase in the eosinophilic granularity of the proximal convoluted tubules of the kidneys. The same slight renal change was also observed in one of five male rats at 1,000 ppm. Another detectable effect in rats and mice was slight-to-moderate degeneration of olfactory epithelium in the nasal cavities. A NOAEL for inhalation toxicity in rats was established at 300 ppm (1.62 mg/L) for males and at 1,000 ppm (5.39 mg/L) for females, whereas a NOAEL for inhalation toxicity in mice was not established because the lowest dose at 300 ppm induced a minimum effect on the nasal cavity of mice. The change in nasal cavity is likely caused by acetic acid from PMA hydrolysis at the exposure site.

In reproductive/developmental oral toxicity study [OECD TG 422], there were no statistically significant adverse effects on reproductive parameters and no evidence of malformations at any doses. Likewise, in developmental/teratogenicity inhalation study, there were no statistically significant adverse effects on reproductive and teratogenic parameters at any doses, although some systemic toxicities were observed in dams at 2,000 and 4,000 ppm. A NOAEL was established at 1,000 mg/kg bw/day for reproductive/developmental toxicity by gavage and at 4,000 ppm (22,464 mg/m^3) for developmental/teratogenicity toxicity by inhalation, respectively.

Two bacterial mutation tests, unscheduled DNA synthesis in rat hepatocytes and chromosomal aberration test *in vitro* show negative results.

PMA tested in the animal studies contained approximately a maximum of 2 % of the beta-isomer.

Environment

PMA is readily biodegradable (OECD TG 301F: 99 % after 28 days). This chemical is stable to chemical hydrolysis in water at pH 4 and 7, whereas it is hydrolyzed at pH 9 with half-life of 8.10 days at 25 °C.

The toxicity to aquatic plants (algae; *Selenastrum capricornutum*) was >1,000mg/L for EC_{50} (72 hr) and NOEC (72 hr). The acute toxicity data in fish (medaka; *Oryzias latipes*) were >100 mg/L for 96h LC_{50}, 63.5 mg/L for 14d LC_{50} and 47.5 mg/L for 14d NOEC. In *Daphnia magna*, EC_{50} (48h) for acute toxicity and NOEC (21-d reproduction) for chronic toxicity were 373 mg/L and ≥100 mg/L, respectively. When assessment factor of 100 was applied to the 14d LC_{50} for medaka and the chronic toxicity for *Daphnia*, PNECs were calculated as 0.635 and ≥1.0 mg/L, respectively. The lowest PNEC was thus determined to be 0.635 mg/L.

Exposure

The production volume in Japan was approximately 15,000 tonnes/year in use, while estimated global production is 100,000-500,000 tonnes/year according to IUCLID 1999. Commercially available PMA contains less than 0.5 % of the ß-isomer. PMA has a variety of uses including as a solvent for paints, inks, lacquers, varnishes and cleaners, coatings and ink-removers, and as a pesticide inert.

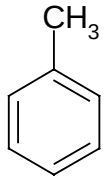
Generic fugacity models (Level III Fugacity Model and Unit World Equilibrium Model) show this chemical would be distributed mainly to water if it was released into water.

As this chemical is contained as a solvent for specific paint products and used in industrial sites, user exposure may take place in the industry and consumer. PMA occurred in 366 chemical products on American market according to MSDS-OHS 2000.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-88-3
Chemical Name	Toluene
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Toluene is a toxicologically well-investigated chemical. Inhalation is the most important route of human exposure because of the high vapour pressure of the substance. Also absorption through the skin may however be of importance, because the substance passes the skin. Around 50 % is absorbed after inhalation. Adipose tissues may be a reservoir for toluene and concentrations in e.g. the brain are higher than in the blood. Toluene readily passes the placenta and is secreted into maternal milk. The half-life in human tissue may be up to three days. Toluene does not persist in the body. Around 20 % of absorbed toluene is eliminated via the expired air, whereas around 80 % is metabolised mainly in the liver by enzymatic oxidation and subsequent conjugation with glycine and glucuronic acid. It is excreted in the urine mainly as hippuric acid. Benzoylglucuronide may be formed and excreted at heavy exposure.

Toluene has a low acute dermal, oral and inhalative toxicity, however it may cause sleepiness and dizziness, and general narcosis after inhalation of high concentrations. The chemical causes de-fatting and irritation of skin and some eye irritation, but does not cause skin sensitisation.

A great number of repeated dose and chronic toxicity studies have been performed. An oral NOAEL of 625 mg/kg bw/day after 13 weeks of exposure has been observed in rats and mice. Neural cell death was observed in the rats in doses above the NOAEL. Lifetime inhalation exposure of rats caused degeneration of nasal epithelium and increased incidence of stomach ulcers with a NOAEC of 300 ppm and a LOAEC of 600 ppm. Other effects observed in laboratory animal inhalation studies include adaptive proliferation of the liver and long-lasting or irreversible ototoxicity, the latter being enhanced, when the animals were also exposed to certain other chemical agents or noise. A NOAEC of 700 ppm (2660 mg/m^3) for hearing loss in rats has been established. Also for humans there is evidence that toluene may cause ototoxicity even though these studies do not allow establishment of a NOAEL or LOAEL. Long-term inhalative exposure has been shown to cause long lasting (> 6 months) effects on brain neurochemistry in rats and neuron loss in hippocampus, however these effects cannot readily be interpreted in functional terms. Several investigations on humans suggest that toluene, after inhalation of high concentrations may cause long-term effects on the brain / central nervous system, i.e. neuro-psychological effects. The evidence that toluene may cause or even the existence of "the organic solvent brain syndrome" is however disputed by some experts.

Toluene has been tested for mutagenicity and other types of genotoxic effects in a multitude of *in vitro* and *in vivo* experiments and is evaluated as being non-mutagenic. The carcinogenicity of toluene has been investigated in two

inhalation studies in rats and mice respectively, and in a skin painting study in mice. The rat study was negative, non-malignant tumours were observed in the pituitary gland in the mice study, and malignant skin tumours occurred after skin application in mice at doses causing skin irritation. These effects were, however, not statistically significant. Toluene is evaluated as not carcinogenic.

Toluene did not affect rat fertility (NOAEC was 2000 ppm (7500 mg/kg/m^3, 6h/day, 90 days)), but significantly decreased sperm count and epididymis weight. No human studies of the effects of toluene on sperm count are available, but limited human data fail to show clear indications of effects on fertility in men or menstrual function in women. Case studies of children born of women exposed to high toluene levels during pregnancy (via "sniffing") provide some evidence of human developmental toxicity (physical and neurological abnormalities). Two recent studies suggest an increased risk of spontaneous abortions associated with exposure to toluene at the workplace, one study gives an exposure level of 50-150 ppm, whereas the other study cannot be interpreted because of mixed exposure. The studies cannot be used to definitively establish a causal relationship between toluene exposure and late spontaneous abortions in humans, but suggest an increased risk. Rat inhalation studies provide strong evidence of developmental toxicity (lower birth weight and long-lasting developmental neurotoxicity) in the absence of maternal toxicity. The NOAEC for lower birth weight and delayed postnatal development is 600 ppm (2250 mg/kg/m^3). A LOAEC for developmental neurotoxicity is 1200 ppm (4500 mg/kg/m^3), whereas a NOAEC cannot be established.

The above-mentioned toxicological endpoints and their NOAELs and LOAELs, the severity of the effects seen, and the possible uncertainties concerning the effects have been taken into consideration in the evaluation of the various MOSes for the different types of human exposure situations considered in the risk characterisation.

Environment

Toluene is estimated to be stable to hydrolysis and photo-degradation in surface water. The photochemical oxidative degradation is measured to have a half-life of 1-2 days. Toluene is readily biodegradable, but simulation types of data suggest a decreased biodegradation at environmentally realistic low concentration in surface water: The half-life in Sewage Treatment Plants (STP) is estimated to be 0.0289 days (rate constant of $1hr^{-1}$) and in surface water around 30 days. Only scarce data are available for degradation in soil, and the half-life is estimated to be 90 days under aerobic conditions according to "the realistic worst case" concept. Toluene has a low adsorption capacity with an estimated Koc of 177 indicating a moderate to high mobility potential. The log Kow 2.65 indicates a low bioaccumulation potential, which was confirmed in tests where BCF in two fish species were 13 and 90, respectively.

Toluene has been tested in a wide variety of aquatic species. Due to the nature of the substance (high volatility) only a few of the studies were considered valid. The acute toxicity to fish ranges from an LC_{50} of 5.4 for Pink salmon to 26 mg/l for Fathead minnow. The lowest valid acute toxicity for *Daphnia magna* was 11.5 mg/l. Other crustaceans ranged from 3.5 mg/l for *Crangon franciscorum* to 33 mg/l for *Artemia salina*. For algae, the acute toxic EC_{50} was not available in valid tests, but in two species (*Selenastrum capricornutum* and *Skeletonema costatum)* the NOECs were 10 mg/l. In absence of algae EC_{50}-values, the predicted values of 12.2 mg/l and 11mg/l were calculated using the QSAR-programmes ECOSAR and QTOXMIN, respectively. The long-term toxicity NOEC for fish ranged from 1.4 mg/l for *Oncorhynchus kisutch* to 4 mg/l for *Pimephales promelas*. The chronic NOEC for *Daphnia magna* ranged from 0.53 mg/l to 1.0 mg/l and for *Ceriodaphnia dubia* 0.74 mg/l. For the terrestrial compartment, the earthworm acute EC_{50} was >150 but <280 mg/kg soil, NOEC values for mortality and cocoon production was ≤150 and <280 mg/kg, respectively, whereas a NOEC based on visual inspection was between 15 and 50 mg/kg soil. For plants, a yield decrease was observed in *Lactuca sativa* at 1000 mg/kg. For soil micro-organisms, NOEC for nitrification was <26 mg/kg soil dw. For micro-organisms in the STP, EC_{50} for respiration was between 110 and 292 mg/l whereas EC_{50} for nitrification was 84 mg/l. In regard to toxicity to green plants exposed via the air a NOEC of 60 mg/m^3 after 14 days exposure has been observed.

An assessment factor of 10 was used to calculate a predicted no effect concentration (PNEC) for toluene in the aqueous environment since long-term data was present for fish, crustacea and algae: $PNEC_{aqua}$ = 0.074 mg/l. For STP the most sensitive microbial process (nitrification) along with an assessment factor of 10 were used to derive the $PNEC_{STP}$= 8.4 mg/l. For the terrestrial environment, an assessment factor of 50 was used because of availability of two long-term tests on soil organisms: $PNEC_{soil}$ = 0.3 mg/kg. Toluene may after reactions catalysed by light contribute to formation of ozone and other air pollutants in near surface atmosphere. Green plants, animals and humans seem roughly to be equally sensitive to the toxic effects of ozone.

Exposure

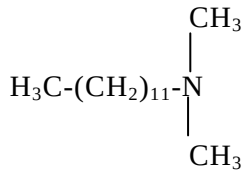
Toluene is a high production volume substance. In 1995, the production volume of toluene in EU was 2600 Ktonnes. Import and export volumes were imprecise, but the total EU consumption is estimated to be approximately 2800 Ktonnes (1995 value). Toluene occurs naturally and is present in crude oil. Most of the refinery streams containing toluene are used as a base or blending feedstock to produce motor gasoline. The commercial toluene is isolated from the refinery streams and is used as an intermediate in closed systems to manufacture other chemicals and as a solvent carrier in paints, thinners, adhesives, inks and pharmaceutical products and as an additive in cosmetic preparations. Toluene is used in a large number of industrial branches and consumer products.

Toluene may be released to the environment when substances containing toluene or preparations thereof are produced, distributed and handled. Besides the releases from use, distribution and handling of commercial toluene are the releases from natural sources (volcanoes, forest fires, etc.) and from the use and combustion of fuels. As these latter sources may well be of the same order or higher than releases from manufactured (isolated) toluene, they are likely to contribute as main sources for the observed background concentrations.

NATURE OF FURTHER WORK RECOMMENDED

In the context of the EU risk assessment programme, risk reduction measures are being considered for protection of human health and the environment. For human health, risk reduction is considered for consumers and for the workplace (production and use of toluene as well as of toluene containing products like glues, paints and other products). It is furthermore recommended that an in depth evaluation is performed under the appropriate EU Air Quality Directives regarding the contribution of toluene to the near ground atmospheric formation of ozone and other harmful air pollutants. For the environment, risk reduction is in the EU mainly considered for a number of downstream uses of toluene in relation to the aquatic and terrestrial environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	112-18-5
Chemical Name	N,N-Dimethyldodecylamine
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

There are two industrial products containing N,N-dimethyldodecylamine with different purities, Genamin 12R 302 D (> 95 % C12-Dimethyldodecylamine) and the structural related Genamin 302 D (approximately 70 % C12-, 25 % C12-14- and 5 % C16-dimethylalkylamine).

The SIAR covers the C12- as well as the C12-14 alkyldimethylamine (Cas-No. 84649-84-3).

Human Health

Genamin 12 R 302 D and Genamin LA 302 D have been found to be harmful following oral administration to rats. Both compounds showed strong irritating or corrosive effects after either four hours or three minutes exposure. In a 28-day subchronic toxicity study, the 'No Observed Effect Level' (NOEL) was 50 mg/kg bw/day. The reference compound Genamin 12 R 302 D was not mutagenic in the Ames test with and without metabolic activation. 302 D was also not mutagenic in a micronucleus test in vivo. The corrosive property of the compounds prompt workers to limit the potential exposure to this chemical. Due to the related self-warn effect, exposure will be self-restricted to a minimum.

Environment

N,N-dimethyldodecylamine can be classified as readily biodegradable. A high potential for adsorption onto sludge is assumed. In an activated sludge simulation test with domestic activated sludge a mean primary degradation of 99.6% was found. The following effect values were found: *Brachydanio rerio*: 96h-LC50 = 0.71 – 1 mg/l; *Daphnia magna*: 48h-EC50 = 0.083 mg/l, *Scenedesmus subspicatus*: 72h-EC50 < 23.5 µg/l and 14 µg/l. In addition ecotoxicity tests using river water as test medium are available. For the green algae *Scenedesmus subspicatus* a 72h-EC50 of 56 mg/l and a NOEC of 20 µg/l was found. In a reproduction test with Daphnia magna a 21d-NOEC of 36 µg/l was obtained. Based on these data a PNECriverwater of 0.4 µg/l can be derived using an assessment factor of 50. A sediment test with the nematode *Caenorhabditis elgans* was conducted, in which a NOEC of 1620 mg/kg dw was found. With an assessment factor of 100 a PNECsed of 16.2 mg/kg dw was derived. Acute terrestrial test with earthworm and plants are available. The lowest effect value was found for Brassica napus with an 21d-EC50 of 120 mg/kg dw for the endpoint shoot height. A PECsoil of 120 µg/kg dw can be derived from this value using an assessment factor of 1000.

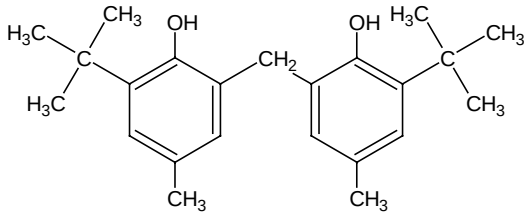
Exposure

N,N-dimethyldodecylamine is produced from lauryl alcohol and dimethylamine. In 1999 C12-14 alkyldimethylamine was produced and processed in the EU in an amount of 27.000 t and in the USA in an amount of 29.500 t. There are 4 European companies and 2 US companies that produce and/or process C12-14 alkyldimethylamine. C12-14 alkyldimethylamine is used as an intermediate for manufacture of amineoxides and quarternary amino compounds. The subsequent products are used as disinfectants; detergents; dyeing auxiliaries, wetting agents, antistatic agents and bleaching agents in textile industry; pharmacy; corrosion inhibitors; fuel oil antiicing; pourpoint additives; molecular weight regulators in plastic industry; prevention of waterspots in photography; complexing developers and dyes. Releases into the environment may occur during production, and use of the subsequent products. Processing to amineoxides and quarternary amino compounds is assumed to be a waste-water free process, therefore, no releases into the hydrosphere are expected by this life-cycle step.

NATURE OF FURTHER WORK RECOMMENDED

One production site was identified where risk reduction measured might be warranted.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	119-47-1
Chemical Name	6,6'-di-*tert*-butyl-2,2'-methylenedi-*p*-cresol
Structural Formula	 $C_{23}H_{32}O_2$

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acute toxicity of this substance is low; oral LD_{50} values in animals is greater than 5,000 mg/kg. The substance is not irritating to skin and moderately irritating to eyes. There is no skin sensitization in humans. In repeated dose toxicity studies, including a rat 28-day repeated dose toxicity test [Japan TG], a preliminary reproduction toxicity screening test [OECD TG 421] and a rat 18 month chronic toxicity test, effects on sperm in the cauda epididymis and histopathological changes in the testis, such as degeneration of step 19 spermatids and vacuolation of Sertoli cells, were observed in the 42.3 mg/kg and higher dose groups. Based on the above results, the NOAEL for repeated dose toxicity is considered to be 12.5 mg/kg/day. In a reproductive/developmental toxicity study [OECD TG 421], the effects on reproductive parameters, such as decrease in number of corpora lutea, implantation scars and pups born, were observed in the 200 mg/kg/day and higher dose groups but not 50 mg/kg/day. Therefore, NOAEL for female reproductive toxicity is considered to be 50 mg/kg/day. However, NOAEL for male reproductive toxicity is 12.5 mg/kg/day because of the testicular toxicity as described above. As for the developmental toxicity, low body weight gain of offspring and increased number of stillbirths were observed at 800 but not 200 mg/kg/day. The teratogenic effects were not observed in a study with rats up to 375 mg/kg/day. Based on these findings, the NOAEL for developmental toxicity is considered to be 200 mg/kg/day. Three bacterial reverse mutation tests and mammalian chromosomal tests with and without metabolic activation show negative results [OECD TG 471, 472, 473]. No tumors were observed in a 18-month chronic feeding study with rats up to 1,000 ppm, however this study is not qualified to be regarded as a carcinogenicity study. Therefore, no conclusion could be reached on the carcinogenicity.

Environment

The substance is not readily biodegradable (MITI (I), corresponding to the OECD 301C ; 0 % after 28 days) and seemed not highly bioconcentrated according to OECD 305; BCF 23 – 125. The fugacity

level III calculations suggest that the majority of the substance would distribute into sediment if released to aquatic compartment. Relevant to the environmental hazard of the substance, only the toxicity to aquatic organisms (i.e. green algae, water flea and fish) has been actually measured. Due to low water solubility of the substance, homogenous solution could be attained only at the nominal concentration of 5.0 mg/L with the maximum allowable dispersant concentration of 100 mg/L. The acute $L(E)C_{50}$ values for these aquatic species are all greater than this solubilization limit (i.e. >4.8 – >5.0 mg/L). The lowest chronic value (i.e. 21day-NOEC) is 0.34 mg/L determined for the reproduction of *Daphnia magna*, and is also above the water solubility. There is some uncertainty connected to these toxicity values of apparent aquatic toxicity because they were all considerably above the water solubility. Assessment factor of 50 is used to this chronic value and the PNEC for the aquatic environment is estimated to be 0.0068 mg/L. Although no measured result on the toxicity to sediment dwelling organisms can be evaluated, the provisional PNEC for the sediment compartment is tentatively estimated to be 2.0 mg/kg according to the equilibrium partitioning method specified in the EU-TGD.

Exposure

Production volume of the substance is estimated ca. 1,000 - 1,200 t/year in Japan, and ca. 3,300-3,500 t/year world-wide.

The substance is applied exclusively for the use resulting in inclusion into or onto matrix; it is used in the polymers industry as antioxidants and/or stabilizers, and in the rubber industry as additives.

Consumer exposure: In consideration of the application of the substance (mostly for industrial use), consumer use is regarded not relevant in Japan (the migration of the substance is practically none; i.e. consumer exposure from the polymer/rubber is expected to be negligible).

Occupational exposure: During production, processing and use in Japan, occupational exposure at a production and industrial use sites is the only case for serious consideration; based on exposure monitoring at a production site, it was estimated as the worst case that the highest daily intake (EHE) is 0.0068 mg/kg/day if a worker is assigned to implement without any industrial hygiene protection.

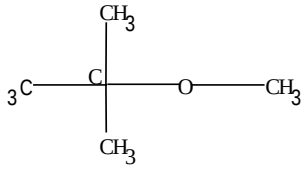
Exposure to the environment: During production, processing and use in Japan, only the aquatic release of the substance at the production site seems to be possible.

NATURE OF FURTHER WORK RECOMMENDED

Exposure assessment at production, processing and use sites would be recommended at the national or regional levels because the low NOAEL of this chemical for repeated dose toxicity is established from the critical effect on testes.

Considering the distribution characteristics of the substance (i.e. distribution tendency to sediment if released to aquatic environment), and due to lack of measured toxicity value to the sediment dwelling organisms, further work characterizing aquatic hazards possibly including the sedimentary environment would be recommended. But this work would be conducted if significant emission to the environment is evidenced from the above exposure assessment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1634-04-4
Chemical Name	Methyl tertiary-Butyl Ether (MTBE)
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

MTBE is a liquid with a high vapour pressure, therefore most exposure takes place via inhalation. The substance is well absorbed and rapidly metabolised to formaldehyde and *tert*-butanol. *t*-Butanol is further metabolised, but at a lower rate, to 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid, the latter being the main metabolite. Although the rat appears to metabolise MTBE more efficiently than humans, the profile of metabolites is the same.

MTBE exhibits low acute toxicity via the oral, dermal and inhalation routes in mammals. In rats, the average oral LD50 is 4000 mg/kg. Dermal LD50 is over 10000 mg/kg and LC50 by inhalation approximately 100 mg/l. MTBE is considered a skin irritant but not an eye irritant nor a respiratory irritant. MTBE was not sensitising in guinea pigs and there are no reports available concerning sensitisation in humans. In repeated dose toxicity studies, the principal affected organs are the liver and the kidneys, mainly at inhaled concentrations of 3000 ppm and above or at oral doses of 250 mg/kg or higher. MTBE produced protein droplet nephropathy, probably associated with the male rat specific accumulation of α2u-globulin in tubular cells. MTBE increased liver weight and induced hepatocyte hypertrophy in rats and mice. In female mice, MTBE induced a variety of microsomal P450 activities without hepatotoxicity or an increase in sustained nonfocal hepatocyte DNA synthesis. Overall, an oral NOAEL of 300 mg/kg and a respiratory NOAEL of 800 ppm were derived.

MTBE has been extensively tested for genotoxicity in a variety of test systems both *in vitro* and *in vivo*. Although all the results have not been consistently negative, the weight of evidence conclusion is that the substance is not a genotoxicant.

A mildly increased incidence of renal tubular cell carcinomas and adenomas was found in male Fisher-344 rats at 3000 ppm of MTBE. It is reasonable to assume that these neoplasms are associated with the cytoxicity and proliferative response of α_{2u}-globulin nephropathy. No increase of tumours was seen at 400 ppm. In female CD-1 mice, 8000 ppm of MTBE induced hepatocyte hypertrophy and an increased incidence of liver adenomas. At high dose levels MTBE clearly had an antioestrogenic effect on the

mouse uterus although its mechanism could not be identified. MTBE did not show promoter activity when tested in female mice after N-nitrosodiethylamine (DEN) initiation. Although the eventual role of MTBE in mouse liver tumour promotion is presently unclear as to the exact mechanism, oestrogen antagonism may be involved. High levels of MTBE (≥3000 ppm by inhalation, 1000 mg/kg/day orally) caused testis interstitial (Leydig) cell adenomas in Fisher-344 and Sprague-Dawley rats. In Fisher-344, there was a clear dose-response relationship but the tumour incidences were within the laboratory historical control values. Whilst high MTBE doses did decrease serum testosterone in Sprague-Dawley rats possibly resulting from enhanced metabolism, and there were also mild perturbations in T_3 and prolactin, stimulation of the hypothalamic-pituitary-testis axis was not found. Therefore, as the mode of action is presently unclear, no definitive conclusions can be drawn regarding the relevance of this tumour for man. Equally unknown are the mechanisms for the increase of lymphoblastic lymphoma (notably in the lung) found in female Sprague-Dawley rats dosed orally with 250 and 1000 mg/kg MTBE. Formaldehyde, a known mutagen, is not presumed to express intrinsic reactivity in MTBE metabolism because it is rapidly eliminated. By contrast, it is noteworthy that *tert*-butyl alcohol, the primary metabolite of MTBE, caused thyroid adenomas in female mice and kidney tumours in male rats. In summary, MTBE is suspected to function as an epigenetic promoter in animal carcinogenesis models at high dose levels. In view of the lacking or limited relevance of the findings for man, and the low potency demonstrated in animal studies, human cancer hazard is presumed to be low.

MTBE has been tested for effects on fertility in one- and two-generation studies in the rat, and for developmental toxicity in the rat, mouse and rabbit. No remarkable reproductive toxicity or specific developmental toxicity was found.

Environment

MTBE does not adsorb to soil and leaching with water is the predominant abiotic fate process in the subsurface ground. The biodegradability of MTBE in soil in aerobic and especially in anaerobic conditions is slow. MTBE is not readily biodegradable in aquatic environment according to the standardised tests. Certain special types of inoculums, pure cultures and mixed cultures are, however, capable to degrade MTBE. In the air the degradation half-life of MTBE is approximately 3 to 6 days. MTBE does not bioaccumulate (BCF 1.5).

MTBE exhibits low toxicity to aquatic organisms in acute tests. Marine invertebrates seem to be the most sensitive organisms with EC50 values ranging from 136 to 306 mg/l. Acute toxicity values to freshwater invertebrates range from 340 to 960 mg/l . Long term NOEC for *Daphnia* is 51 mg/l and for marine invertebrate *Mysidopsis bahia* 26 mg/l. Acute toxicity to fish varies from 574 to 1358 mg/l. Chronic IC20 to freshwater fish is 279 mg/l. Acute toxicity to freshwater algae varies from 184 to > 800 mg/l and the IC20 value is 103 mg/l. PNEC to aquatic organisms is 2.6 mg/l.

There is no ecotoxicological data for sediment-dwelling or terrestrial organisms. PNEC calculated using the equilibrium partitioning method result in a $PNEC_s$of 2.05 mg/kgwwt for sediment organisms and a PNEC of 0.73 mg/kgwwt for terrestrial organisms.

The use of MTBE in gasoline has resulted in growing detection of MTBE in groundwater in some European Union Member States. This is mainly caused by leaking underground storage tanks and spillage from overfilling the tanks. MTBE in groundwater has not been routinely monitored in EU countries and therefore it is difficult to draw firm conclusions about the present extent of the problem at EU level. The available data from Member States demonstrate that there are numerous pollution cases and that the variability in the incidence of these cases is considerable.

In relation to groundwater pollution it is justified to consider, in addition to the ecotoxicological and toxicological aspects, the overall quality of the groundwater. Although the low odour and taste thresholds of MTBE may be seen useful early warning indicators of groundwater pollution the water resource will in practice be polluted and unusable when the odour and taste threshold levels are exceeded. In number of cases within EU MTBE has been detected in ground water and drinking water in

concentrations clearly exceeding odour and taste thresholds.

Exposure

The estimated use of MTBE was 3.3 million tonnes in 1999 in the EU and >20 million tonnes globally. MTBE is mainly used as a petrol additive (approximately 99%). It is also used for the production of isobutylene and as an extraction solvent in pharmaceutical industry and laboratory work. Workers are exposed during production and reformulating with petrol and during distribution. Other related exposures are maintenance tasks, service stations, and automotive repair. Consumers are potentially exposed at petrol stations and during refuelling. Indirect exposure via the environment may occur via drinking water and ambient air (exhausts, leakage and evaporation). An extensive set of measured data on emissions from the production, formulation and processing sites in the EU is available.

NATURE OF FURTHER WORK RECOMMENDED

The SIDS requirements are met. This substance has been discussed in the European Union Risk Assessment programme under Regulation EEC/793/93, and the conclusion is that there is need to limit the risk:

- to workers because of concerns for repeated dose local skin effects as a consequence of exposure arising from maintenance operations and automotive repair;
- to aquatic ecosystems because of exposure arising from releases to surface water from terminal site storage tank bottom waters; and,
- to ground water and drinking water aesthetic quality because of exposure arising from leaking underground storage tanks and spillage from overfilling the storage tanks.

Other member states are therefore recommended, as post-SIDS activity, to review the exposure situation in their countries to determine the need for similar measures.

The US is considering a ban on the use of this material in automotive fuel.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	25265-71-8 and 110-98-5
Chemical Name	Dipropylene glycol, mixed isomers and dominant isomer
Structural Formula	CH_3-CHOH-CH_2O-CH_2-CHOH-CH_3

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Dipropylene glycol (DPG) is not acutely toxic by oral (LD_{50} $\geq$13 g/kg bw/day from 7 rat studies and 17.6 g/kg bw/day from a guinea pig study), dermal (LD_{50} > 5g/kg bw/day in 2 rabbit studies) or inhalation (no deaths observed in rats and guinea pigs at 6 to 8 g/m^3) routes of exposure. DPG is slightly irritating to the skin and eyes of rabbits. Based on human data, DPG is not a skin sensitizer. Repeated exposures of rats to DPG did not result in adverse effects at levels up to 5% (estimated NOAEL is about 6.2 g/kg bw/day) in drinking water. At about 12.5 g/kg bw/day (10%), kidney lesions appeared in about 30% of the rats. Results from an OECD 422 combined repeat dose/reproductive/developmental toxicity test on the structural analogue, tripropylene glycol (TPG), demonstrated a NOAEL of 200 mg/kg bw and a LOAEL of 1000 mg/kg bw for repeated dose toxicity, with increased relative weight for liver and kidney. Metabolic fate data on TPG demonstrates that TPG is readily converted to DPG, PG, and CO_2 in rats. Thus, data from TPG are relevant to DPG. DPG did not cause fetal toxicity or teratogenicity in rats (NOAEL = 5 g/kg bw/day) or rabbits (NOAEL = 1.2 g/kg bw/day). No reproductive studies have been conducted on DPG. However, the structural analogues, propylene glycol and TPG, have been tested for reproductive effects and shown to have NOAELs of 10.1 g/kg bw in mice and 1 g/kg bw in rats, respectively. Thus, the lack of reproductive effects from TPG and the high NOAEL for PG reproductive toxicity indicate that no reproductive effects are expected in animals exposed to DPG, in the absence of maternal toxicity. DPG is not a genetic toxicant based on *in vitro* (bacterial and mammalian cells in culture) and *in vivo* (micronucleus) studies.

Environment

Dipropylene glycol (DPG) is not volatile, but is miscible with water. Air monitoring data are not available, but concentrations of dipropylene glycol in the atmosphere are expected to be extremely low because of its low vapor pressure and high water solubility. Low levels of DPG (0.4 ng/l) in drinking water were reported in one study. It is biodegraded in water and expected to be biodegraded in soil, as indicated by >70% degradation after 28d in a Zahn-Wellens test. It is not expected to bioaccumulate, with measured BCFs between 0.3 and 4.6 in fish. Measured aquatic toxicity data on fish and amphibians report toxicity at >5,000 and 3,181 mg/L, respectively. Based on QSAR data for Daphnia and algal toxicity, and the measured data for fish and amphibians, DPG is not expected to be toxic to aquatic organisms except at very high concentrations. Using an assessment factor of 100 and the fish 96-hour LC_{50}, the PNEC is >50 mg/l; if the amphibian data are used, the PNEC is 32 mg/l.

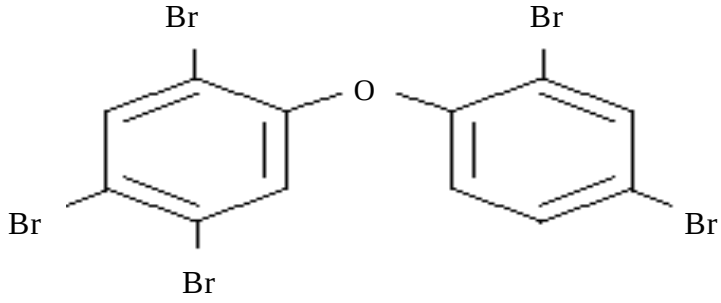
Exposure

Dipropylene glycol is produced as a byproduct of the manufacture of propylene glycol. The US production capacity of DPG was 131 million pounds (59.5 kilotonnes) in 1998; the demand was 108 million pounds (49 kilotonnes). DPG is used (percent of demand) as follows: plasticizers, 38 percent; unsaturated polyester resins, 23 percent; cosmetics and fragrances, 10 percent; polyurethane polyols, 8 percent; alkyd resins, 7 percent; miscellaneous, including solvents and functional fluids (specialty de-icers, inks, lubricants), 14 percent.

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	32534-81-9
Chemical Name	Diphenyl ether, pentabromo derivative (Commercial substance)
Structural Formula	 2,2',4,4',5-pentabromodiphenyl ether (example component)

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Toxicokinetic evidence indicates that the substance can be absorbed into the body, although the extent of absorption cannot be assessed from the data available. There are no data on inhalation or dermal absorption. However, comparison with structurally similar substances such as polybromo- and polychlorobiphenyls suggests that the substance may be well absorbed by all routes of exposure. Once absorbed it is distributed to adipose tissue and lipids. Given its high lipophilicity and slow rate of metabolism it can be assumed that the substance will bioaccumulate in these tissues. Following pregnancy it is excreted as a component of breast milk.

The substance is of low toxicity via the inhalation, oral and dermal routes of exposure. It produces minimal to mild, generally reversible, signs of skin and eye irritation in animals following single exposure. In animals, signs of respiratory tract irritation were observed only at airborne exposure concentrations of >8000 ppm. No effects were observed at 80 ppm, which suggests that it is unlikely to produce significant respiratory tract irritation. Evidence from studies in guinea pigs indicates that it is not sensitising to the skin. The absence of skin sensitising properties and the generally unreactive nature of the substance suggests that it would not be sensitising to the respiratory tract.

Studies in rats and mice indicate that the liver is the key target organ. Effects include increases in liver weight, hepatocytomegaly, cellular microscopic changes, induction of enzymes and disturbances in cholesterol and porphyrin synthesis. Due to the induction of liver enzymes, thyroid hormone levels are reduced in rats and mice leading to increases in thyroid weight. However, due to species differences in thyroid metabolism the effects on thyroid status are not likely to be of relevance to human health. The liver and thyroid changes produced by a commercial preparation of pentabromodiphenyl ether are

apparent within 4 weeks of repeated oral dosing, with effects on the liver at 2 mg/kg/day and above, and changes in thyroid status at 10 mg/kg/day and above. In a 90-day dietary study in rats, which included microscopic examination of the tissues, there was evidence for functional disturbance of the liver at 10 mg/kg/day, with 2-fold increases in liver porphyrin levels, accompanied by increases in liver weight and histopathological changes of uncertain character in enlarged parenchymal liver cells of both sexes. At 100 mg/kg/day (the next highest dose used) the liver disturbance was more pronounced, including a 400-fold increase in liver porphyrin levels. From a well conducted 30-day study in rats administered a commercial preparation of pentabromodiphenyl ether, a NOAEL of 1 mg/kg/day was identified. As this NOAEL is derived for a commercial product (DE-71), which contains 50-62% penta- component, and given a maximum oral absorption of 90%, a NOAEL for the penta congener of 0.45 mg/kg bw/day is determined. The human health significance of these rodent liver effects is unclear. At this dose, detailed investigations revealed no effects on liver function or histopathological appearance, nor on thyroid status. Repeated dermal exposure of the substance to the rabbit ear induces a proliferative reaction, characterised by moderate epithelial hyperplasia, similar to a 'chloracne-like' response. A NOAEL for this response cannot be determined from the available data.

Evidence from several well conducted bacterial mutagenicity studies and mammalian *in vitro* cytogenetics assay indicate that the substance is not mutagenic. No studies have been carried out *in vivo*. However, given the negative results obtained *in vitro* and the apparent limited metabolism of pentabromodiphenyl ether, it would be expected that it would not be genotoxic *in vivo*.

No carcinogenicity data are available.

No fertility studies have been conducted in animals. However, no gross or histopathological evidence of damage to male or female gonads was seen in a 90-day study in rats with oral doses of a commercial preparation of the substance of up to 100 mg/kg/day.

In a developmental study in rats no indications of adverse effects on the foetus were observed at doses up to at least 200 mg/kg/day. Developmental effects at higher doses were accompanied by severe maternal toxicity. From the limited data available there is no evidence for developmental toxicity.

A study investigating possible neurobehavioural effects in neonatal mice following single exposure to the substance is available, the results of which suggest differences in behavioural patterns between treated and control animals. However, there remain uncertainties with respect to the significance of the differences observed and their relevance to human health.

Environment

The environmental database meets the requirements for the SIDS data package. No effects were seen in fish at concentrations up to the water solubility during short-term exposures. A 60-day NOEC of 8.9 µg/l was obtained in a fish early life stage toxicity study with rainbow trout (*Oncorhynchus mykiss*). The substance is toxic to aquatic invertebrates (*Daphnia*) over both short- (48-h EC_{50} = 14 µg/l) and longer-term (21-day NOEC = 5.3 µg/l) exposure. In a 96-hour test with algae (*Selenastrum capricornutum*), slight inhibition of growth was seen over the first 24 hours exposure at concentrations around 3.3-6.5 µg/l, but this effect had disappeared by 48 hours. Although no significant effects on algal growth were seen over the whole 96 hour period, the available data do not rule out the possibility that the substance may have the potential to cause effects on algal growth at concentrations above around 3.3-6.5 µg/l if these concentrations are maintained. Prolonged (28-day) toxicity tests have been performed for three sediment-dwelling organisms (the midge *Chironomus riparius*, the oligochaete *Lumbriculus variegatus* and the amphipod *Hyalella azteca*), the lowest NOEC being 3.1 mg/kg dry weight for *Lumbriculus*. The PNEC is estimated to be 0.53 µg/l for water (using an assessment factor of 10 on the *Daphnia* NOEC), and 0.31 mg/kg dry weight for sediment (using an assessment factor of 10 on the *Lumbriculus* NOEC).

Three toxicity studies have been performed on soil-dwelling organisms. The 28-day NOEC from a soil microorganism nitrogen transformation test was >1 mg/kg dry weight. The lowest NOEC for six plant

species studied in a 21-day emergence and growth test was 16 mg/kg dry weight (calculated as an EC_5) for corn (*Zea mays*). A 14-day NOEC of >500 mg/kg dry weight was determined for survival and growth for earthworms (*Eisenia fetida*). Using an assessment factor of 50 on the plant NOEC, the PNEC for soil can be estimated as 0.32 mg/kg dry weight.

Exposure

Global production was around 4,000 tonnes/year in 1994. There is no current production in Europe, and imports have been declining in recent years (the current import tonnage is ~150 tonnes/year (1999), although it is uncertain how much is imported in articles). In Europe it is used as an additive flame retardant mainly for flexible polyurethane foam in furniture and upholstery. Unconfirmed uses include in textiles and electronics. The commercially supplied substance is a complex mixture, typically consisting of 50-62% pentabromodiphenyl ether, 24-38% tetrabromodiphenyl ether, 4-12% hexabromodiphenyl ether, with traces of tri- and heptabromodiphenyl ether. It is a viscous liquid or semi-solid of low volatility (4.69×10^{-5} Pa at 21^{o}C) and low water solubility (2.4 µg/l for the penta- component, 13.3 µg/l for the commercial mixture), with a log octanol-water partition coefficient (log K_{ow}) of 6.57.

In Europe, environmental exposure is likely to occur during production and processing of polyurethane foam, and from diffuse losses from treated articles. The substance is thought to be hydrolytically stable but may photodegrade in water (the likely extent and rate of this reaction are unknown). It is not readily biodegradable. The high log K_{ow} value implies a high potential for bioaccumulation and strong sorption to sewage sludge, soils and sediments. It appears to be slightly mobile in the environment on the basis of widespread monitored levels. A number of laboratory studies indicate that the components of the commercial substance are bioaccumulative, the highest BCF for fish being ~27,400 l/kg for the commercial product. These properties are such that accumulation in food chains is of concern and consideration of the substance, as a candidate persistent organic pollutant may be needed.

The potential for inhalation exposure to the substance in the occupational setting is considered to be very low, particularly in view of its very low saturated vapour pressure. There are no measured data on dermal exposure, but modelled data suggest that this may be the most significant route of exposure in workers. Consumer exposure to the substance present in polyurethane foams used in enclosed products is likely to be negligible. There is only very limited information available on exposure to humans via the environment. There is evidence that the substance is highly persistent and bioaccumulative. Of particular note, it has been detected - albeit at relatively low levels - in human breast milk, the levels increasing with time. It is unclear whether or not this trend will continue in to the future.

NATURE OF FURTHER WORK RECOMMENDED

The SIDS requirements are met. This substance has been discussed in the European Union Risk Assessment programme under Regulation EEC/793/93, and the conclusion is that there is a need to limit risks arising from the production, processing and use of polyurethane foam, on the basis of risks identified for the environment and uncertainties about risks to human health (especially infants exposed via breast milk). Other member states are therefore recommended, as a post-SIDS activity, to review the exposure situation in their countries, and in particular from treated articles and waste disposal to determine the need for similar measures. Some additional studies could also be performed, as follows:

- Information on the extent of dermal exposure in workers using an appropriate dermal absorption study (e.g. an *in vitro* study using human or pig skin); depending upon the outcome of this study (i.e. an indication of significant skin absorption) then it may be necessary to undertake an oral toxicokinetic study in order to provide adequate comparative information for interpretation of the oral dosing toxicity studies available.

- Health surveillance data to investigate signs of chloracne in workers.

- Further information on the effects of prolonged (e.g. lifetime) exposure for a substance that has the potential to accumulate within the body. A methodology should be developed to address this situation. This may involve the conduct of a lifetime study in rodents.

- Information on the toxicokinetics with respect to breast milk including uptake from breast milk into the infant, the time course of the excretion via breast milk during lactation in humans and the future trends in levels in human breast milk.

- Information on the relative toxicity to the liver in young (neonatal) and adult animals.

- Further studies on potential effects on behaviour following neonatal dosing in order to determine the reproducibility of effects, the effects of repeated dosing and the significance of the effects to human development.

- A multi-generation reproduction study in order to investigate whether or not other effects might be observed through exposure to breast milk. Designed correctly, such a study could address the issue of whether or not the young animal is more sensitive to liver effects and whether or not differences in behaviour are produced.

In view of the time that would be required to conduct these studies, the sponsor country is unlikely to pursue these data gaps in view of the risk reduction strategy in Europe.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	4457-71-0
Chemical Name	3-Methyl-1,5-pentanediol
Structural Formula	$HOCH_2CH_2CH(CH_3)CH_2CH_2OH$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

A single oral administration of 3-methyl-1,5-pentanediol to rat induced ataxic gait and decreased locomotor activity only at 2,000 mg/kg [OECD TG 401]. Oral LD50 was greater than 2,000 mg/kg. There is no information available on skin irritation, eye irritation and skin sensitisation. In an OECD combined repeat dose and reproductive/developmental toxicity screening test [TG 422], male and female rats were received by gavage at doses of 0, 100, 300 and 1,000 mg/kg/day for at least 42 days. Salivation was observed in both sexes of 1,000 mg/kg. A lack of fat deposits and an increase of glycogen accumulation in the liver accompanied by increased liver weight were observed in the females of the 1,000 mg/kg dose group only. Based on these slight changes, NOAEL is considered to be 300 mg/kg/day. In the above study [OECD TG 422] this chemical showed no reproductive/developmental toxicity and the NOAEL is considered to be 1,000 mg/kg/day. Two kinds of *in vitro* genotoxicity studies, bacterial test [OECD TG 471] and mammalian test [OECD TG 473], show negative results with and without metabolic activation.

Environment

This chemical is readily biodegradable (67-95 % after 28 d), and bioaccumulation potential seems to be low based on Log Pow (-0.03). It is is hydrolytically stable between pH 4 to 9, but it is classified as "readily biodegradable". In the atmosphere, indirect photodegradation by the reaction with OH radical is expected with gaseous 3-methyl-1,5-pentanediol. The half-life is estimated to be 27 hours. A generic fugacity model (Mackey level III) shows this chemical would be distributed mainly to water.

According to a Japanese manufacturer, 0.1 kg/year of 3-methyl-1,5-pentanediol is released with 5.8×10^6 tonnes/year of effluent into inland sea. Local predicted environmental concentration (PEC_{local}) is 1.7×10^{-8} mg/l, employing the calculation model. The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. The concentration in drinking water is assumed to be less than 1.7×10^{-8} mg/l.

3-Methyl-1,5-pentanediol has been tested in fish (*Oryzias latipes*), *Daphnia* and Algae (*Selenastrum capricornutum*). All acute and chronic values compiled in this report were ≥ 100 mg/L. Thus, this

chemical does not seem to be hazardous to aquatic organisms.

A PNEC of 1 mg/L for the aquatic organisms was calculated from NOEC for alga (100 mg/L) using an assessment factor of 100.

Exposure

The production volume of 3-methyl-1,5-pentanediol in Japan was 2,000 tonnes in 1994, of which 1,800 tonnes was exported. This chemical is used as an intermediate in synthesis in the chemical industry.

Consumer Exposure is negligible, because 3-methyl-1,5-pentanediol is not contained in consumer products.

NATURE OF FURTHER WORK RECOMMENDED

No further work recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	57-55-6
Chemical Name	Propylene glycol (1,2-dihydroxypropane)
Structural Formula	CH_3-CHOH-CH_2OH

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Propylene glycol (PG) is not acutely toxic. The lowest oral LD50 values range between 18 and 23.9 grams (5 different species) and the reported dermal LD50 is 20.8 grams. PG is essentially non-irritating to the skin and mildly irritating to the eyes. Numerous studies support that PG is not a skin sensitizer. Repeated exposures of rats to propylene glycol in drinking water or feed did not result in adverse effects at levels up to 10% in water (estimated at about 10 g/kg bw/day) or 5% in feed (dosage reported as 2.5 g/kg bw/day) for periods up to 2 years. In cats, two studies of at least 90 days duration show that a species-specific effect of increased Heinz bodies was observed (NOAEL = 80 mg/kg bw/day; LOAEL = 443 mg/kg bw/day), with other haematological effects (decrease in number of erythrocytes and erythrocyte survival) reported at higher doses (6-12% in diet, or3.7-10.1 g/cat/day). Propylene glycol did not cause fetal or developmental toxicity in rats, mice, rabbits, or hamsters (NOAELs range from 1.2 to 1.6 g/kg bw/day in four species). No reproductive effects were found when propylene glycol was administered at up to 5% in the drinking water (reported as 10.1 g/kg bw/day) of mice. Propylene glycol was not a genetic toxicant as demonstrated by a battery of *in vivo* (micronucleus, dominant lethal, chromosome aberration) and *in vitro* (bacterial and mammalian cells and cultures) studies. No increase in tumors was found in all tissues examined when propylene glycol was administered in the diet of rats (2.5 g/kg bw/day for 2 years), or applied to the skin of female rats (100% PG; total dose not reported; 14 months) or mice (mouse dose estimated at about 2 g/kg bw/week; lifetime). These data support a lack of carcinogenicity for PG.

Environment

Propylene glycol is not volatile, but is miscible with water. Air monitoring data are not available, but concentrations of propylene glycol in the atmosphere are expected to be extremely low because of its low vapor pressure and high water solubility. It is readily biodegraded in water or soil. Four studies reported >60% biodegradation in water in 10 days. PG is not expected to bioaccumulate, with a calculated BCF <1. Measured freshwater aquatic toxicity data for fish, daphnia and algae report LC/EC_{50} values of >18,000 mg/l. Therefore, PG is not acutely toxic to aquatic organisms except at very high concentrations. Using an assessment factor of 100 and the *Ceriodaphnia* data (48-hour EC_{50} = 18,340 mg/l), the PNEC is 183 mg/l.

Exposure

PG production capacity in the US was 1312 million pounds (596 kilotonnes) in 1998. Domestic demand was 1050 million pounds (477 kilotonnes). PG is used as an ingredient in cosmetics at concentrations of <0.1% to >50%. Approximately 4000 cosmetic products contained PG in 1994. Uses of PG, with percent of demand, are: unsaturated polyester resins, 26 percent; antifreeze and de-icing fluids, 22 percent; food, drug and cosmetics uses, 18 percent; liquid detergents, 11 percent; functional fluids (inks, specialty anti-freeze, de-icing lubricants), 4 percent; pet foods, 3 percent; paints and coatings, 5 percent; tobacco, 3 percent; miscellaneous, including plasticizer use, 8 percent.

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	760-23-6
Chemical Name	3,4-Dichlorobut-1-ene
Structural Formula	CH_2=CH-CHCl-CH_2Cl

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Oral LD_{50} and inhalation LC_{50} of 3,4-dichlorobut-1-ene (3,4-DCB) are about 940 mg/kg and 2100 ppm, respectively. Inhalation repeated dose study in rats conducted for 14 days, 6 hours/day, 5 days/week at doses of 104 mg/m^3 (20 ppm) and 1037 mg/m^3 (200 ppm) of 3,4-DCB. Relative liver weight increased and change in liver cell morphology was observed at 1037 mg/m^3 dose. This chemical is slightly irritating to skin and eyes. Acute skin irritation in rabbits according to OECD TG 404 causes erythema but does not cause systemic intolerance reaction. Acute eye irritation study by instillation into the conjunctival sac of rabbits according to OECD TG 405 causes corneal opacity and conjunctival redness but does not cause systemic intolerance reaction.

In an oral study in rats by OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422] at doses of 0, 0.4, 2, 10 and 50 mg/kg/day for at least 44 days, organ weight and histopathological changes were induced. In males, absolute kidney weights were slightly increased with 10 mg/kg and absolute and relative weights of the liver and kidneys were increased with 50 mg/kg. Blood chemical examination revealed an increase in total protein. The histopathological examination revealed increased hyaline droplets in the renal tubular epithelium with doses of 10 and 50 mg/kg and hepatocellular hypertrophy with dose of 50 mg/kg. In females, an increase in relative kidney weights was observed at the dose of 50 mg/kg. However, no histopathological changes related to the change of the kidney weight were detected. Hepatocellular hypertrophy was observed at the dose of 50 mg/kg. The NOAELs in this repeat dose study are 2 mg/kg/day for males and 10 mg/kg/day for females, but the renal toxicity in males is considered to be male rat specific, probably due to $alpha_{2U}$-globulin involvement. Therefore, the NOAEL for repeated dose toxicity is considered to be 10 mg/kg/day.

In a reproductive/developmental toxicity, there were no statistically significant adverse effects noted at any doses. Therefore a NOAEL for reproductive/developmental toxicity was considered to be 50 mg/kg/day. Evidence of malformations was not observed at any dose.

Three *in vitro* genotoxicity tests, bacterial reverse mutation, HPRT assay in CHO cells and chromosomal aberration in CHL/IU, indicate positive results. It also induced chromosomal aberration in rat bone marrow *in vivo* by inhalation. The carcinogenicity study of 3,4-DCB has not been reported, but 1,4-dichlorobut-2-ene, an isomer of 3,4-DCB, was reported to induce nasal tumors in rats following long term inhalation exposure. Based on weight of evidence, this chemical could be considered as a potential carcinogen.

Environment

3,4-DCB is classified as not readily biodegradable [OECD TG 301C: 1-28% (av. 11%, based on BOD), 44-45% (av. 45 %, based on GC) after 28-days, OECD TG 301D: 0 % (based on BOD) after 28-days], but bioaccumulation potential is low (OECD TG 305C: <0.28 to 13.34). According to the fugacity calculation, this chemical mainly exists in the compartment where it is released. Considering the actual production and use, the chemical is released mainly in water. This chemical has been tested in a certain number of aquatic species. For the alga *Selenastrum*, 72 h EbC50 was 49 mg/L, and 72 h NOEC (biomass) was 14 mg/L. For *Daphnia*, the acute toxicity value of 10 mg/L (48 h EC50 for immobilization) and the chronic value of 0.83 mg/L (21 d NOEC for reproduction) were obtained. For fish acute toxicities, values of 27 mg/L (96 h LC50 for *Oryzias latipes*) and 7.17 mg/L (96 h LC50 for *Pimephales promelas*) were considered to be reliable. Assessment factor of 100 was chosen and applied to the lowest chronic value (NOEC for *Daphnia*; 0.83 mg/L) to determine PNEC, which is 8.3 micro-g/L.

Exposure

3,4-DCB is manufactured in closed system as the intermediate of chloroprene in Europe, US, and Japan. The production volume in Japan and Germany was approximately 50,000 and 50,000 - 100,000 tonnes/year in 1998, respectively. The worldwide production volume of this compound amounts to 300,000 - 400,000 tonnes/year by estimation.

All of the 3,4-DCB produced is also used in a closed system as an intermediate for the production of chloroprene. The use is limited to chloroprene manufacturing at the same facilities. Therefore, it does not have widespread use. Possible occupational exposure occurs through dermal contact and inhalation of vapour. The process is constructed by closed system and workers wear protective mask, gloves and goggles during the operation, so significant exposure is not expected. Marketed product, polychloroprene, does not contain 3,4-DCB as impurity. Therefore, there is no possibility of release of this compound to the environment from the consumer use.

NATURE OF FURTHER WORK RECOMMENDED

An exposure assessment is recommended in situations where there is the potential for exposure during the manufacture and/or use of the chemical (because of genotoxicity concerns).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7664-93-9
Chemical Name	Sulfuric acid
Structural Formula	H_2SO_4

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The LC50 values for sulfuric acid aerosol observed in acute inhalation studies conducted in different species are low and are most likely due to the corrosive/irritant effect of this chemical. . For guinea pigs, the LC50 (8 hours; particle size approximately 1µm) ranges from 0.018 to 0.050 mg/l, depending on the age of the animals. Depending on the duration of exposure, the LC50 ranges from 0.37 to 0.42 mg/l in rats, 0.6 to 0.85 mg/l in mice and 1.47 to 1.61 mg/l in rabbits. Only one acute oral toxicity study was available. This study indicated an LD50 of 2140 mg/kg in the rat.

Sulfuric acid is corrosive to the skin, eyes and mucous membranes. 10% solutions of sulfuric acid appear not to be irritating to the skin in difference species. Conflicting results (not irritating or severely irritating) are observed in eye irritation studies using 10% sulfuric acid, depending on the protocol used (OECD/EU or US). Sulfuric acid is not considered as an allergen by skin contact in humans.

In numerous repeated inhalation studies with sulfuric acid aerosol, toxicity was confined to changes in the structure and function of the respiratory tract, suggesting that it has a local effect and no systemic effects. The observed changes are related to the irritant properties of sulfuric acid and are most likely due to the H+ ion. In a 28-day inhalation study in the rat exposed to sulfuric acid aerosol, minimal squamous metaplasia was observed in the laryngeal epithelium following exposure to the lowest concentration used (0.3 mg/m3). This effect was fully reversible. Exposure to 1.38 mg/m3 caused more severe metaplasia accompanied by cell proliferation.

Sulfuric acid has been shown to be without effect in genetic toxicity studies *in vitro* (bacterial test). It has been shown to cause chromosomal aberrations in a non-bacterial test *in vitro*. The chromosomal effects are well known to be a consequence of reduced pH, being seen using any strong acid. There are no *in-vivo* mutagenicity studies available.

No carcinogenic effect was observed in carcinogenicity studies conducted by inhalation with sulfuric acid aerosol using 3 different animal species. Small increases in tumor incidence were reported in rats and mice after chronic gastric intubation or intratracheal instillation of sulfuric acid solution, but no clear conclusion can be drawn from these studies.

Several epidemiological studies have suggested a relationship between exposure to inorganic acid mists containing sulfuric acid and an increased incidence of laryngeal cancer. IARC has concluded that

"occupational exposure to strong inorganic mists containing sulfuric acid is carcinogenic for humans (Group 1)." Concerns have been raised that confounding factors could not be fully excluded.

Because sulfuric acid is a direct-acting toxicant, and because it is unlikely to reach the reproductive organs, reproductive effects in mammals are not likely to occur following exposure to sulfuric acid by any route. In a developmental toxicity/teratogenicity study conducted by inhalation with sulfuric acid aerosol, the NOAEL for maternal toxicity appears to be 20 mg/m3 in mice and rabbits. No evidence of foetotoxicity or teratogenicity was seen in either species.

Environment

Sulfuric acid is a strong mineral acid that dissociates readily in water to sulfate ions and hydrated protons, and is totally miscible with water. Its pKa is 1.92 at 25 °C. At pH 3.92, for example, the dissociation is 99 %, and sulfate ion concentration is 1.2 x 10^{-4} moles = 11.5 mg/l. So at environmentally relevant concentrations, sulfuric acid is practically totally dissociated, sulfate is at natural concentrations and any possible effects are due to acidification. This total ionisation will imply also that sulfuric acid, itself, will not adsorb on particulate matters or surfaces and will not accumulate in living tissues.

The NOECs selected were obtained on a natural (cold water) lake artificially contaminated by the controlled addition of sulfuric acid:

- NOEC in phytoplankton community structure = pH 5.6 = 0.13 mg/l sulfuric acid
- NOEC in zooplankton population repartition = pH 5.6 = 0.13 mg/l sulfuric acid.
- NOEC in fish population recruitment = pH 5.93 = 0.058 mg/l sulfuric acid

There is only one validated NOEC available for warm water fish (*Jordanella floridae*), 0.025 mg/l, which is derived from the LOEC/2.

Exposure

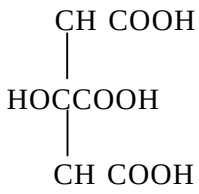
Estimated worldwide production of sulfuric acid is 160 million ton/year. The main uses are non dispersive (industrial uses). In some countries, sulfuric acid is approved for agricultural use. The occurrence of sulfuric acid in the environment comes mainly from the hydrolysis of sulfur oxides produced by combustion processes (natural and anthropogenic), wet deposition, generally as a mixture with nitrogen oxides and nitric acid and not from the manufacturing and use of the acid. The emissions to the aquatic environment generally occur from manufacturing industrial locations after neutralisation and are mainly in the form of sulfate ions. Alternatively, following manufacturing and use, it can enter the terrestrial environment as stable gypsum (calcium sulfate).

NATURE OF FURTHER WORK RECOMMENDED

Environment: the collection of information about exposure during agricultural use should be considered.

Health: the collection of information about occupational exposure to sulfuric acid mist should be considered due to the carcinogenic potential.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	77-92-9
Chemical Name	Citric acid
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Based on many experimental data in animals and on human experience, citric acid is of low acute toxicity. The NOAEL for repeated dose toxicity for rats is 1200 mg/kg/d. The major, reversible (sub)chronic toxic effects seem to be limited to changes in blood chemistry and metal absorption/excretion kinetics. Citric acid is not suspected of being a carcinogen nor a reprotoxic or teratogenic agent. The NOAEL for reproductive toxicity for rats is 2500 mg/kg/d. Further, it is not mutagenic *in vitro* and *in vivo*. Also, the sensitising potential is seen as low. In contrast, irritation, in particular of the eyes but also of the respiratory pathways and the skin, is the major toxicological hazard presented by citric acid; this conclusion is confirmed by a series of reports relating to eye and skin irritation.

Environment

Due to its physico-chemical characteristics citric acid is highly mobile in the environment and will partition to the aquatic compartment. Citric acid is rapidly degraded in both sewage works and surface waters and in soil. Citric acid is of low acute toxicity to freshwater fish, daphnia and algae and also to the few marine species tested; longer-term tests show comparable effect values. Similarly, citric acid has no obvious toxic potential against protozoans and many species or strains of bacteria including activated sludge micro-organisms. Based on the available data, citric acid is not judged to be a substance that presents a hazard to the environment.

Exposure

Citric acid is a water soluble organic solid. It is a natural substance that appears as an intermediate in the basic physiological citric acid or Krebs cycle in every eukaryote cell. Citric acid has been produced for many years in high volumes, current global production is estimated to approach 1,000,000 t/a. It has wide dispersive use, being added to processed food and beverages, used in pharmaceutical preparations

and in household cleaners as well as in special technical applications.

A large body of physico-chemical, toxicological and environmentally relevant data exists for citric acid, many of which are relatively old and some located only in standard reference works and reviews. While the quality of a single result often may be hard or even impossible to assess, the sheer volume and high congruence of the data result in a uniform picture all the same.

NATURE OF FURTHER WORK RECOMMENDED

No further work recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-41-4
Chemical Name	Methacrylic acid
Structural Formula	CH_2=CH(CH_3)-COOH

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No relevant data are available concerning possible effects of methacrylic acid (MAA) in humans.

MAA is rapidly absorbed in rats after oral and inhalation administration.

The main clinical sign in animal tests on acute toxicity of MAA is severe irritancy at the site of contact. Oral LD 50 values of 1320-2260 mg/kg for rats, a dermal LD 50 value between 500 and 1000 mg/kg for rabbits and a LC 50 (rat) of 7.1 mg/l/4h were determined. MAA causes adverse effects at the site of application, depending on the concentration and frequency or time of exposure. The undiluted acid causes skin and eye corrosion and respiratory tract lesions. MAA is not sensitizing as demonstrated by human experience and by animal tests.

The main effect of MAA in acute and subchronic animal studies is irritation/corrosivity at the site of contact. In repeated dose inhalation studies the relevant toxic effect was irritation of the nasal mucosa. Rhinitis was observed in rats $\geq$20 ppm (71.4 mg/m³) and mice at 300 ppm (1071 mg/m³) when animals were exposed on 90 days. Additionally, in mice degenerative lesions of the olfactory epithelium occurred at doses from 100 ppm (357 mg/m³). A NOAEL for the local effects of 20 ppm (71.4 mg/m³) was derived from a study on mice. The NOAEC for systemic toxic effects was identified to be 100 ppm in mice and 300 ppm in rats. Toxic effects after dermal or oral application routes are unknown.

MAA is negative in a bacterial gene mutation test. Taking into consideration the data on the methyl ester of MAA (methyl methacrylate, MMA) - which indicate that MMA does not express a genotoxic potential *in vivo* - there is no need for further testing of MAA. No cancer studies on MAA are available. Focal hyperplasia of the respiratory epithelium or lymphatic hyperplasia of mandibular lymph nodes in a 90-day inhalation study were not interpreted as a preneoplastic lesion but considered to represent reactive or inflammatory processes due to the irritant effect of MAA. With respect to MMA data, there is no concern on carcinogenic properties of MAA.

Data on reproductive toxicity of MAA in animals or humans does not exist. From studies with MMA no concern in relation to reproductive toxicity of MAA has to be assumed.

No specific human population at risk could be identified within the general population.

Environment

Approximately 45 000 t/a of methacrylic acid (MAA) are assumed to be available on the European market. MAA is used as an internal and external intermediate in the chemical industry for the production of methacrylic acid esters and as a co-monomer in different kinds of polymers.

MAA has a water solubility of 89 g/l, a vapour pressure of 0.9 hPa and a log Kow of 0.93. According to the physico-chemical properties the target compartment for this substance is the hydrosphere.

MAA is stable in neutral solution and is classified as "readily biodegradable". There is no considerable potential for bio- or geoaccumulation. An atmospheric half-life of 11 h was calculated for this substance.

The following results from ecotoxicity tests with aquatic species are available:

In a short-term test with fish a 96h LC50 of 85 mg/l was found for *Oncorhynchus mykiss*: For invertebrates acute and long-term studies on *Daphnia magna* had been conducted. A 48h EC_{50} between 100 and 180 mg/l and a 21d NOEC of 53 mg/l were found in these tests. The most sensitive environmental species to MAA is the alga *Selenastrum capricornutum* with a 72h EC50 of 45 mg/l and a 72h-EC10 of 8.2 mg/l. Based on these data there is a moderate hazard concern to aquatic organisms. With an assessment factor of 50 a PNEC of 164 µg/l is determined.

For the production and processing of MAA and for the use of polymeric products made from MAA most of the estimated PECs are well below the PNEC and no further work is recommended. However, from the use of a grouting agent containing hydroxyethyl-methacrylate high releases of MAA to the hydrosphere via drainage water were identified. Measured effluent concentrations up to 4 mg/l are reported for a specific tunnel construction site leading to local water concentrations up to 200 µg/l.

Exposure

No information.

NATURE OF FURTHER WORK RECOMMENDED

Environment

This substance has been agreed in the European Risk Assessment Program under Regulation EEC/793/93 with the following conclusion:

A risk to the aquatic environment in the vicinity of a tunnel construction site was identified. A quantitative extrapolation to other construction sites seems not possible but similar conditions can be anticipated. It is recommended to develop a risk reduction strategy to achieve an environmentally safe handling of the grouting agent.

Human Health

MAA is a respiratory tract irritant. There is a need for limiting the risks of respiratory tract irritation in several working areas (particularly in the industrial area without use of LEV). Risk Reduction Measures at the community level are recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	80-62-6
Chemical Name	Methyl methacrylate
Structural Formula	$CH_2=CH(CH_3)-COOCH_3$

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

MMA is rapidly absorbed after oral or inhalatory administration. *In vitro* skin absorption studies in human skin indicate that MMA can be absorbed through human skin. After inhalation to rats 10 to 20% of the substance is deposited in the upper respiratory tract where it is metabolised by local tissue esterases.

Acute toxicity of MMA by the oral, dermal, and inhalative routes is low as judged by tests with different species: The oral LD50 for rats, mice, and rabbits is found to exceed 5000 mg/kg bw. Acute inhalation toxicity for rats and mice is described by LC50 values of > 25 mg/l/4 hours. Acute dermal toxicity is reported for rabbits to exceed 5000 mg/kg bw. Skin and respiratory irritation are reported for subjects exposed to monomeric MMA. The substance has been shown to produce severe skin irritation when tested undiluted on rabbit skin. There are indications from studies in animals that MMA can be irritating to the respiratory system. In contact with eyes MMA has shown only weak irritation of the conjunctivae. MMA has a moderate to strong sensitising potential in experimental animals**.** Cases of contact dermatitis have been reported for workers exposed to the monomeric chemical. There is no convincing evidence that MMA is a respiratory sensitizer in humans.

The lead effect caused by MMA is a degeneration of the olfactory region of the nose being the most sensitive target tissue. 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. Concerning systemic effects, two different valid studies have been considered for identifying a N(L)OAEL. Due to different dose selections, different values for N(L)OEALs are available. The LOEALs and the NOEALs for female rats ranges between 400 and 500 ppm and from 100 to 250 ppm respectively. In subchronic inhalation studies systemic toxic effects were seen in rats >1000 ppm, respectively in mice >500 ppm, including degenerative and necrotic lesions in liver, kidney, brain, and atrophic changes in spleen and bone marrow. These effects were not seen in chronic studies up to 1000 ppm. Oral administration to rats resulted in a NOAEL of 200 mg/kg bw/d.

MMA has *in vitro* the potential for induction of mutagenic effects, especially clastogenicity. However, this potential is limited to high doses with strong toxic effects. Furthermore, the negative *in vivo* micronucleus test and the negative dominant lethal assay indicate that this potential is not expressed *in vivo*. There is no relevant concern on carcinogenicity of MMA in humans and animals. Epidemiology data on increased tumour rates in exposed cohorts are of limited reliability and cannot be related to

MMA as the solely causal agent.

MMA did not reveal an effect on male fertility when animals had been exposed to up to 9000 ppm. From the available developmental toxicity investigations, including an inhalation study according to OECD Guideline 414, no teratogenicity, embryotoxicity or fetotoxicity has been observed at exposure levels up to and including 2028 ppm (8425 mg/m^3). The available human data on sexual disorders in male and female workers cannot be considered to conclude on reproductive toxicity effects of MMA due to the uncertain validity of the studies.

Environment

In the European Union methyl methacrylate (hereafter referred to as MMA) is produced and isolated as chemical intermediate. According to industry statements for 1996, the total EU production capacity amounts to 610,000 t/a and the actual production volume to 470,000 t/a. Significant dynamics of the methacrylate-chemistry market are reported.

MMA is mainly used as an intermediate for the production of polymers. The most important polymer types are cast acrylic sheets and molding / extrusion compounds, besides emulsions, dispersions and solvent based polymers. Another significant use is the production of various methacrylate esters, which are subsequently used for polymer production. Minor amounts are distributed and used as monomer, e.g. in reactive resins, but even in these applications the MMA monomers eventually will be polymerized; the final polymerization step takes place at the site of use.

About 2/3 of the total production quantity are sold to customers and not processed at the production sites.

Releases of MMA to the environment are to be expected mainly during production and processing with waste water and exhaust gas as well as during the use of water based emulsion polymers, e.g. paints and varnishes.

Residual monomeric MMA-contents, which are the basis for release estimations from different polymeric products, are reported to range between 0.005 and 1.1 %.

Direct releases to agricultural or natural soil are not expected to a relevant extent.

MMA has a water solubility of 16 g/l, a vapour pressure of 42 hPa , and a log Pow of 1.83. The environmental behavior of MMA is determined by its range of 1.1 - 9.7 hours atmospheric half life and moderate volatility. MMA is readily biodegradable. Hydrolysis is not significant at neutral and acidic pH, but increases in the upper pH range. The average K_p value of 1.0 l/kg indicates no relevant adsorption onto sediment or soil. Based on the physico-chemical properties of MMA, the air and to a much lower extent the hydrosphere are the preferred target compartments for distribution and neither relevant bioaccumulation nor geoaccumulation are expected. In waste water treatment plants 89.2 % of the substance are estimated to be removed predominately by biodegradation.

For fish, only two relevant results from acute tests are currently available. For *Lepomis macrochirus*, a 96h LC_{50} of 191 mg/l is reported, for the rainbow trout *Oncorhynchus mykiss* a LC_{50} of > 79 mg/l and a 96h NOEC of 40 mg/l.

For invertebrates acute and long-term studies on *Daphnia magna* had been conducted. The most relevant EC value is 21d NOEC = 37 mg/l; the acute study reports 48h EC_{50} = 69 mg/l.

The most relevant study on algae has examined *Selenastrum capricornutum* according to OECD-guideline 201. The highest test concentration of 110 mg/l caused growth inhibition below 50 %, the NOEC was 110 mg/l for growth rate and 49 mg/l for biomass as endpoints.

Based on these data there is a moderate hazard concern to aquatic organisms. For derivation of the **P**redicted **N**o **E**ffect **C**oncentration (PNEC) the lowest valid effect concentration, i.e. 37 mg/l from the long-term daphnid test, is divided by an assessment factor of 50 as proposed in the TGD for the present data basis: $PNEC_{aqua}$ = 740 µg/l.

It is not possible to derive a PNEC for the atmospheric compartment due to the lack of experimental data.

Data on effects to terrestrial organisms are not available. In an indicative risk assessment for the soil compartment, the aquatic PNEC of 740 µg/l can be used and compared to the concentration in soil pore water.

Exposure

No information.

NATURE OF FURTHER WORK RECOMMENDED

This substance has been agreed in the European Union Risk Assessment Program under Regulation EEC/793/93 with the following conclusion: There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account:

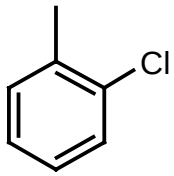
A potential risk to the local aquatic environment is identified from wet polymerization processes by downstream users of monomeric MMA (default calculations for generic site and four out of 29 known sites). Although an improvement of exposure data would be possible for the wet polymerization scenarios, e.g. by performing effluent measurements, it is concluded that a sufficient and appropriate data basis cannot be acquired within an acceptable time frame and with acceptable efforts. Additionally, due to the dynamic methacrylate market, significant year-to-year variations of MMA tonnages used at individual sites hamper reliable PEC estimations.

On the effects side of the risk assessment data improvement would be possible because an assessment factor of 50 is used for the PNEC derivation and it might be possible to lower the PNEC by further testing, i.e. the assessment factor can be lowered to 10 if a long-term fish test is performed. But regarding the locally limited risks that are identified due to the specific scenario this kind of data improvement is not proposed by the rapporteur.

It is concluded, that local risk reduction measures have to be considered, if the MMA processing capacity exceeds 5000 t/a at one single site. It should be noted, that waste water reutilization / recycling systems are applied by some known polymerization sites, avoiding any significant MMA emission to hydrosphere. Sites applying such advanced process engineering would not require further consideration of risk reduction measures.

There is a need to limit the risks of MMA concerning skin sensitization and respiratory tract irritation at several workplaces in the chemical industry, industrial area and skilled trade and during use of casting resins. For inhalation exposure scenarios, systemic toxicity gives additional rise to concern.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-49-8
Chemical Name	2-Chlorotoluene
Structural Formula	

RECOMMENDATIONS

Human Health: If substantial exposure cannot be ruled out, there is need for further work.

Environment: The substance is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute oral toxicity: LD_{50} (Rat, male): 3227 mg/kg bw; LD_{50} (Rat, female): 3860 mg/kg bw
The acute inhalation toxicity: LC_{50} (Rat): 37517 mg/m^3 (4 h)
The acute dermal toxicity: LD_{50} (Rat): > 1083 mg/kg bw; LD_{50} (Rabbit): > 2165 mg/kg bw
2-Chlorotoluene, tested according to OECD Guideline 404, is slightly irritating to the skin. However, when tested under occlusive conditions, the substance is corrosive.
2-Chlorotoluene, tested according to OECD Guideline 405, was irritating to the eye in 1 out of 3 animals.
2-Chlorotoluene, tested according to OECD Guideline 406, is not sensitizing to the skin of guinea pigs.

The NOEL for repeated dosing (3 months) by gavage in rats is 20 mg/kg bw. In higher dosage (80 or 320 mg/kg bw) unspecific signs of toxicity were observed, e.g. reduced body weight gain in male animals, elevated BUN, elevated WBC count, reduced prothrombin time.

The NOEL for repeated dosing via capsule (3 months) in dogs is 20 mg/kg bw. In higher dosage (80 mg/kg bw) one animal showed vomiting, and red blood was detected in faeces, which might be due to the slightly irritating property of 2-chlorotoluene.

In range finding study tests, the LOAELs after inhalation were 4 mg/l (approx. 4000 mg/m^3, 14 d) in rats and 8 mg/l (approx. 8000 mg/m^3, 23 d) in rabbits. There is no NOEL from these data.

2-Chlorotoluene showed no mutagenic activity in bacterial and in mammalian cell test systems *in vitro*.
2-Chlorotoluene showed no clastogenic activity *in vitro* and *in vivo*.

Regarding reproductive toxicity there are 3 months-studies on rats and dogs which evaluated also the reproductive organs.

In the rat study, males and females received 2-chlorotoluene 0, 20, 80, or 320 mg/kg bw solution by gavage for 103-104 days. Gross and histological evaluation revealed that the administration of 2-chlorotoluene to rats did not produce any treatment-related pathology in these organs. Histopathologic examination of the reproductive organs showed that in 1/20 male rats and in 3/20 female rats in the lowest dose group testicular atrophy or hydrometra occurred.

In the dog study, males and females received 0, 5, 20, or 80 mg/kgbw as via capsule for 95-96 days. Also in this study, there were no treatment related changes regarding gross examination of the organs, and the histological examination showed no pathological alteration.

However, there are data from structurally related compounds showing effects on fertility.

Developmental toxic effects in rats and rabbits occur in the presence of maternal toxicity and without a clear dose-response relationship, however as a specific malformation, brachydactyly.

Rats: NOAEL: 1.0 mg/l (maternal toxicity) and no NOAEL, LOAEL 1.1 mg/l (developmental toxicity)
Rabbit: NOAEL: 1.0 mg/l (maternal toxicity) and 4 mg/l (developmental toxicity)

Environment

2-Chlorotoluene is a colourless liquid, with a solubility in water of 47 mg/l and with a vapour pressure of 360 Pa at 20 °C. The log Kow was measured to 3.42.

The favourite target compartment for 2-chlorotoluene is air with 98.8 % according to Mackay I. In air 2-chlorotoluene is indirectly photodegradable with $t_{1/2}$ = 8.8 d. The substance is not readily biodegradable. Nevertheless under the conditions of sewage treatment plants the substance will be eliminated by stripping and adsorption. Hydrolysis is not expected to occur under environmental conditions. The bioconcentration factor in fish was measured to 20-112.

2-Chlorotoluene has to be classified as toxic to aquatic organisms. In short-term tests the most sensitive organism was Oncorhynchus mykiss with a 96 h-LC_{50} of 2.3 mg/l. In long-term ecotoxicity tests with aquatic organisms the following effect values were found:

- *Pimephales promelas*: 30d-NOEC = 1.4 – 2.9 mg/l
- *Daphnia magna*: 21d-NOEC = 0.14 mg/l
- *Scenedesmus subspicatus*: 72h-EbC50 > 100 mg/l; 72h-EbC10 = 60 mg/l

The result from the long-term daphnia study is based on measured concentrations.

With an assessment factor of 10 a PNECaqua of 0.014 mg/l was derived.

From ecotoxicity tests with terrestrial plants a PNECsoil of 89 µg/kg can be derived.

Exposure

130,000 t/a chlorotoluenes are produced worldwide, about 60,000 to 70,000 t/a o-chlorotoluene.

In Germany, Bayer AG is the only producer of 2-chlorotoluene. 10,000 to 50,000 t/a chlorotoluene isomer mixture is produced at Bayer AG. More than 50 % of the produced isomer mixture is processed on-site to cresoles. About 5,000 t/a 2-chlorotoluene are separated from the isomer mixture for serving as basic chemical in the chemical industry for producing intermediates. 2-chlorotoluene is also directly used as a solvent for chemical processing as well as a solvent for the formulation of agricultural pesticides.

NATURE OF FURTHER WORK RECOMMENDED

Human Health: The route and level of possible exposure has to be clarified. Depending on the level of exposure further data on toxicity to reproduction are necessary.

Environment: The relevance of the releases to the terrestrial compartment due to the use as solvent in agricultural pesticides should be clarified.

SIDS INITIAL ASSESSMENT PROFILE

Alfa Olefin Category

CAS No.	592-41-6	111-66-0	872-05-9
Chemical Name	1-hexene	1-octene	1-decene
Structural Formula	CH_2=CH-$(CH_2)_3$-CH_3	CH_2=CH-$(CH_2)_5$-CH_3	CH_2=CH-$(CH_2)_7$-CH_3
CAS No.	112-41-4	1120-36-1	
Chemical Name	1-dodecene	1=tetradecene	
Structural Formula	CH_2=CH-$(CH_2)_9$-CH_3	CH_2=CH-$(CH_2)_{11}$-CH_3	

RECOMMENDATIONS

The chemicals are candidates for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Category Definition

This profile includes an evaluation of SIDS-level testing data, using a category approach, with five individual monoolefins (1-hexene, 1-octene, 1-decene, 1-dodecene, and 1-tetradecene). For the purposes of the OECD SIDS Programme, the category was defined as olefins bearing a single medium-length (C_6 – C_{14}), even-numbered, unbranched aliphatic chain with no other functional groups.

Human Health

Based on screening level tests, all five alpha olefins have been tested and indicate low toxicity concerns for acute oral, dermal and inhalation exposure. These materials are slightly irritating to the skin and eyes of rabbits. In repeated dose studies, 1-hexene, 1-octene and 1-tetradecene have shown comparable levels of low toxicity to female rats (alterations in body and organ weights and changes in certain hematological values) at the higher doses tested (NOAELs of $\geq$ 100 mg/kg oral or $\geq$ 1000 ppm inhalation) and male rat-specific kidney damage that is likely associated with the $alpha_{2u}$-globulin protein (LOAELs $\geq$ 100 mg/kg oral only). Based on screening level testing, they appear not to be neurotoxic (for 1-hexene and 1-tetradecene), produce no adverse effects on reproduction or fetal development (1-hexene and 1-tetradecene), and are not genotoxic (all five of the alpha olefins). As a result, all the above tested endpoints indicate a low hazard potential for human health.

Environment

The potential for exposure of aquatic organisms to C_6-C_{14} alpha olefins will be influenced by their physicochemical properties. The predicted or measured water solubilities of these alpha olefins range from 50 mg/L at 20^0C for 1-hexene to 0.0004 mg/L at 25^0C for 1-tetradecene, which suggests there is a

lower potential for exposure to the higher alpha olefins due to their low solubility. Their vapor pressures range from 140 mmHg at 20^0C for 1-hexene to 0.015 mmHg at 25^0C for 1-tetradecene, which suggests the lower alpha olefins will tend to partition to the air at a significant rate and not remain in the other environmental compartments for longer periods of time.

Several acute aquatic toxicity studies show that 1-hexene and 1-octene have LC/EC50 values below their respective water solubility values (1-hexene: 96 hour LC50 in rainbow trout of 5.6 mg/L and 1-octene: 24 hour EC50 in daphnids of 3.2-10 mg/L). The daphnid value is from an experiment using less than standard exposure conditions (24 hours versus 48 hours). Chronic aquatic toxicity may occur for all of the alpha olefins except 1-tetradecene (predicted 30 day fish toxicity values range from 0.5 to 0.004 mg/L for 1-hexene and 1-dodecene, respectively. Algal toxicity studies were done with all five category members, but the most valid data were with 1-hexene (96 hour EC50 of 22 mg/L). A better understanding of whether these materials are released to water and at what quantities will determine the need to perform chronic aquatic toxicity testing.
Biodegradation data confirm that the C_6-C_{14} alpha olefins degrades in soil and water. They are also expected to degrade in the atmosphere at a rapid rate based on their atmospheric oxidation potentials. Consideration of these degradation processes supports the assessment that these substances will degrade relatively rapidly in the environment and not persist.

Exposure

C_6 – C_{14} Alpha-olefins are major industrial products, which are primarily used as intermediates in the production of the other chemicals and polymers. Other emerging uses are as components of some drilling fluids, and as potential replacements for certain hydrocarbon solvents. Occupational exposures are most likely by the inhalation and dermal routes. Inhalation exposures from industrial manufacture and commercial use are generally considered to be minimal (less than 1 ppm) under normal working conditions. The lower alkenes are minor components of gasoline, or are produced incidentally in combustion of gasoline and polymers, so their presence has been detected in urban air. Such levels were reported to be in the ppb range with a maximum reported value of 0.1 ppm. These alkenes also occur in natural products, although no quantitative values have been reported.

Non-occupational human exposure to alpha olefins is not expected since the compounds are used as industrial intermediates. Atmospheric emissions of alpha olefins from manufacturing are expected to be small and to result primarily from fugitive emission sources originating from compromised hardware (i.e.. faulty seals prior to repair) used in production and storage. On-site waste treatment processes are expected to remove these compounds from aqueous waste streams to the extent that they will not be detectable in effluent discharge. Alpha Olefins will not persist in the environment because they can be rapidly degraded through biotic and abiotic processes. Therefore, environmental exposure to the environment is expected to be minimal.

Category Discussion/Conclusions

A category analysis was done for all the SIDS endpoints by examining available data to determine whether the proposed test plan – to treat the five chemicals as a category – was satisfactory. Results indicate that they were and so no further SIDS-level testing is necessary.

The data indicate an increasing or decreasing trend or pattern from the shortest category member (C_6) to the longest category member (C_{14}) for various physicochemical properties and ecotoxicity (using a mixture of experimental data and estimation techniques), whereas there appears to be no difference across category members for biodegradation and health endpoints.

Melting point, vapor pressure, and water solubility decrease with increasing chain length while boiling point and octano:water partition coefficients increase with increasing chain length. Measured and predicted acute aquatic toxicity data indicate that 1-hexene, 1-octene, and 1-decene exhibit acute effects to aquatic organisms at levels at or below their water solubility; whereas 1-dodecene and 1-tetradecene

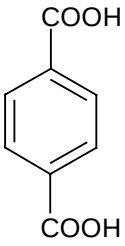
are not likely to be acutely toxic, probably because they cannot achieve a high enough water concentration to produce acute effects below their water solubility. Predictions of chronic aquatic toxicity suggest that 1-hexene may be less toxic than the rest of the category members and 1-octene, 1-decene, and 1-dodecene are expected to be similarly toxic (estimated values within approximately one order of magnitude among them). The model used (ECOSAR) could not predict the chronic aquatic toxicity of 1-tetradecene. There is no apparent difference regarding biodegradability; available data on four/five category members indicate there are no significant differences among the group. Data presented relative the health effect endpoints of the $C_6 - C_{14}$ alpha olefins indicate no differences among the five category members for acute toxicity, repeat dose toxicity, genotoxicity and reproductive/developmental toxicity.

Given the fact that not all category members were tested for each SIDS endpoint, this analysis shows that where test data exist for more than one category member, it is reasonable to interpolate (and sometimes extrapolate) for the same endpoint(s) to untested category members. Thus, it is not necessary to test each category member for all SIDS endpoints. It is concluded that using a category approach to evaluate the SIDS-level endpoints for the five alpha-olefins identified above was successful.

NATURE OF FURTHER WORK RECOMMENDED

Further work is recommended in the environmental area. There are no measured data available for chronic toxicity to aquatic organisms, however, computer modelling suggests that 1-octene,1-decene and 1-dodecene may be highly toxic (Chronic value<0.1 mg/L) under chronic exposure conditions. Therefore it is recommended that further data be collected from member countries regarding actual release data from manufacturing and processing facilities to the water compartment at local and national levels. In the event that releases to the water compartment are occurring at levels anticipated to pose a hazard to the aquatic environment, then consideration should be given to determining if chronic aquatic (including sediment-dwelling organisms) toxicity testing would be appropriate.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-21-0
Chemical Name	Terephthalic acid
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Results from repeated dose and acute toxicity studies via the oral, dermal and inhalation routes indicate that terephthalic acid is of low order of toxicity, and it is non-irritating to the skin and eyes. A 15 week oral repeat dose study in rats reported a LOAEL of 3837 mg/kg b.w./day for male rates and 4523 mg/kg/day for female rats. The NOAEL is 1220 mg/kg b.w./day for male rats and 1456 mg/kg b.w./day for female rats. Repeated exposure inhalation studies up to 10 mg/m^3 (6 hours/day, 5 days/week) using rats or guinea pigs showed no adverse effects, except for mild respiratory irritation in one study with rats.

The primary adverse effect of high doses of terephthalic acid to rats is almost completely restricted to the urinary tract. These effects include formation of bladder calculi, and inflammatory changes and hyperplasia of the bladder epithelium. These urinary changes did not occur when exposure was by inhalation. Rats fed terephthalic acid (greater than 2%) 1000 mg/kg b.w./day for two years developed bladder calculi, bladder hyperplasia, and bladder tumors.

It is believed that the calculi injure the bladder epithelium and induce cell proliferation, which is probably a critical factor in the induction of bladder tumors by terephthalic acid. Bladder calculi cannot occur unless the solubility of the stone components is exceeded (i.e., unless the product of the concentrations of Ca^{++} and terephthalate in urine exceeds the solubility product of the calcium-terephthalate complex). Based on urinary solubility of Ca-terephthalate, normal human urine would become saturated with Ca-terephthalate at a terephthalic acid concentration of approximately 8 to 16 mM. Assuming that the average volume of urine excreted by humans is 1.5 liters/day, the amount of terephthalic acid that would have to be absorbed to produce the minimum saturating concentration of terephthalic acid is 2400 mg/day. It is unlikely that humans would ingest enough TPA to induce bladder calculi, and this therefore is of little concern to human health.

Terephthalic acid is not a reproductive toxicant; however, in a one-generation reproduction feeding study, postnatal developmental effects were observed in rats (LOAEL and NOAEL approximately equivalent to 1120 mg/kg b.w./day and 280 mg/kg b.w./day respectively). The adverse effects observed in the offspring appear to be the result of

maternal toxicity and the formation of renal and bladder calculi in the weanling animals. No developmental effects were seen in rats when the exposure was by inhalation (NOAEC 10 mg/m^3, the highest dose tested). Terephthalic acid is not genotoxic. Terephthalic acid did not induce an increase in micronucleated polychromatic erythrocytes (micronuclei) in male or female mice *in vivo*.

Environment

Terephthalic acid (TPA) is non-toxic to aquatic organisms at concentrations lower than its water solubility (15 mg/l at 10^{o}C). Tests were performed with a more soluble sodium salt. The values for fish acute toxicity ranged from a 96-hour LC_0 of greater than 500 mg/l to a 96-hour LC_{50} ranging from 798 to 1640 mg/l. The EC_{50} for *Daphnia* was greater than 982 mg/l and the 96-hour NOEC for *Scenedesmus subspicicatus* was greater than 1000 mg/l. Using the lowest reported LC_{50} value of the three base set tests, a PNEC value of 8 mg/l is calculated. TPA is not expected to bioaccumulate. It is subject to hydroxy radical oxidation in the atmosphere, and biodegrades in soil and surface water under aerobic conditions. Detection of terephthalic acid in air and water samples has been in the low ppt range.

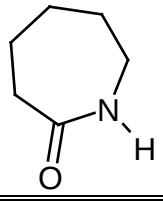
Exposure

Terephthalic acid is an industrial chemical intermediate, and occupational exposures are low. In 1993, the worldwide production was estimated to be 17 to 21 million tonnes. Manufacture of polyester fibers and films accounts for a majority of TPA use. End products of polyester fiber may include yarns for carpet, apparel, fill fibers for consumer products, and industrial filaments. PET containers, the next major use, are used for a wide variety of food and beverage packaging and in other food contact uses.

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	105-60-2
Chemical Name	ε-caprolactam
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The LD50 for the rat after oral application is 1475-1876 mg/kg bw. After inhalation of the substance as an aerosol by rats, the LC50 is 8.16 mg/l/4h. The LD50 for rats after dermal application is >2000 mg/kg bw. Main symptoms following exposure are clonic convulsions (oral), and irregular respiration (inhalation). Key effect following inhalation exposure to Caprolactam in humans and rats is irritation (skin, eyes, respiratory tract). Caprolactam was not sensitising in a guinea pig maximisation test and in a Buehler test with guinea pigs. The observed dermal effects in the study were regarded to be due to irritation. However, there are very few cases of sensitization in humans (see below).

Caprolactam given by feed (up to 1333 mg/kg bw) to rats in a 90-day study caused a species and sex-specific effect on the kidney of the male rat (hyaline-droplet-related nephropathy), which is supposed to be of no relevance for other species, including humans (NOEL 33 mg/kg bw). Furthermore there are no lesions in the kidney in two 2-year carcinogenicity bioassays.

A 13 week-inhalation study with caprolactam (aerosol, MMAD 3 um) resulted in local nasoturbinal and laryngeal tissue changes and transient clinical signs in all treated rats. There is no NOEC from this study. These effects have been interpreted as an adaptive response by the authors. However, recovery from these effects was not complete after 4 weeks. Keratinization of the metaplastic epithelium in the larynx (reversible within 4 week recovery) was observed in the highest dose group indicating a NOAEC for local effects in the upper respiratory tract, of 70 mg/m^3 (14 mg/kg bw./day;). Systemic toxic effects also with respect to ophthalmology and neurobehaviour were not observed, NOAEC 243 mg/m^3 (49 mg/kg bw./day). Caprolactam showed neither mutagenic nor clastogenic potential with respect to most of the different genetic endpoints tested. Positive results in *in vitro* cytogenetic tests are observed only with high concentrations tested (> 10 mM). However, several tests in vitro and in vivo show induction of mitotic recombination. The relevance of this effect remains unclear, especially taking into account the negative results in rats and mice carcinogenicity bioassays. Caprolactam was not carcinogenic in two 2 year oral studies in rats and mice when tested up to 7500 ppm and 15000 ppm by feed (750 and 2143 mg/kg bw/day.).

No adverse effect to reproductive organs was found in a three-generation feeding study with rats (feed: 1000-10 000 ppm=83-833 mg/kg bw; NOAEL parental: 417 mg/kg bw, NOAEL F1/F2/F3 generation: 83 mg/kg bw, NOAEL fertility: 833 mg/kg bw. Maternal as well as fetal effects are reduced body weight gain. Developmental studies

performed in rats and rabbits with doses of caprolactam that were non-detrimental to the parental animals showed no evidence of a fetotoxic effect. Observed effect again is reduced maternal and fetal body weight gain. Teratogenicity from the gavage application of caprolactam was not observed in rats and rabbits (rats: NOAEL maternal toxicity: not established; NOAEL teratogenicity: 1000 mg/kg bw; NOAEL fetotoxicity 500 mg/kg bw; rabbit: NOAEL maternal toxicity: 50 mg/kg bw; NOAEL teratogenicity: 250 mg/kg bw; NOAEL fetotoxicity 50 mg/kg bw). According to the data from rats and mice, Caprolactam appears to be absorbed rapidly. Excretion is also rapid and predominantly via the urine, mainly in metabolized form with only a small portion of unchanged substance.

In humans, irritation of the skin and the mucous membranes were reported. No signs of irritation was observed at 33 mg/m^3 for Caprolactam vapor. The irritation threshold was reported to be at 56 mg/m^3 and an irritation effect was noted at 61mg/m^3 for vapor. There is no information on severity of irritating effects by dust compared to vapors, however, effects seem to be more severe in dry air. Caprolactam fume at 68 mg/m^3 is irritating to the skin .In some rare cases allergic contact dermatitis, resp. Positive patch-test reactions were reported. Disturbance of the menstrual function and an increased number of toxicosis, premature delivery and post-natal hemorrhages were reported in female employees in the processing industry, where exposure to other compounds was also possible (no evaluation possible).

Environment

The distribution of the substance between the compartments air, biota, sediment, soil and water was calculated according to Mackay Level I. The main compartment is water 99,98%.

The low vapour pressure (0.13 Pa at 20 °C) and complete water solubility (4560 g/l at 20 °C) of caprolactam suggest that volatilization from water and soil surfaces would not be an important fate process. The substance has no considerable potential for bio- and geoaccumulation (log P_{OW} = 0.12, measured). It is readily biodegradable (OECD 301 C 82% after 14 days). The hydrolysis rate is extremely slow ($t_{1/2}$ > 1 year). The photodegradation rate is fast under environmental conditions (50% after 4.9 hours).

The following aquatic effects are available:

Salmo gairdneri LC_{50} (96 h) = >500<1000 mg/l
Daphnia magna EC_{50} (48 h) > 500 mg/l; 2430 mg/l
Scenedesmus subspicatus EC_{50} (72 h) = 130 mg/l; *Selenastrum capricornutum* 4550 mg/l
Pseudomonas putida EC_{50} (17 h) = 4200 mg/l

From the effect value for the most sensitive species, *Scenedesmus subspicatus*, a PNECaqua of 130 µg/l was derived by applying an assessment factor of 1000. This factor is justified as only short-term effect values are available.

No data are available on terrestrial organisms.

Exposure

The production volume of this chemical in EU was 500,000 –1,000,000 t in 1999. More than 1,000,000 tonnes are produced in Asia and 500,000 – 1,000,000 tonnes in North America. The substance is used as an intermediate (non-disperse use) in chemical industry to produce polyamides. Currently 73% of the polyamide is being used for fibre-based applications (carpets and clothing), while the remainder 27% is used for the production of engineering plastics (gear wheels, drive systems, intermediates into Nylon-6). SIAM was informed that exposure to workers is adequately controlled in the industry of the sponsor countries (Germany, Japan and the USA).

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	126-73-8
Chemical Name	Tributyl phosphate
Structural Formula	$(C_4H_9O)_3PO$

RECOMMENDATIONS

The chemical is a candidate for further work under conditions specified below.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The toxicology database for tributyl phosphate (TBP) is large and well documented. There are adequate data with which to evaluate the potential hazard to human health of this compound. Acute oral toxicity values in rodents range from 1390 to 3350 mg/kg-bw in rats and from 400 to 1240 mg/kg-bw in mice. A rat six-hour LC50 of > 4.2 mg/L (highest dose tested) was reported. Dermal studies exist in rabbits (LD50s of >3100 mg/kg-bw and > 10,000 mg/kg-bw) and in guinea pigs (LD50 of 9700 – 19,400 mg/kg-bw). Repeat dose studies have been performed in animals via the inhalation (4 month studies in rats and rabbits) and oral (gavage studies in rats [one week to 18 weeks] and rabbits [two weeks] and dietary feeding studies in rats [nine weeks to two years] and mice [four weeks to two years]) routes. Effects observed in the inhalation studies were depressed cholinesterase levels (reversible after exposure stopped) at the highest tested dose (13.6 mg/m^3) in both rats and rabbits. Overall, the results of the rodent dietary/gavage studies consistently showed cellular and/or weight changes in the liver, kidney, and bladder. In the rat, two-year dietary study, the NOAEL is 200 ppm (9 mg/kg-bw/day males and 12 mg/kg/day females) for cytotoxicity/hyperplasia in the urinary bladder. In an 18 month dietary study using CD-1 mice the NOAEL was 150 ppm (28.9 mg/kg/day for females and 24.1 mg/kg/day for males), the lowest dose tested. TBP did not affect reproductive performance in a two-generation feeding study in rats (NOAEL of > 225 mg/kg-bw/day). Developmental toxicity was observed in the two-generation study, but only at levels at which maternal toxicity was observed (NOAEL < 15 mg/kg-bw/day; reduced pup weights along with reduced maternal body weight gain and decreased food consumption). In three separate teratology experiments (two with rats and one with rabbits), teratogenic (delayed ossification and rudimentary ribs) and developmental (reduced fetal weights) effects were observed only at maternally toxic doses and only in rats (NOAEL in rabbit study was the highest dose tested – 400 mg/kg-bw/day). The NOAEL for teratogenic effects was 750 mg/kg-bw/day, but the NOAEL for maternal toxicity was 62.5 mg/kg-bw/day. TBP is an animal carcinogen when administered in the diet at levels greater than 200 ppm in rats (9 mg/kg-bw/day) or 150 ppm in mice (24 mg/kg-bw/day). Overall the results of genetic toxicity studies indicate that TBP is not genotoxic. These include *in vitro* and *in vivo* data. A mechanistic study in rats found that the effects of TBP on the bladder were reversible upon withdrawal of treatment and thus likely due to the direct urothelial cytotoxicity of the chemical itself (or its metabolites), and not a result of urinary changes. The neurotoxicity of TBP has been studied in several species including the rat, hen, and rabbit. In these studies, TBP produced either no signs of neurotoxicity or only slight or transient effects on measured endpoints. TBP is irritating to the skin and eye of humans and laboratory animals but does not cause sensitization in humans. The primary exposure to TBP is through dermal contact in the occupational setting. Based on this exposure route and the NOAEL levels reported, the most likely effects of TBP exposure are irritation of the skin and eyes.

Environment

In both soil and water, TBP is expected to adsorb to sediments or particulate matter and biodegrade. In the atmosphere, TBP will exist as a vapour and will be subject to rapid photodegradation. Bioconcentration is not expected to occur. Numerous acute and chronic toxicity data are available for fish, invertebrates, and algae. The acute toxicity values for fish (96-hr LC50) from over a dozen studies range from 4.2 to 18 mg/L. Toxicity values for six species of algae ranged from a 72-hr EC50 (biomass) of 1.1 mg/L (*Scenedesmus subspicatus)* to a 48 hr EC50 of 5-10 mg/L (*Chlorella emersonii).* Algal NOECs have been reported in two different studies (0.37 mg/L as an EC10 for biomass in *Scenedesmus subspicatus* and 2.2 mg/L in a 96-hr study with *Selanastrum capricornatum*). Daphnid chronic NOECs range from 0.87 mg/L (21-day study) to 3.1 mg/L (14-day study). The lowest fish NOEC occurred at a concentration of 0.82 mg/L (95-day early life-stage study). Using an assessment factor of 10, since long-term NOECs are available for three species representing three trophic levels (fish, *Daphnia*, and algae), and the lowest valid NOEC (0.37 mg/L for algae, the resulting aquatic predicted no-effect concentration (PNEC) is 0.037 mg/L.

Exposure

The production volume of TBP is estimated at 3,000 – 5,000 tonnes worldwide. The major uses of TBP in industry are as a component of aircraft hydraulic fluid and as a solvent for rare earth extraction and purification. Minor uses of TBP include use as a defoamer additive in cement casings for oil wells, an anti-air entrainment additive for coatings and floor finishes, as well as a carrier for fluorescent dyes. The major uses of TBP comprise over 80 percent of the volume produced. No current consumer product uses of TBP have been identified. The primary occupational exposure to TBP results from its use as an ingredient in aircraft hydraulic fluids. The potential for exposure to TBP varies with the type of maintenance activity, but is almost always via a dermal pathway.

NATURE OF FURTHER WORK RECOMMENDED

The chemical is considered a candidate for further work, in the context of a risk assessment, if it is used as a herbicide or has other dispersive uses.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	141-97-9
Chemical Name	Ethyl acetoacetate
Structural Formula	CH_3-C(=O)-CH_2-C(=O)-O-CH_2- CH_3

RECOMMENDATIONS

The substance is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Absorption of ethyl acetoacetate via the oral route is demonstrated in animals, absorption via the lungs can be assumed.

It may be anticipated that ethyl acetoacetate is partially cleaved already in the gastrointestinal tract due to acidic pH values or by bacterial activity. In a first metabolic step the absorbed portion of ethyl acetoacetate will be hydrolysed into 3-oxobutanoic acid and ethanol by the unspecific esterases of the blood. The acid moiety is an endogenous product within the lipid metabolism and is further metabolized predominantly to carbon dioxide and water; ethanol will be metabolized on known pathways.

For predicting in humans rates of ester hydrolysis using data derived from animal studies it has to be considered that in dependence on the prevailing substrate, esterase activities in human plasma are far lower than in rats as a rule. Therefore it is to anticipate, that the stability (half-life) of systemically available ethyl acetoacetate is clearly higher in humans than in rats. The main route of elimination of ethyl acetoacetate and its metabolites is urinary excretion or exhalation of the metabolic product carbon dioxide in the breath.

Human data on acute toxicity and on local irritation caused by ethyl acetoacetate are not available. In animals, acute toxicity by the oral, dermal, and inhalative routes is low as judged by tests with rats. The substance demonstrated no or only mild skin irritation and mild eye irritation in tests with rabbits. Valid human or animal data on sensitization are not available.

Following repeated oral exposure of ethyl acetoacetate in rats, no treatment-related adverse effects (including haematology, clinical chemistry, gross necropsy and histopathology) were reported up to 1000 mg/kg bw/d. There is no information on health effects in humans following repeated exposure to ethyl acetoacetate via any route.

On the basis of the in vitro data (bacterial mutation test and chromosomal aberration assay) there is no evidence of a genotoxic potential of ethyl acetoacetate.

There are no data on cancerogenicity of ethyl acetoacetate. From experience on other comparable compounds in combination with the knowledge on the metabolites there is no reason to assume a concern regarding cancerogenic effects of the substance.

There are no human data available on toxicity for reproduction. The potential to adversely affect reproduction and development was investigated in a screening study with oral administration to rats. No relevant effects were

observed at doses up to 1000 mg/kg bw/d.

Environment

Ethyl acetoacetate has a water solubility of 125 g/l, a vapor pressure of 1 hPa and a log Kow of 0.25. According to the physico-chemical properties the target compartment for this substance is the hydrosphere. Ethyl acetoacetate is in principal hydrolysable, the half life for the hydrolysis in neutral solution was calculated to 149 days. The substance is classified as "readily biodegradable". There is no considerable potential for bio- or geoaccumulation. An atmospheric half-life of 10 days was calculated for this substance.

The following results from ecotoxicity tests with aquatic species are available:

In a short-term test with fish a 48h LC_{50} of 275 mg/l was found for *Leuciscus idus*. For invertebrates acute studies on *Daphnia magna* had been conducted. A 24 h EC_{50} between 790 and 800 mg/l were found in these tests. In a study with *Scenedesmus subspicatus* no effects could be observed after 72 h at a concentration of 500 mg/l. Long-term toxicity tests with fish and invertebrates are not available. With an assessment factor of 1000 a PNEC of 275 µg/l is determined.

Exposure

The production volume of Ethyl acetoacetate in the EU is ca. 2900 to 3400 t/a. Most of the Ethyl acetoacetate is used as an intermediate in chemical synthesis for the production of plant protection agents and pharmaceuticals. Less than 5 % of the chemical is used as an odour agent in household chemicals, solvent in paints and lacquers and as an additive in paper.

NATURE OF FURTHER WORK RECOMMENDED

This substance has been agreed in the European Union Risk Assessment Program under Regulation EEC/793/93 with the following conclusion:

Environment: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human Health: 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.	1717-00-6
Chemical Name	1,1-dichloro-1-fluoroethane (HCFC 141b)
Structural Formula	Cl_2 FC - CH_3

RECOMMENDATIONS

The chemical is currently of low priority for further work as it is subject to withdrawal under international activity (Montreal protocol).

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute toxicity of HCFC 141b is low. No mortality was observed in rats receiving oral doses of 5,000 mg/kg. Dermal exposure of rats or rabbits to 2,000 mg/kg caused no mortality and no signs of toxicity. Single exposures of mice for 30 minutes indicated that the LC_{50} was between 296,640 and 494,400 mg/m^3 (61,800 ppm to 103,000 ppm) and the 4-hr LC_{50} in rats was 62,000 ppm (approximately 297,600 mg/m3). Also, a 6-hr exposure of mice at 41,000 ppm (approximately 196,800 mg/m3) caused narcosis but not lethality. In a controlled-exposure study, exposure of humans to levels up to 1,000 ppm (4800 mg/m3) for periods of 3 or 4 hours produced no reports of any adverse effects. HCFC 141b is considered non-irritating to rabbit's skin and a mild eye irritant. A skin sensitization test in guinea pigs was negative.

In repeat inhalation exposure studies of 6 hr/d, 5d/wk for periods from 2 to 13 weeks, the NOEL was judged to be 8,000 ppm (approximately 38,400 mg/m3). The next highest exposure level, 20,000 ppm (96,000 mg/m3), induced only reduced bodyweight gain and slightly increased levels of cholesterol, triglycerides and glucose. No treatment-related hematological or histopathological changes were noted in any exposure level group.

There was no evidence of teratogenic or embryotoxic effects in pregnant rabbits exposed to 1,400, 4,200 or 12,600 ppm (6720 mg/m3, 20,000 mg/m3, and 60,480 mg/m3, respectively) or in pregnant rats exposed to 3,200 or 7,900 ppm (15,360 or 38,000 mg/m3) of HCFC 141b although signs of maternal toxicity were observed at and above 3,200 ppm (15,360 mg/m3) in rats and 4,200 ppm (20,000 mg/m3) in rabbits. A two- generation inhalation study in rats demonstrated a NOEL of 8,000 ppm (38,400 mg/m3) for reproductive parameters. At a higher concentration, 20,000 ppm (96,000 mg/m3) a non-reproducible decrease in the number of litters, in the number of pups per litter and also some retardation of sexual maturation of male pups, which may have been caused by the slight body weight growth retardation, was observed.

In *in vitro* studies, negative results were obtained in bacterial reverse mutation assay and both negative and positive results were obtained in cytogenetic assays. *In vivo*, negative results were obtained in two mouse micronucleus assays. Consequently, the data indicates that the genotoxicity occasionally observed *in vitro* is not expressed *in vivo*. Rats were exposed by inhalation in a lifetime study to concentrations of 1,500, 5,000 and 20,000 ppm (7200; 24,000; and 96,000 mg/m3, respectively). No significant evidence of toxicity was seen, however, at the highest exposure concentration reduced body weight gain was observed. HCFC 141b did not produce neoplastic changes in female rats at any test concentration. In male rats no neoplastic changes were noted at 1,500 ppm but increased incidences of testicular interstitial cell (Leydig cells) hyperplasia and adenoma were observed at 5,000 ppm (24,000 mg/m3)

and 20,000 ppm (96,000 mg/m3). These changes appeared late in life and were not correlated with increased mortality. Because of the genotoxicity profile of HCFC 141b these effects on the rat Leydig cells are considered as to be of epigenetic origin and associated with senile endocrine disturbances, and therefore of no relevance to tumourigenic hazard for man.

Environment

The low octanol/water partition coefficient (log P_{ow} = 2.3) indicates a low potential for bioaccumulation. HCFC 141b is not readily biodegradable. The predominant degradation of HCFC 141b will occur in the air, but at a very slow rate. Acute ecotoxicity studies are available for algae, daphnia, and fish. The 96-hr LC_{50} for zebra fish was 126 mg/L and the 48-hr EC_{50} for daphnia was 31.2 mg/L. The 72-hr NOEC for both growth rate and biomass for algae was > 44 mg/L. Applying an uncertainty factor of 100 to the 48-hr EC50 value of 31.2 mg/L for daphnia, a PNEC of 0.31 mg/L was derived.

Exposure

HCFC 141b is produced and used as a substitute for fully halogenated chlorofluorocarbons with comparable physical properties since it has less unfavorable environmental properties. Production for 1999 was 127 thousand tonnes most of which was for foam blowing. The remainder was for a variety of uses such as precision cleaning. Based on its use pattern, releases of HCFC 141b are anticipated to be to the air compartment. It was estimated, using a level III fugacity model, that when primary releases occur to the air compartment that 99.9% of HCFC 141b will remain in that compartment. The global atmospheric lifetime is 10.8 years, which is supported by a trophospheric half-life of 4.9 years due to removal by reaction with OH radicals. Based on this lifetime, the stratospheric ozone depletion potential (ODP) is 0.11 and the global warming potential calculated by IPPC 1995 for an integration horizon of 100 years is 0.12. Both are low compared to CFC 11 which is 1.0. The majority of HCFC 141b released into the environment degrades in the lower atmosphere forming carbon dioxide and inorganic chlorides and fluorides.

Because of its ODP, the production and consumption of HCFC 141b are covered by the Montreal Protocol. In the case of developed countries, a phase-out of HCFC 141b 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, the use as blowing agent for expanded polystyrene being prohibited from January 1, 2002. In the U.S., HCFC 141b production is scheduled for phase-out in 2003

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

Due to be phased out under the Montreal Protocol.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	84852-15-3 and 25154-52-3
Chemical Name	Phenol, 4-nonyl-, branched and Nonylphenol
Structural Formula	$HO\text{-}C_6H_4\text{-}C_9H_{19}$ where C_6H_4 is a 1,4-substituted benzene ring

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Nonylphenol is rapidly and probably extensively absorbed from the gastrointestinal tract and undergoes extensive first pass metabolism. The major metabolic pathways are likely to involve glucuronide and sulphate conjugation. Because of first pass metabolism, the bioavailability of unconjugated nonylphenol is probably limited following oral exposure, at no more than 10-20% of the administered dose. Nonylphenol is distributed widely throughout the body, with the highest concentration in fat. The major routes of excretion are via the faeces and urine. Regarding bioaccumulation, there are insufficient data to allow a conclusion to be drawn on whether or not nonylphenol has this potential. On the basis of the oral absorption data and high partition coefficient, it would be prudent to assume that significant absorption via inhalation can occur. Furthermore, because first pass metabolism will not take place following exposure by the inhalation route, the systemic bioavailability is likely to be substantially greater than is associated with the oral route. *In vitro* data indicate that nonylphenol is poorly absorbed across skin, although some limited skin penetration, especially to the stratum corneum, can occur.

At sufficient doses, toxicity may occur following a single ingestion or contact to the skin. In studies in animals, erosion of the stomach mucosa is sometimes seen following the administration of a lethal dose. For acute toxicity, rat oral LD_{50} values are in the range 1200 to 2400 mg/kg and via the dermal route a rabbit LD_{50} of about 2000 mg/kg is available. No data are available on the acute inhalation toxicity, although the corrosive nature of nonylphenol suggests that acute toxicity could be elicited following exposure by this route. Liquid nonylphenol can be corrosive to the skin (full thickness necrosis and ulceration within 24 hours of a 1 or 4 hour exposure) although its potency might vary according to source and exact composition. The liquid is also a severe eye irritant (irreversible effects within 7 or 21 days observation periods). Exposure to the saturated vapour (calculated to be 400 ppm) elicited mild sensory irritation of the respiratory tract in mice, but no reaction was elicited at a nominal concentration of 30 ppm. The results of several guinea pig maximisation tests indicate that nonylphenol is not skin sensitiser. It can be predicted from its low chemical reactivity that nonylphenol is unlikely to be a respiratory allergen.

In addition to 28-day and 90-day studies, information on repeated dose toxicity was available from a multigeneration study in the rat involving oral exposure for up to 20 weeks. A lowest adverse effect level (LOAEL) for repeated dose of 15 mg/kg/day was identified, based on histopathological changes in the kidneys (tubular degeneration or dilatation), although such changes were not apparent at this dose level in a 90-day rat study. At higher dose levels the liver may also be a target organ; minor histopathological changes in the liver (vacuolation in the periportal hepatocytes or occasional individual cell necrosis) were seen at doses of 140 mg/kg/day and above in some studies. No repeated-dose studies involving dermal or inhalation exposure have been conducted. The oral toxicity of

nonylphenol appears to be enhanced when dosed by gavage, with mortalities being reported at dose levels of 100 mg/kg/day.

Concerning mutagenicity, nonylphenol tested negative in two bacterial assays and an *in vitro* mammalian cell gene mutation assay. An *in vivo* micronucleus test, conducted using the intraperitoneal route, was negative. A second *in vivo* micronucleus test, which used the oral route, was also negative, although there were methodological weaknesses in this study. These results show that nonylphenol is not mutagenic.

Carcinogenicity has not been directly studied. On the basis of the information currently available concerns for cancer caused by a genotoxic or non-genotoxic mechanisms are low. As to reproductive and developmental toxicity, no human data are available. The observations of oestrogenic activity in the *in vitro* and *in vivo* screening tests, minor perturbations in the reproductive system of offspring in the multigeneration study, and testicular changes in gavage studies collectively raise concerns for reproductive toxicity, possibly mediated through action on the oestrogen receptor. The effects on reproduction related parameters in the multi generation study were marginal and there was no evidence of functional changes in reproduction; furthermore any changes that were seen occurred at exposure levels in excess of the LOAEL for repeated dose toxicity (LOAEL for renal toxicity is 15 mg/kg/day, no observed adverse effect level for reproductive changes is 15 mg/kg/day). Evidence of testicular toxicity was reported in two repeated exposure studies designed to specifically investigate the effects on this organ, but only at doses which also caused mortality. No evidence of testicular toxicity was seen in standard repeated dose studies involving dietary administration. Development was not affected in a standard rat oral gavage development toxicity study.

Environment

The environmental effects database meets the requirements for the SIDS data package. Both short- and long-term aquatic toxicity data are available for freshwater fish, invertebrates and algae. In acute studies, the lowest valid values are as follows: for fish a 96-hour LC_{50} of 0.128 mg/l (*Pimephales promelas*); for invertebrates a 96-hour EC_{50} of 0.0207 mg/l (*Hyalella azteca*); and for algae a 72-hour EC_{50} (biomass) of 0.0563 mg/l (*Scenedesmus subspicatus*). Comparable toxicity is observed with saltwater species (the alga *Skeletonema costatum* is slightly more sensitive than the freshwater species with a 96-hour EC_{50} (cell growth) of 0.027 mg/l, compared to a 72-hour EC_{50} (growth rate) of 0.323 mg/l for *Scenedesmus subspicatus*).

In long-term/chronic studies, the lowest valid values are as follows: for fish a 33-day $NOEC_{survival}$ of 0.0074 mg/l (*Pimephales promelas*); for invertebrates a 21-day $NOEC_{surviving\ offspring}$ of 0.024 mg/l (*Daphnia magna*); and for algae a 72-hour EC_{10} (biomass) of 0.0033 mg/l (*Scenedesmus subspicatus*). A 28-day $NOEC_{length}$ of 0.0039 mg/l was also obtained for the saltwater invertebrate *Mysidopsis bahia*.

As long-term NOECs from at least three species representing three trophic levels are available, an assessment factor of 10 may be applied to the chronic NOEC for algae to give an aquatic PNEC of 0.33 µg/l (as in the EU risk assessment; different levels have been derived by other authorities). A mesocosm study has been performed, giving a 20-day NOEC of 0.005 mg/l. Due to possible issues with the test design, this study is taken as supportive of the PNEC, but cannot be used as the sole basis for deriving a PNEC to protect the aquatic compartment. Concentrations of nonylphenol at which oestrogenic effects are observed appear to be higher than those producing other effects. The calculated PNEC should therefore be protective for oestrogenic effects in fish as well. A PNEC for the sediment compartment of 0.039 mg/kg can be derived from the aquatic PNEC assuming equilibrium partitioning.

For the terrestrial compartment long-term data are available for micro-organisms, plants and invertebrates. The most sensitive species group appears to be the terrestrial invertebrates with a 21-day EC_{50} (Reproduction) of 13.7 mg/kg and a 21-day EC_{10} (Reproduction) of 3.44 mg/kg reported for earthworms (*Apporec-todea calignosa*). 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 end point (in accordance with EU technical guidance), giving a $PNEC_{soil}$ of 0.3 mg/kg. A $PNEC_{oral}$ of 10 mg/kg food for secondary poisoning can also be derived from the mammalian NOAEL of 15 mg/kg body weight for reproductive effects (more details below).

Exposure

Total European Union (EU) production was 73,500 tonnes in 1997 (consumption was estimated at 78,500 tonnes). Nonylphenolis used as a chemical intermediate in the production of nonylphenol ethoxylates, plastics/resins and phenolic oximes, and as a processing aid for polymers.

It is a viscous yellow liquid with a vapour pressure of ~0.3 Pa at 25°C, a water solubility of ~6 mg/l at 20°C and pH 7, and a log octanol-water partition coefficient (log K_{OW}) of 4.48. In general, hydrolysis and photolysis in water are negligible but nonylphenol is considered inherently biodegradable. –In aquatic species, bioconcentration factors (BCFs) (on a fresh weight basis) are reported up to 1,300 in fish. Releases to the aquatic compartment arise mainly from the manufacture and use of the ethoxylates (due to degradation). Nonylphenol adsorbs strongly to soils, sludges and sediments.

Exposure may occur in workers during breaches of closed systems and during spraying of formulations produced with nonylphenol. Consumers may be exposed directly via ingestion and/or contact with very low levels of residual unreacted nonyl phenol in substances used to make pesticide products, cosmetics, pharmaceuticals (being phased out in EU), hair dyes and food (via migration from packaging polymers and papers). Indirect exposure via the environment may occur via oral intake of food and, to a lesser extent, drinking water.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address hazard classification for all SIDS endpoints and for other non-SIDS endpoints. However, the chemical is a candidate for further work as follows:

- National or regional exposure information gathering and risk assessment may need to be considered, especially for nonylphenol ethoxylate use as an indirect source of nonylphenol in the environment (based on an existing regional risk assessment for Europe, where a need to limit risks has been identified for a number of uses for both human health and the environment). Note: nonylphenol ethoxylates are being assessed separately by the US under the OECD HPV programme.

- No toxicity data are available for sediment organisms. These data could be generated as a post-SIDS activity if a concern for the sediment compartment is identified (as in the European risk assessment). In addition, various workers continue to generate data for this substance (especially in the field of endocrine disruption), and new data may need to be reviewed on a periodic basis.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	34590-94-8 (isomers: 13429-07-7, 20324-32-7; 13588-28-8; and 55956-21-3)
Chemical Name	Dipropylene Glycol Methyl Ether
Structural Formula	CH_3-$(OC_3H_6)_2$-OH

RECOMMENDATIONS

The chemical is currently of low priority for further work, based on the low hazard profile.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Commercial Dipropylene Glycol Methyl Ether (DPGME) is a mixture of four isomers. DPGME exhibits low acute toxicity by the oral, dermal, and inhalation routes. The oral LD50 ranges 5180-5400 mg/kg b.w. in rats to 7500 mg/kg b.w. in dogs. Dermal LD50 values were reported to range from 9500 to >19000 mg/kg b.w. in rabbits. Acute inhalation exposures to 500 ppm (3000 mg/m^3, highest attainable concentration) DPGME produced no lethality and mild, but reversible narcosis in rats. In animal and human studies, DPGME is neither a skin sensitizer nor a skin irritant, and was only slightly irritating to the eye. In repeated dose inhalation studies, NOAELs of >50 ppm to 200 ppm (> 303 mg/m^3 to 1212 mg/m^3) have been observed using rats, mice, rabbits, guinea pigs, and monkeys. Effects observed at higher dose levels (1818 mg/m^3 to 2424 mg/m^3; 300 – 400 ppm) showed signs of central nervous system depression and adaptive liver changes. In rats exposed to up to 1000 mg/kg-day DPGME via gavage for 4 weeks, tentative salivation (immediately after dosing) and adaptive liver changes were observed in animals exposed to the highest dose. No effects were observed in rats exposed to 200 mg/kg-day. Studies in rats and rabbits showed that DPGME is not teratogenic (two inhalation studies with NOAELs of 1818 mg/m^3; 300 ppm). It should be noted that the beta isomer of PGME is known developmental toxicant. This isomer is unlikely to be a metabolite of DPGME. The available data indicate that DPGME is not genotoxic. Information collected for a structurally similar chemical (PGME) suggests that DPGME is not a reproductive toxicant, and is not carcinogenic. Additionally, no effects were seen on the testes and ovaries in a 90-day repeat dose inhalation toxicity study on DPGME.

Environment

DPGME is not persistent in the environment and is not expected to bioaccumulate in food webs. DPGME has a water solubility value of 1000 mg/L, a vapor pressure of 0.37 hPa and a log Kow of 0.0061. The half-life of DPGME in air was measured at 5.3 hours and is estimated to be 3.4 hours due to direct reactions with photochemically generated hydroxyl radicals. DPGME is readily biodegraded under aerobic conditions, but only slightly degraded under anaerobic conditions. Although environmental monitoring data are not available for DPGME, fugacity-based modelling indicates that DPGME is likely to partition to water compartments in the environment (surface water, groundwater). Acute toxicity testing in fish, invertebrates, and algae indicate a low order of toxicity with effect concentrations exceeding 1000 mg/L. Applying an uncertainty factor of 100 to the 48-hour LC50 value of 1919 mg/L for Daphnia, a PNEC of 19 mg/L was derived.

Exposure

Production in the U.S. was estimated at 35 million pounds (16 thousand tonnes) for 2000. DPGME is used in the

manufacture of a wide variety of industrial and commercial products, including paints, varnishes, inks, and cleaners. In the US in 1999, DPGME was used as follows: 58% paints/coatings/inks, 28% cleaners, 10% DPGME acetate production, and 3% miscellaneous production.

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-68-3
Chemical Name	1-chloro-1,1-difluoroethane
Structural Formula	$ClF_2C - CH_3$

RECOMMENDATIONS

The chemical is currently of low priority for further work as it is subject to withdrawal under international activity (Montreal protocol).

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1-chloro-l,l-difluoroethane is a colourless gas with slight ethereal odour:

Acute toxicity of 1-chloro-l,l-difluoroethane is low (LC50/6h >1,640,000 mg/m3 (400,000ppm) in rats). Inhalation of high concentrations induced signs of lung irritation and Central Nervous System depressing effects of anesthetic type in rats and cardiac sensitisation in dogs. Consequently, 1-chloro 1,1-difloroethane may be hazardous to humans in case of accidental exposure to high concentrations occurring in confined area where replacement of air by the gas could at the same time reduce oxygen in the atmosphere. In repeated inhalation exposure studies, 1-chloro-1,1-difluoroethane did not induce specific chronic toxicity in rats and dogs exposed 6 h/d, 5 d/week during several months (no target organs identified ; the no observed adverse effects were higher than 41 000 mg/m3 (10,000ppm) in dogs exposed during 3 months and higher than 82 000mg/m3 (20,000ppm) in rats exposed for their lifetime). There was no carcinogenic effect in rats exposed for their life time (6h/d, 5d/week at concentrations up to 82 000 mg/m3 (20,000ppm)). In genotoxicity studies, 1-chloro-1,1-difluoroethane was mutagenic *in vitro* on bacteria (Ames test) and gave equivocal results in a cell neoplastic transformation assay. However, in *in vivo* mutagenicity studies it was inactive (in a Dominant lethal assay and in a Bone Marrow cytogenetic assay in rats exposed by inhalation during 15 and 13 weeks respectively). Overall, these results suggest that 1-chloro-1,1-difluoroethane does not pose a significant genotoxic hazard to humans. In the reproduction field, 1-chloro 1,1-difluoroethane did not induce adverse effect on fertility of male mice exposed up to 82 000 mg/m3 (20,000ppm) (in a Dominant lethal assay) and did not induce male and female lesions of sexual organs in rats and dogs exposed for several months. Also the gas did not induce teratogenic or embryo/foetotoxicity effect and no maternal toxicity in two inhalation developmental toxicity studies where rats were exposed during pregnancy up to 41000 mg/m3 (10,000ppm).

Environment

Based on its physico-chemical properties, the air compartment is the preferred target one for 1-chloro-1,1-difluoroethane. The global atmospheric lifetime of 142b is 18.5 years corresponding to a 1/2-lifetime of 12.8 years. The tropospheric lifetime due to removal by reaction with OH is 19.5 years.

Atmospheric degradation products are essentially the aldehyde form of 142b which further degrade to form CF2(=O) which will hydrolyse in atmospheric water to form HF (also in the OECD HPV Chemicals Programme) and CO2.

The ozone depletion potential (ODP) of 1-chloro-1,1-difluoroethane is the main concern of this substance. Due to its ODP value of 0.065, it is considered as an ozone depleting substance. The calculated Global Warming Potential of 1-chloro-1,1-difluoroethane is 1800 (IPCC 1995) for an integration horizon of 100 years. Its contribution to the Greenhouse effect is small i.e. 0.00108 W/m2 from IPCC 1995 data.

In water, 1-chloro-1,1-difluoroethane is not readily biodegradable under aerobic condition (about 5 % of biodegradation after 28 days). It is not expected to bioaccumulate (log Kow = 1.64 - 2.05).

1-chloro1,1-difluoroethane has a low acute toxicity to fish and daphnia. The lowest available LC 50 being higher than 100mg/liter. No acute toxicity tests are available for algae. Algae appear to be more sensitive than fish and daphnids to 1-chloro1,1-difluoroethane with a calculated 96h EC50 of 45mg/l.

From these results, a PNEC of 45 µg/l is proposed applying a factor of 1000 to the lowest figure obtained from the QSAR for algae (45 mg/l).

Exposure

The expected production volume of 1-chloro-1,1-difluoroethane in year 2000 is 36,000 tonnes in Europe, 42,000 tonnes in the USA and an amount of 84,000 tonnes for the total world. Its main uses are as a chemical intermediate to produce fluoropolymers and as a blowing agent. A small portion is used as a component of refrigerant fluids.

Because of its ODP, the production and consumption of 1-chloro1,1-difluoroethane are covered by the Montreal Protocol. In the case of developed countries, a phase-out of 1-chloro1,1-difluoroethane 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 (HCFCs) is required on January 1, 2010, the use as blowing agent for expended polystyrene being prohibited from January 1, 2002.

NATURE OF FURTHER WORK RECOMMENDED

None recommended.

Due to be phased out under the Montreal protocol.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-06-1
Chemical Name	Acrylamide
Structural Formula	$CH_2 = CH - CONH_2$

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The human health effects database meets the requirements for the SIDS data package. Few significant human data are available so this assessment of the hazardous properties of acrylamide is based mainly on animal data.

Acrylamide has been comprehensively studied in animals. It is rapidly and extensively absorbed by oral and dermal routes and presumably also by the inhalation route.

At sufficient doses, toxicity may occur following a single ingestion or contact to the skin. For acute toxicity oral LD50 values of 175 and 203 mg/kg in the rat, 107 and 203 mg/kg in the mouse, and a rabbit and Guinea pig value in the range 150-180 mg/kg are available. The principle effects prior to death are severe clinical effects related to neurotoxicity. Severe effects on spermatid development was also observed in mice. A rabbit dermal LD50 value of 1148 mg/kg is available, but no LC50 values are available. However, as it is presumed that acrylamide would be well absorbed by the inhalation route, it could also be presumed that toxicity may occur following inhalation at sufficiently high concentrations.

No signs of skin irritation were observed in a well-conducted study in rabbits. Case reports and workplace surveys have demonstrated skin effects usually attributable to occupational exposure to aqueous solutions of acrylamide. However, based on human experience it appears that acrylamide is a skin irritant. Information on eye irritation is available from a well-conducted animal study. Acrylamide was clearly irritating to the eyes, producing corneal opacity and iridial reactions. The animal data provide clear evidence that acrylamide is a skin sensitiser.

Human evidence from case reports and workplace surveys demonstrate neuropathological effects, principally peripheral neuropathy, following exposure to acrylamide. Exposures are considered likely to be a combination of inhalation and dermal. One case report of accidental oral ingestion, which was likely to have involved repeated rather than single exposure, also demonstrated neuropathic effects.

For oral exposure, most of the information in animals related to neurotoxicity and provide supporting evidence for the effects observed in humans. In rodent studies, histopathological examination of tissues in a 2-year rat chronic study where acrylamide was administered in the drinking water, gave a clear no observed adverse effect level (NOAEL) for neurotoxicity of 0.5 mg/kg/day, with only slight peripheral nerve lesions in the absence of any clinical signs of toxicity seen at 2 mg/kg/day. These observations were consistent with 90-day rat studies and studies in mice of shorter duration, which demonstrated similar effects at slightly higher exposure levels.

No firm conclusions could be drawn from the available animal studies using the dermal route of exposure; however the effects are predicted to be similar by this route.

Acrylamide was negative in standard bacterial assays but clearly a direct-acting clastogen in mammalian cells *in vitro*, producing chromosome aberrations and polyploidy. Supporting evidence for *in vitro* clastogenicity was also evident in mammalian cell gene mutation assays. There is a large body of evidence clearly demonstrating acrylamide is mutagenic *in vivo*. Positive results were observed in the bone marrow micronucleus test and metaphase analysis, mouse mammalian spot test and a mouse transgenic assay. In the case of germ cells, acrylamide has been demonstrated to induce heritable mutations. Positive results have been obtained in a number of different germ cell assays; chromosome aberrations, micronucleus assays, UDS, dominant lethal assays, heritable translocation, and specific locus assays. Thus, acrylamide is genotoxic *in vivo* to both somatic and germ cells.

For carcinogenicity, two well conducted studies are available in male and females F344 rats, where they received aqueous acrylamide in drinking water for up to 2 years. In both studies there were increases in a number of benign and malignant tumours in a variety of organs, some of which showed a possible relationship with disturbed endocrine function. There is inconclusive evidence from both studies that acrylamide may induce neoplastic neural lesions; tumours were observed in the brain and spinal cord of both sexes, but were not statistically significant and did not show a clear dose-response. The results of both studies clearly demonstrate that acrylamide is carcinogenic in animals. Given the genotoxicity profile of acrylamide, genotoxic activity cannot be conclusively discounted from contributing to tumour formation.

Fertility data are available from studies in rats and mice using the oral route of exposure. Overall, there is sufficient evidence to conclude that acrylamide impairs male fertility in rats and mice (reduction in the number of pregnant dams). In some studies it was possible to identify NOAELs; no effects on fertility in rats were observed in a 2-generation reproduction study in which males and females of each generation received 5 mg/kg/day for 10-11 weeks. No clear effects on fertility were seen in a continuous breeding study in mice exposed to about 9 mg/kg/day acrylamide for up to 27 weeks.

Data on developmental toxicity are available in rats and mice using the oral route of exposure. In the absence of marked maternal toxicity there was no evidence of selective developmental toxicity in rats or mice.

Studies in rats attempted to investigate whether acrylamide could induce toxicity in pups during lactation. However, the dose level used induced significant effects in dams and on lactation. Thus, no conclusions could be drawn with respect to acrylamide-specific effects mediated via breast milk.

Environment

The environmental effects database meets the requirements for the SIDS data package. Short term aquatic toxicity data are available for fish, invertebrates and algae (all from validated sources) and micro-organisms (not valid). The lowest 96-hour LC_{50} reported for fish is 100 mg/l (*Lepomis macrochirus*); the lowest 48-hour EC_{50} for invertebrates is 98 mg/l (*Daphnia magna*); and the lowest 72-hour EC_{50} for algal growth inhibition is 33.85 mg/l (*Selenastrum capricornutum*) (based upon a 72-hour EC_{50} of 67.7 mg/l for a 50% acrylamide solution). In addition there are two valid long-term toxicity results: a 28-day NOEC of 2.04 mg/l (based upon mortality) for the saltwater shrimp *Mysidopsis bahia*; and a 72-hour NOEC of 16 mg/l (growth inhibition) for *Selenastrum capricornutum*. An aquatic PNEC of 20.4 µg/l can be derived by applying a factor of 100 to the lowest long term NOEC from species representing two trophic levels (i.e. invertebrates and algae) where the most sensitive species group in the long term studies is not the most sensitive in the acute studies.

For the terrestrial compartment the only available data are for plants. Acrylamide shows a slight toxic effect to plant growth at concentrations of 10 mg acrylamide/kg soil. An EC_{50} of 220 mg/l (based upon root elongation) is reported for plant seedlings. As the EC_{50} is a short term toxicity test an assessment factor of 1000 (in accordance with EU guidance) may be applied giving a PNEC for terrestrial species of 220 µg/l. This calculation is based on only one terrestrial toxicity result. Due to the partitioning behaviour of acrylamide, the PNEC for the aquatic compartment (20 µg/l) can also be used directly as an alternative PNEC for terrestrial organisms (as a soil pore water concentration)

using the equilibrium partitioning method.

Exposure

Total European Union (EU) production is 80,000-100,000 tonnes/year (~1995). It is used to make polyacrylamides, with a residual monomer content of <0.1% w/w. About 80-90% of polyacrylamide is used in waste water treatment, paper and pulp processing, and mineral processing. Other uses of the polymer include crude oil production, cosmetic additives (such as soap, shaving foam, and hair gels), and soil and sand stabilisation. Acrylamide can also be used in the formulation of grouting agents for sewer line sealing and manhole sealing (and also structural water control and geotechnical applications). About 0.1% of the acrylamide produced in the EU may also be sold directly for on-site preparation of polyacrylamide electrophoresis gels in research establishments, universities and hospitals.

Acrylamide is a powder (normally supplied as a 30-60% w/w aqueous solution) with a vapour pressure of 0.9 Pa at 25 °C, a water solubility of 2,155 g/l at 30 °C and a log octanol-water partition coefficient (log K_{OW}) of ~ -1.0. It does not polymerise significantly at temperatures up to its melting point (~84°C) in the absence of light. However, above its melting point it can polymerise rapidly and exothermically. Hydrolysis and photolysis in water are environmentally insignificant but it is considered readily biodegradable meeting the 10-day test window. The log K_{OW} value implies a low bioaccumulation potential in aquatic species (confirmed by fish bioconcentration factors (BCFs) of 0.26 - 2.53) and low adsorption to soils and sediments. The substance chiefly partitions to water.

In workers, there may be potential for inhalation from exposure to acrylamide or polyacrylamide dust, vapour from sublimation of the solid or vapour from liquid forms. Dermal exposures may occur where workers come into contact with splashes of solid or liquid forms, or from contact with condensed vapour. In consumers, there is potential for dermal exposure, primarily from cosmetic products. There may be potential for oral intake of acrylamide due to contamination of drinking water.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address hazard classification for all SIDS endpoints and for other non-SIDS endpoints. However, the chemical is a candidate for further work as follows:

- National or regional exposure information gathering and risk assessment may need to be considered.
- A regional risk assessment has been carried out for Europe indicating concern in particular for grouting applications. The US has conducted a risk and exposure assessment for grouting applications to support possible restrictions on this use.
- In addition, various workers continue to generate data for this substance (especially, in the field of the mechanisms for carcinogenicity) and new data may need to be reviewed on a periodic basis.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	822-06-0
Chemical Name	1,6-Hexamethylene diisocyanate
Structural Formula	O=C=N-$(CH_2)_6$-N=C=O

RECOMMENDATIONS

This chemical is currently a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,6-Hexamethylene diisocyanate (HDI) has acute effects: LD50, rat (oral): 746 – 959 mg/kg bw, LC50 rat (inhalation): (0.124 mg/l) 18.2ppm/4h, LD50, rabbit (dermal): 599 mg/kg bw. The observed symptoms are indicative of respiratory tract irritation. 1,6-Hexamethylene diisocyanate is corrosive to the skin and the eye. 1,6-Hexamethylene diisocyanate was found to induce dermal and respiratory sensitization in animals and humans. There is no threshold known for this effect.

Inhalation studies with repeated exposures to 1,6-hexamethylene diisocyanate vapor show that the respiratory tract is the target with 1,6-hexamethylene diisocyanate showing primarily upper respiratory tract lesions (nasal cavity). 1,6-Hexamethylene diisocyanate did not show a neurotoxic effect in a combined reproduction/developmental/ neurotoxicity study. Life-time inhalation exposure to rats revealed a progression of non-neoplastic respiratory tract lesions, primarily to the nasal cavity, and represented the sequelae of non-specific irritation. Based on the presence of only reversible tissue responses to irritation at the low concentration of 0.005 ppm, this concentration was a NOAEL. No carcinogenic potential in rats was observed after life-time inhalation.

1,6-Hexamethylene diisocyanate showed no mutagenic activity *in vitro* in bacterial and in mammalian cell test systems. 1,6-Hexamethylene diisocyanate showed no clastogenic activity *in vivo*. 1,6-Hexamethylene diisocyanate has no effect on fertilty and post-natal viability through post-natal day 4 in the rat after inhalation up to 0.299 ppm. The overall NOEL was 0.005 ppm. Inhalation of 1,6-hexamethylene diisocyanate during the pregnancy of rats produced maternal effects (nasal turbinate histopathology) at concentrations ≥ 0.052 ppm. No developmental toxicity was observed up to 0.308 ppm.

Environment

HDI has a melting point of –67 °C. The substance forms oily droplets in water and hydrolyses rapidly. The vapour pressure of HDI is 0.7 Pa/20 °C. A log K_{ow} is not determinable due to the instability in water.

Hydrolysation of HDI was 90 % after a reaction period of 30 min in water at 20 °C. Hydrolysis products are hexamethylene diamine (HDA) and polyurea. Biodegradation tests on hexamethylene diamine (HAD) show the substance to be inherently biodegradable. Polyurea is more or less inert and because of it's molecular size not bioavailable. The favourite compartment for HDA is water as suggested by the high water solubility. Mackay level I distribution for HDA is not applicable as this substance is protonated under environmental pH conditions. Due to the high solubility in water of HDA (800 g/l at 15.6 °C) and its log Kow of 0.02 no bioaccumulation is expected.

In air HDI is indirectly photodegradable with t½ = 48.4 h.

As the inherent property of HDI is to hydrolyse rapidly in an aquatic environment the ecotoxicological tests were conducted with the hydrolysis product(s) under defined conditions. The acute toxicity has been determined for fish (*Brachydanio rerio*) with a 96 h-LC_0 of >= 82.8 mg/l, for *Daphnia magna* with a 48h-EC_0 of >= 89.1 mg/l, and for algae (*Scenedesmus subspicatus*) a 72 h-EC_{50} of >77.4 mg/l and a 72h-NOEC of 11.7 mg/l A PNECaqua of 77.4 µg/l is derived from the EC_{50}-value for algae using an assessment factor of 1000. This factor is chosen because only short-term tests are available.

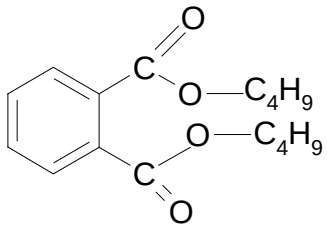
Exposure

The world production capacity of 1,6-Hexamethylene diisocyanate (HDI) amounts to about 110,000 t/a, thereof about 49,000 t/a are produced in the USA (2 producers), about 11,000 t/a in Japan (3 producers), and about 50,000 t/a in Western Europe (3 producers). HDI is not used as the monomer but is industrially processed to higher molecular weight compounds. These are used in industrial applications (mainly surface coatings) where especially lightfastness and weatherstability are required. Exposure to consumers cannot be excluded because there are a limited number of products that consumers can use which contain low concentrations of HDI. In certain occupational settings exposure may occur from the inappropriate use of products containing small concentrations of HDI.

NATURE OF FURTHER WORK RECOMMENDED

The chemical is an irritant and a respiratory sensitizer without a known threshold. There is a need for further work (exposure assessment) in situations where there are dispersive uses (e.g. car lacquers). SIAM was informed that it is adequately controlled during manufacture (at 8 sites) and in industrial processes.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	84-74-2
Chemical Name	Dibutylphthalate
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Dibutylphthalate is rapidly absorbed, orally up to more than 90%. After 48 hours .63-90% % is excreted in the urine. The dermal absorption is around 20% in rats. Data on absorption after inhalation are not available. Dibutylphthalate has a low toxicity after oral, dermal and inhalation exposure. Oral LD50 for the rat is $\geq$ 6300 mg/kg b.w. The dermal LD50 is > 20000 mg/kg bw for the rabbit. The 4 h LC50 inhalation for the rat is $\geq$ 15.68 mg/l. Dibutylphthalate is not irritating to the skin or eye and is not a skin sensitiser. Several studies are available for repeated dose toxicity. In a 3 month dietary study effects on haematology and clinical chemistry combined with liver effects and increased relative kidney weight were observed at $\geq$ 752 mg/kg bw. A NOAEL of 152 mg/kg bw was the lowest of the repeated dose toxicity studies. Neurofunctional tests did not show abnormalities. In studies with rats with special attention to testicular effects the LOAEL was 250 mg/kg b.w. In an inhalation study of 28-days duration in rats, no systemic effects including neurotoxic effects were observed up to and including the highest exposure concentration of 509 mg DBP/m^3. At all exposure concentrations (1.18, 5.57, 49.3 and 509 mg/m^3) adverse local (histopathological) effects in the upper respiratory tract were observed, but no signs of inflammation. In addition, at the highest exposure concentration of 509 mg/m^3 red crust formation at the snouts was observed after cessation of daily exposure (recovered within 18 hours) in a maximum of 4/10 animals at a maximum duration from day 13-27. It is concluded that 509 mg/m^3, the highest concentration tested, is a NOAEC for systemic effects including neurotoxic effects. The lowest exposure concentration of 1.18 mg/m^3 is a LOAEC for local effects in the upper respiratory tract.

Based on *in vitro* as well as *in vivo* genotoxicity studies and taking into consideration the non-genotoxic properties of other phthalate esters, dibutylphthalate can be considered a non-genotoxic substance.

Dibutyl phthalate is considered a reproductive toxicant; causing embryotoxicity and impaired fertility. Several studies on reproductive organs have been performed. In a one- and two-generation study, embryotoxicity such as effects on pup weight (both studies), growth of pups during entire lactation (first generation study) and number of live pups per litter (second generation study) were observed. In the first generation study after 7 weeks post weaning testicular effects, including histopathological effects

were observed at 500 mg/kg bw and some maternal toxicity. A NOAEL from this study was 50 mg/kg bw. The two-generation was performed with a continuous breeding protocol including improved sensitive endpoints (such as sperm parameters, estrous cycle characterization and detailed testicular histopathology) and with exposure of both male and female animals. The protocol of this study was supposed to adequately identify compounds with endocrine activity. In this study embryotoxic and testicular effect were observed at the lowest dose tested 52 mg/kg b.w. without maternal toxicity. Including all reproduction studies (the other studies showing similar effects at higher doses) a NOAEL of 50 mg/kg b.w. was derived. Developmental studies in rats with exposure during gestation or during gestation and lactation had delayed preputial separation and reproductive tract malformations in male offspring at oral dose-levels at $\geq$ 250 mg/kg bw. Maternal toxicity was seen at doses $\geq$ 500 mg/kg b.w. At the lowest oral dose-level of 100 mg/kg b.w. studied in developmental studies in rats, still delayed preputial separation in male progeny was seen. A NOAEL could not be derived for these studies. In some special *in vitro* studies DBP showed weak estrogenic activity. These effects were not confirmed in *in vivo* studies. Therefore the relevance of the estrogenic effects observed *in vitro* for the *in vivo* estrogenic toxicity of DBP is questionable. The results of a recent assay indicate an anti-androgenic activity of DBP. However, in contrast with classical anti-androgens DBP required dosing immediately following weaning for the induction of weight changes in male reproductive organs.

Environment

Both short-term and long-term dibutylphthalate toxicity data are available for aquatic organisms. There are also a number of studies with bacteria and protozoa's. Short term LC50-values for fish range from 0.35-7.3 mg/l. The NOEC for fish is based on *Oncorhynchus mykiss*: 100 µg/l. *Daphnia magna* EC50 values and other aquatic invertebrates range from 0.76 – 17mg/l. NOEC aquatic invertebrates range from 0.1- 1.05 mg/l. EC50 for algae range from 1.2-9 mg/l. NOEC algae range from 0.2-2.8 mg/l. For *Tetrahymena pyriformis* the EC50 was 2.2 mg/l, a NOEC Of > 10 mg/l for *Pseudomonas* was derived. For the terrestrial environment a NOEC of 200 mg/kg soil was derived for *Zea mays*. For the atmospheric compartment several studies on plants were available. Cabbage was found to be the most sensitive species. A NOEC could not be derived from a study on *Brassica*; the EC100 was 11.8 ug/m^3.

Exposure

In the EU dibutylphthalate is mainly used as a plasticiser in resins and polymers such as polyvinyl chloride. It is further used in printing inks, adhesives, sealants/grouting agents, nitrocellulose paint, film coating and glass fibres. The ubiquity of dibutylphthalate in consumer products is demonstrated by its wide usage in cosmetics: a perfume solvent and fixative, a suspension agent for solids in aerosols, a lubricant for aerosol valves, and antifoamer, a skin emollient and a plasticiser in nail polish and fingernail elongators. The total EU production volume for 1998 was estimated to be 26,000.

Identity and Physico-chemical properties

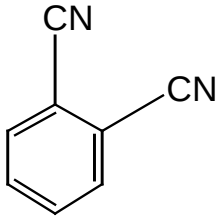
Dibutylphthalate is a oily liquid substance with a low vapour pressure (9.7 x 10^{-5} hPa, 25°C), low solubility in water (10 mg/l, 20°C) and log Kow of 4.57. Dibutylphthalate hydrolyses at pH 9 (50°C) with a half-life of 65.8 hours and is stable at pH4 and 7. The DT50 of dibutylphthalate in the atmosphere is estimated to be 1.8 days. Dibutylphathalate is considered as ready biodegradable. Henry's Law constants (0.27 Pa.m3/mol) indicate that DBP is distributed in air, water and soil. The bioaccumulation of the parent compound in fish is low. The experimental BCF value is 1.8, although 14C-based BCF is 2125 and is several orders of magnitude higher.

NATURE OF FURTHER WORK RECOMMENDED

There is a need for further information and further consideration of exposure and risk assessment for the environment and human health.

The substance has been agreed in the European Union Risk assessment program under Regulation EC. (No.) 793/93. The EU risk assessment concludes that for environment more information is needed on potential risks of dibutylphthalate on plants. For the occupational exposure, there is a need for limiting the risks for aerosol forming activities and adverse local effect due to repeated inhalation exposure cannot be excluded in all occupational exposure scenarios

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	91-15-6
Chemical Name	o-Phthalodinitrile
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The chemical is acutely toxic by ingestion (rat oral LD_{50}: 85 mg/kg bw). The major effect is neurotoxicity. No mortality by inhalation occurred in rats exposed to saturated atmosphere with low dust formation for 8 hrs at 20 °C. It is considered as non-irritating to the skin and eyes. There are no available information on skin sensitization. In compliance with an OECD combined repeat dose and reproductive/ developmental toxicity screening test [TG 422], the chemical was given to male and female rats by gavage at doses of 0, 1, 6, 30 mg/kg bw /day for at least 42 days. Histopathological examination for the males of 30 mg/kg bw /day revealed centrilobular hypertrophy of hepatocytes in the liver, hyaline droplets in the proximal tubular epithelium, basophilic degeneration of the renal tubules and atrophy of the seminiferous tubules with cell debris in the tubules. In addition, the number of sperm in the epididymis significantly decreased in males of 30 mg/kg bw /day. No adverse effects were observed at 6 mg/kg bw/day. In a 13-week oral feeding study with rats conducted according to OECD TG 408 and US EPA guideline for neurotoxicity study, a reduced body weight gain which correlated with a reduced feed consumption was described. The substance caused an increase in motor activity, but no macroscopical or neurohistopathological correlations were found in the central and peripheral nervous system. Clouding of the lens was detected in eye examinations at the end of the study in both sexes in the high dose group and in some females in the intermediate dose group, an effect that was not evident after 4 weeks. Therefore the NOAEL for repeat dose toxicity was prescribed 3 mg/kg bw/day.

For gene mutations, the test results were uniformly 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 mammalian cells *in vitro* because of an increase of polyploid cells. However, this chemical did not show any cytogenetic effects in the well-planned *in vivo* micronucleus test. A weight of evidence suggests this chemical is not genotoxic *in vivo*.

In the above screening test [OECD TG 422], this chemical was given from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. As all dams from the 30 mg/kg group died in late pregnancy, no data were obtained for after-delivery parameters. In the 1 mg/kg and 6 mg/kg groups, no changes due to administration of the chemical were observed. Therefore NOAEL for reproductive toxicity is considered to be 6 mg/kg/day in males and females. Any developmental toxicity including teratogenicity

was not observed up to 6 mg/kg/day.

Available data (on carcinogenicity) were found to be invalid.

Old report indicates that irritation of skin and mucous membranes and cases of acute intoxication with dizziness, vomiting, unconsciousness, epileptiforme convulsions, and retrograde amnesia were described in workers after exposure to skin and by inhalation during handling. However, a morbidity and a mortality study, and chromosome examinations in workers showed no abnormal findings.

Environment

This chemical has been tested in a limited number of aquatic species including fish, *Daphnia* and algae. For algae, acute toxicity values are 68 and 421 mg/L (72 h EbC_{50}) in *Selenastrum capricornutum* and *Scenedesmus subspicatus*, respectively. NOEC (72 h, biomass) of *Selenastrum* is 31.6 mg/L. For *Daphnia magna*, the acute toxicity values are 211 and 219 mg/L (48 h EC_{50} for immobilization), and the chronic value is 14 mg/L (21d NOEC for reproduction). For fish, only acute data are available; 96 h LC_{50} (*Oryzias latipes*) is 22.6 mg/L. PNEC of 0.14 mg/L for the aquatic organisms is calculated from 21 d-NOEC for *Daphnia* (14 mg/L) using an assessment factor of 100. This chemical is considered to be harmful to aquatic organisms.

Exposure

The production volume of this chemical in BASF AG Ludwigshafen, Germany was 1,000-5,000 t in 1999. The production volume is used as an intermediate (non disperse use) in chemical industry.

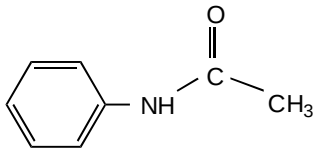
The substance is soluble in water (0.56g/l at 25 °C) and has no considerable potential for bio- and geoaccumulation. (BCF < 5.5, measured; log Kow=0.582 at 25°C) and turned out to be not readily biodegradable (OECD 301 E: 56-59 % after 4 days). However according to OECD 302 B the substance is inherently biodegradable with adapted inoculum (90-100 % after 12 days). In the atmosphere it is photodegraded very slowly (t1/2 = 350 d). Under environmental conditions no hydrolysis was observed. Distribution modeling using Mackay I indicates water to be the target compartment (99.4%) followed by air (0.6 %).

NATURE OF FURTHER WORK RECOMMENDED

O-Phthalodinitrile is an acute neurotoxicity hazard with effects seen at relatively low doses.

The chemical is a low priority for further work taking into consideration that it is manufactured at one site as a chemical intermediate. The SIAM was informed that exposure is adequately controlled at this site.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	103-84-4
Chemical Name	Acetanilide
Structural Formula	$CH_3CONHC_6H_5$ 

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acute toxicity of acetanilide is low since the LD_{50} of oral exposure in rats is 1,959 mg/kg bw.

For repeated dose toxicity, acetanilide was given by gavage at doses of 22, 67, 200, and 600 mg/kg/day to male rats for 30 days and to female rats for 39-50 days in accordance with an OECD TG 422 (combined repeated dose toxicity study with reproduction/developmental toxicity screening test). The adverse effects were red pulp hyperplasia of spleen, bone marrow hyperplasia of femur and decreased hemoglobin, hematocrit and mean corpuscular hemoglobin concentration. The LOAEL for repeated dose toxicity in rats was 22 mg/kg/day for both sexes.

Most of the *in vitro* mutagenic toxicity studies including the Ames assay, mammalian chromosomal aberration test, *Bacillus subtilis* recombination assay and SCE assay showed negative results. Regarding *in vivo* studies, a mammalian erythrocytes micronucleus test performed by OECD TG 474 showed negative results. Therefore acetanilide is not considered to be genotoxic. There is some evidence that this chemical is not carcinogenic in rats, mice and hamsters.

In a reproductive/developmental toxicity study performed according to OECD TG 422, no treatment-related changes in precoital time and rate of copulation, impregnation, pregnancy were shown in any treated group. However, viability of offsprings at 600 mg/kg bw/day and body weight of pups at 200 mg/kg/day were significantly reduced. At 600 mg/kg bw/day, four dams died and body weight was decreased at day 0 and 4 of lactation. At 200 mg/kg bw/day, there were signs of maternal toxicity (cf. repeated dose toxicity). The NOAELs for reproduction and developmental toxicity (offspring toxicity) are considered to be 200 mg/kg bw/day and 67 mg/kg bw/day, respectively.

This chemical is not irritating to skin, but slightly irritating to the eyes of rabbits. There is no information available on skin sensitization.

Environment

Physical-chemical properties of acetanilide are as follows: melting point 113.7 ºC, boiling point 304 ºC at 760 mmHg, water solubility 4 g/L at 20 ºC, Log Pow 1.16 at 23 ºC. EQC model of fugacity level I shows that the chemical will be distributed mainly to water. Acetanilide is readily biodegradable (MITI test : 68.7 % after 14 days as BOD) and an estimated BCF of 1.56 by BCFWIN model based on log Pow (1.16) implies that bioaccumulation of acetanilide is low.

Ecotoxicity data has been generated in a limited number of aquatic species of algae (72 hr-E_bC_{50} ; 13.5 mg/L), daphnid (48 hr-EC_{50} ; > 100 mg/L) and fish (96 hr-LC_{50} ; 100 mg/L). No data on prolonged fish toxicity and toxicity to terrestrial organisms are available. From the acute toxicity values, the predicted no effect concentration (PNEC) of 0.135 mg/L was derived using an assessment factor of 100.

Exposure

The total production of acetanilide was about 2,300 tonnes/year in Korea in 1998, and 196 tonnes in the USA in 1998. Acetanilide is mainly used as an intermediates for the synthesis of pharmaceuticals and as an additive in hydrogen peroxide, varnishes, polymers and rubber. The most probable human exposure would be occupational exposure through dermal contact or inhalation at workplaces where acetanilide is produced or used.

In Korea, 2,320 tonnes of the chemical was used as an intermediate for the synthesis of pharmaceuticals. Only a small amount of 120 kg was used as a stabilizer for hydrogen peroxide solutions for hair colouring agents in 1998 and based on general information the content of the substance in such preparations would be very low and the human exposure is insignificant. Readily available environmental or human exposure data do not exist in Korea at the present time. And potential exposure from drinking water, food, ambient water and in the workplace is expected to be negligible because this chemical is produced in a closed system in only one company in Korea.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-15-3
Chemical Name	Ethylenediamine
Structural Formula	NH_2-CH_2-CH_2-NH_2

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acute toxicity of ethylenediamine (LD50, rat, oral range from 637 mg/kg to 1850 mg/kg; LC50, rat, inhalation >29 mg/l and LD50, rabbit, dermal 560 mg/kg) is considered to be low to moderate. Due to the high alkalinity, ethylenediamine is corrosive to the skin and eyes. It is a dermal and respiratory sensitizer in humans and has been reported to cross-sensitize for chemicals of similar structure. In repeat dose studies, decreased body weight along with decreased water and feed consumption were observed. Every attempt was made to minimize the irritating nature of EDA and reduce the pH by using EDA-2HCL. Hepatocellular pleomorphism was noted in every study following dietary administration of longer than 13 weeks duration. Gavage administration resulted in effects in the eyes and kidneys. Kidney effects consisted of degenerative and regenerative changes in the tubular epithelium. The Lowest-Observable-Adverse-Effect-Level (LOAEL) is 100 mg/kg/day with a No-Observable-Effect-Level (NOEL) of 20 mg/kg/day observed in the chronic dietary feeding study. Ethylenediamine was rapidly excreted with most of the material eliminated in the urine within 24 hours. Ethylenediamine has produced weakly positive results, 2-3 times greater than control values, in several Ames tests, which may or may not be related to an impurity. Subsequent studies conducted with purer material were negative. All other tests including several *in vitro* assays (CHO gene mutation, sister chromatid exchange with CHO cells and UDS with primary rat hepatocytes) and a rat dominant lethal assay were negative. The weight of evidence from both *in vitro* and *in vivo* tests indicates that ethylenediamine is unlikely to be genotoxic. In chronic bioassays via two routes of exposure there was no carcinogenic effect. In developmental toxicity studies, growth retardation was noted at maternally toxic levels. However, there was no evidence of developmental toxicity at maternally toxic doses when compared with a pair-fed control. There was no effect on reproductive parameters at levels, which produced parental toxicity.

Environment

Ethylenediamine's vapor pressure is 12hPa at 20^0C, the log P_{ow} range is from –1.3 to –2.04 and the water solubility is110 g/L. It should be noted that while EDA does not have as high of a stability constant as several higher molecular weight ethyleamines, it does have the potential to chelate copper. Based on physical chemical properties, EDA is not expected to bioaccumulate. Ethylenediamine is expected to be readily biodegradable in the environment with > 80% degraded within 28 days. The estimated photodegradation half-life is 8.9 hours. Using the level III Fugacity Model by Mackay, most of EDA at steady state will partition to the water compartment. The 96 hr LC50 in fish is 115 mg/L while the 96 hr algae biomass EC50 is 61 mg/L. In the most sensitive aquatic organism, *Daphnia magna*, the 48 hr LC50 is 3-46 mg/L with a 21-day reproduction test No-Observable-Effect-Concentration (NOEC) of 0.16 mg/L.

Exposure

In the United States (US), ethylenediamine is a major industrial chemical used primarily as a closed-system intermediate in the production of chelating agents. It is also used to produce polyamide resins, ethylene bis-stearamide, gasoline and lube oil additives and cationic surfactants. Production in Western Europe is 58,000 tonnes, 41,000 tonnes in the US and 5,000 tonnes in Japan. In the US, environmental releases are not anticipated based on the manufacturing process and use conditions. Since it is primarily an industrial intermediate in the US, exposures are anticipated to be restricted to product transfer and maintenance operations. Exposures in the workplace are typically below 10 ppm (TWA). In the U.S., the only known use of EDA in consumer products is via the pharmaceutical industry in the production of aminophylline for the treatment of severe asthma. In the U.S. this use is regulated and restricted to consumers under medical supervision. Based on varied information provided by registries from some OECD member countries (Sweden, France, Switzerland, Finland and Denmark) it would appear that the concentration of unreacted EDA in products sold to consumers is low, typically less than 0.5%. However, it is recommended that each OECD Member country evaluate their exposure scenarios to determine the chemical's priority for further work.

NATURE OF FURTHER WORK RECOMMENDED

Based on data indicating EDA possibly being present in consumer products, national or regional exposure information gathering may need to be considered to clarify the possible extent of exposure to consumers.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-41-5
Chemical Name	Hexylene glycol (2-methyl pentane-2,4-diol)
Structural Formula	CH_3 CHOH CH_2 C (OH)$(CH3)_2$ (NB the commercial substance is a racemic mixture)

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Hexylene glycol is of relatively low acute toxicity to mammals, the acute oral LD_{50} is >2000 and <5000 mg/kg (range >2000-4700 mg/kg) while the dermal LD_{50} is >2000 mg/kg (range >1.84-12.3 g/kg). The acute inhalational LC_{50} is ≥ the saturated vapour concentration. Recent skin and eye irritation guideline studies indicate that hexylene glycol has low potential to irritate the skin and is slightly irritating to the eye. Skin and eye effects are reversible. Hexylene glycol is not a skin sensitiser.

Repeated exposure by oral gavage to rats at 50, 150 or 450 mg/kg/day hexylene glycol for 90 days, with additional animals at the top dose also allowed a 4 week exposure-free recovery period, resulted in hepatocellular hypertrophy and increased liver weight, male rat specific nephropathy and inflammatory changes in the forestomach and to a lesser extent the glandular stomach. The liver changes were reversible and considered an adaptive physiological response to increased metabolic demand. The male rat nephropathy was partially reversible and associated with an increased severity of acidophilic globules, subsequently identified by specific staining (Masson's trichrome) as alpha-2-microglobulins, and considered of questionable biological significance to humans. Changes in the stomach (reversible) and forestomach (partially reversible) were considered attributable to local irritation induced by the gavage procedure. The NOAEL for this local effect being 50 mg/kg/day. The systemic NOAEL for this guideline study is considered to be 450 mg/kg/day with a no effect level for local irritation to the stomach and forestomach of 50 mg/kg/day.

Hexylene glycol is not genotoxic in either mammalian or non-mammalian cells *in vitro*.

No standard fertility studies are available. No effects on the gonads were observed in a good quality 90-day oral gavage study in rats, which were, administered hexylene glycol at doses up to 450 mg/kg/day by oral gavage. Therefore no studies are required under the SIDS regarding fertility.

In a good quality developmental toxicity study, in which rats received 30, 300 or 1000 mg/kg/day hexylene glycol by oral gavage, the LOAEL for maternal toxicity was 1000 mg/kg/day, based on slightly reduced weight gain at this top dose level. Greater pre-implanation loss observed at this dose level may be regarded of questionable biological significance. This dose level was also the LOAEL for foetotoxicity based on a, slight delay in ossification, a greater number of fetuses with extra thoraco-lumbar ribs, and a slight decrease (not statistically significant) in foetal body weight. There was no evidence of teratogenicity up to the limit dose of 1000 mg/kg.

Environment

The environmental effects database meets the requirements of the SIDS data package. Hexylene glycol is of low acute toxicity to aquatic organisms. The lowest valid 96h LC50 for fish was 8510 mg/l (Mosquito fish, *Gambusia affinis*) and the lowest valid 48h EC50 for invertebrates was 2800 mg/l (*Ceriodaphnia reticulata*). Tadpoles of the frog *Rana catesbiana* were tested, with a 96 hour EC_{50} = 11800 mg/l.

The 72 hour EC_{50} for the freshwater alga *Selenastrum capricornutum* is >429 mg/l (highest level tested) based on both growth rate and biomass.

The $PNEC_{aqua}$ derived from the lowest toxicity value is 4.3 mg/l, based on an assessment factor of 100 applied to the algal EC50, in accordance with OECD guidance. No data are available on terrestrial or sediment organisms but PNEC values have been derived for the sediment and terrestrial compartments using equilibrium partitioning, 0.295 mg/kg wt for sediment and 0.0786 mg/kg for soil.

Exposure

The combined market for hexylene glycol in Europe and the USA for 2000 is 15000 tonnes. The principal end uses are in industrial coatings (45%) and as a chemical intermediate (20%). Hexylene glycol occurs as a component in a large number of products for industrial and consumer use.

Hexylene glycol is a liquid, melting point – 50°C, boiling point 197.5°C, vapour pressure 0.07hPa at 20°C, it is fully miscible in water and has a calculated n-octanol water partition coefficient (log K_{ow}) of 0.58. There are no aqueous streams from the production process but small amounts of hexylene glycol will be present in the output to the wastewater treatment plant from spills and cleaning operations. Hexylene glycol can also enter the aqueous and terrestrial environment from end uses such as in agricultural products and down hole lubricants for oil and gas fields. Under normal manufacturing practices there should be no emissions to the atmosphere. Low levels of emissions may occur as a result of spills and cleaning operations. The main application is in industrial surface coatings and there is potential here for release to the atmosphere.

There is a potential for occupational and consumer exposure through inhalation and skin contact although exposures through inhalation are expected to be low due to the low vapour pressure. Consumer exposure to hexylene glycol will occur principally through its use in cosmetics, antifreezes and hydraulic fluids. Exposure to aerosols is possible as a result of industrial spraying with paints containing hexylene glycol. Indirect exposures via the environment (e.g. ingestion of surface water contaminated with hexylene glycol) are also possible.

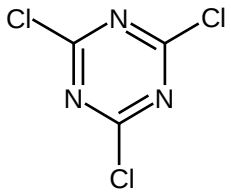
The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of hexylene glycol in air is 9 hours. Hexylene glycol is not expected to undergo direct photolysis and is not susceptible to hydrolysis.

Hexylene glycol is predicted to distribute in the environment primarily to water or water and soil. Based on a calculated log K_{ow} of 0.58 which suggests a log K_{oc} of <1, hexylene glycol has low potential to bioaccumulate (BCF=3) and low potential for sorption to soil. In water, hydrolysis and photodegradation are not expected to occur. Hexylene glycol is at least inherently biodegradable.

NATURE OF FURTHER WORK RECOMMENDED

No further work is indicated.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-77-0
Chemical Name	Cyanuric chloride
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acute toxicity of cyanuric chloride showed an oral LD50 of ~320 mg/kg bw and a dermal LD50 of >2000 mg/kg bw. The high acute inhalation toxicity of cyanuric chloride (LC50 170 mg/m^3) is likely to be secondary to its highly irritating/caustic properties. The compound is highly irritating to the skin, the eyes and the respiratory tract (RD50 5.9 mg/m^3). In humans exposure to cyanuric chloride causes irritation and caustic effects to the skin, eyes and respiratory tract. Cyanuric chloride is sensitizing. Asthma and contact dermatitis are also reported in humans.

In oral repeated dose studies cyanuric chloride induced body weight loss and stomach erosion and ulceration. In a 21-day dermal study decreased body weight was reported at 150 and 500 mg/kg bw. Severe dermal irritation was seen at all dose levels tested. Since it can not be excluded that the effects on body weight were secondary to stress by the treatment, no systemic NOAEL was derived. The LOAEL for local effects is 50 mg/kg bw. From a 90-day inhalation study a NOAEC of 0.25 mg/m^3 (the highest concentration tested) for systemic toxicity was derived. The NOAEC for local effects in the respiratory tract of rats displaying intercurrent respiratory infection was found to be 0.05 mg/m^3. The effects included inflammation in the nose and lungs.

For developmental toxicity an oral teratogenicity study is available. The NOAEL for maternal toxicity is 25 mg/kg bw, based on a decreased body weight gain. For developmental effects a NOAEL of 25 mg/kg bw was derived, based on increased post-implantation loss and a decreased number of fetuses at 50 mg/kg bw. In the 90-day inhalation toxicity study no effects on the gonads were found and therefore no studies of any effects of cyanuric chloride on fertility are required under SIDS.

Cyanuric chloride is found to be not mutagenic in the Ames test and the mouse micronucleus test.

Environment

Released cyanuric chloride will end up in surface water for ~99% (EQC-model). In water cyanuric chloride hydrolyses quickly to cyanuric acid via the intermediates 2,4-dichloro-6-hydroxy-s-triazine and 2-chloro-4,6-dihydroxy-s-triazine (DT_{50} < 5 hours). The DT_{50} for the disappearance of cyanuric chloride in aqueous medium is < 5 minutes.

Cyanuric chloride has a low vapour pressure and logKow of 1.7. Due to its low solubility (440 mg/L) and its hydrolysis properties, the actual concentration of cyanuric chloride in water is very low. For the biodegradation process of cyanuric chloride the hydrolysis products are much more relevant than cyanuric chloride itself. Studies on these hydrolysis products showed very limited biodegradability of these compounds under standard test conditions.

The toxicity of cyanuric chloride to aquatic organisms can not be determined in view of the hydrolytic properties of the substance. For the hydrolysis product 2-chloro-4,6-dihydroxy-s-triazine the LC50 in fish and the EC50 in daphnia were >2000 mg/L. For cyanuric acid the fish LC50 was >1000 mg/L and the daphnia EC50 was >1800 mg/L. No effects of cyanuric acid on algae were found in saturated medium. Algal toxicity was investigated for isocyanuric acid (72-h LC50 620 mg/L, NOEC 62.5 mg/L). No bioaccumulation in carps was found in a test with cyanuric acid.

Exposure

Yearly more than 100,000 tonnes of cyanuric chloride are produced. The compound is used exclusively as an intermediate in the production of pesticides (herbicides), optical brighteners, dyes and plastic additives.

Due to the fact that cyanuric chloride is almost exclusively used in closed systems, worker exposure is expected to be low or negligible. During production cyanuric chloride may be released to the environment via the waste water. The annual release into the atmosphere was 268 kg/year (1990/1991), Consumer exposure is considered not relevant in view of the use as an intermediate.

NATURE OF FURTHER WORK RECOMMENDED

No further work recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	109-66-0
Chemical Name	n-pentane
Structural Formula	CH_3-CH_2-CH_2-CH_2-CH_3

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

N-pentane is liquid at room temperature, and is extremely flammable. The low boiling point (36 ^oC) implies that the substance evaporates easily and inhalation is the predominant route of human exposure. A gas uptake study in rats demonstrated that n-pentane is rapidly eliminated by exhalation or metabolism. The half-life in rats is approximately 0.13 hours. Considering the rapid metabolism and excretion, tissue accumulation is expected to be low. In humans, the tissue/air partition coefficient was determined for several tissues. The highest tissue/air coefficient was measured in fat (39.6) and the lowest in heart (0.2).

N-pentane has a low acute oral and respiratory toxicity. The LD50 was greater than 2000mg/kg and the LC50 was 295,000 mg/m3 (98,662 ppm). However, at high air concentrations n-pentane has the potential to cause anaesthetic effects. Based on the values of kinematic viscosity of n-pentane (3.58×10^{-7} m^2/s), n-pentane is considered an aspiration hazard, as it may cause lung damage if swallowed. n-pentane is not considered irritating to eye, however, n-pentane is a slight skin irritant, and there is suggestive evidence that n-pentane is a slight respiratory irritant in mice. From clinical experience in man it is well known that solvents in general have a defatting action on the skin, which after repeated exposure may cause skin dryness and flaking. This may cause local skin reactions and enhancement in the penetration and uptake of toxic substances. No sensitising effect of n-pentane has been observed.

As regards repeated dose toxicity of n-pentane, no systemic toxicity was reported in a recent 13 week sub-chronic inhalation toxicity study in rats after exposure up to 20,000 mg/m^3 (6660 ppm) n-pentane the highest dose tested, and the NOAEL from this study was set at >= 20,000 mg/m^3. In a four week oral nephrotoxicity screening study no histopathological changes were noted in the kidneys in rats exposed up to 2000 mg/kg bw/day of n-pentane, however, mortality was reported at 500 mg/kg bw/day (2/10) and at 2000 mg/kg bw/day (4/10). In a 16 and 30 weeks neurotoxicity study, neurobehavioral effects were not observed after exposure to 8,970 mg/m^3 (3000 ppm). Normal pentane has been tested for mutagenicity in *in vitro* and *in vivo* studies. In these studies n-pentane was negative and is therefore considered to be non-mutagenic.

In a developmental toxicity study in rats the NOAEL was >= 1000 mg/kg bw for both the dams and the offspring, the highest dose tested. No fertility study for n-pentane is available, however, in the 13 week sub-chronic inhalation toxicity study in male and female rats no signs of toxicity were reported on the reproductive system by macroscopic or microscopic evaluation after exposure to n-pentane up to 20,000 mg/m^3 (6660 ppm). Therefore, further testing investigating effects on fertility after exposure to n-pentane is not considered necessary under the SIDS programme.

Environment

Due to the physical-chemical properties n-pentane released into the environment mainly (≈100 %) ends up in the atmospheric compartment, according to Macay level 1 model. In the aquatic environment n-pentane is expected to be stable to hydrolysis and photo-degradation. n-pentane is readily biodegradable, meeting the 10-day window criterion. The photochemical oxidative degradation half-life is estimated to be 3.95 days in the atmosphere. n-pentane indicates a moderate adsorption capacity with an estimated Koc of 784 l/kg. n-pentane has a log Kow of 3.45 and a calculated BCF of 171, indicating a potential for bioaccumulation. Due to rapid degradation and elimination of n-pentane bioconcentration in the food chain is not expected.

Toxicity studies are available for all trophic levels of aquatic species. The acute toxicity to fish *Oncorhynchus mykiss* was LC_{50} 4.26 mg/l. The lowest valid acute toxicity for invertebrates *Daphnia magna* was 2.7 mg/l. The EC_{50} for growth inhibition for the algae *Selenastrum capricornutum* based on growth rate was 10.7 mg/l. No information is available for the toxicity on micro-organisms and terrestrial organisms. No test data are available regarding toxic effects of n-pentane on plants.

An assessment factor of 100 was used to calculate the predicted no effect concentration (PNEC) for n-pentane in the aquatic environment, leading to a $PNEC_{aquatic}$ = 27 µg/l. This factor seems justified based on the chemical structure and since QSAR data are in agreement with the short term data for fish, crustaceae and algae, indicating that toxicity is through non-polar narcosis. By using the equilibrium partitioning method $PNEC_{sediment}$= 424 µg/kg wwt and $PNEC_{soil}$ = 494 µg/kg was calculated. No $PNEC_{STP}$ could be derived and since no effect data are available for plants no PNEC air can be estimated.

n-pentane contributes to tropospheric VOC and to the formation of tropospheric ozone. Green plants, animals and humans seem roughly to be equally sensitive to the toxic effects of ozone.

Exposure

n-pentane is a high production volume chemical, with a production volume of 55 Ktonnes in EU and a total EU consumption of estimated 50 Ktonnes (1994). Isolated n-pentane is distilled from crude oil. Isolated n-pentane is primarily used as foaming agent in the production of expanded polystyrene and polyurethane. It is also used as a process diluent in the polymer industry and as a solvent in aerosol formulations. Workers may also be exposed to n-pentane as well as consumers, the last via the use of hairspray and anti-persperant formulations, paints and car care products containing n-pentane.

n-pentane may be released to the environment when substances containing n-pentane or preparations thereof are produced, distributed and handled. Beside the releases from natural sources, non-isolated n-pentane is also emitted from the use and combustion of petroleum products, e.g. fuels. The latter sources may be of the same order or higher than releases from isolated n-pentane. They are likely to contribute to a considerable degree to the observed background concentrations in urban areas.

NATURE OF FURTHER WORK RECOMMENDED

The substance is currently of low priority of further work. However it is suggested that the information regarding contribution of n-pentane to tropospheric ozone formation be shared with regulatory agencies and international bodies responsible for air quality.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	112-57-2
Chemical Name	3,6,9-triazaundecamethylenediamine; tetraethylenepentamine (TEPA)
Structural Formula	$NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Use of Analog TETA to supplement TEPA data

Tetraethylenepentamine (TEPA) is similar toxicologically to triethylenetetramine (TETA) based on its structure and chelation properties. Therefore, data obtained using TETA have been used to address the endpoints for reproductive and developmental toxicity.

Human Health

Tetraethylenepentamine (TEPA) has a low acute toxicity when administered orally to rats (LD_{50} = 3250 mg/kg). In an acute inhalation toxicity study with saturated vapor and whole body exposure, the LC50 was calculated to be >9.9 ppm (highest dose tested). TEPA is corrosive to the skin and eyes of rabbits. TEPA is a skin sensitizer in the guinea pig. Dermal acute toxicity LD_{50} values in the rabbit range from 660 - 1260 mg/kg. The higher toxicity via the dermal route is most likely due to the corrosive nature of TEPA to the skin whereas TEPA would be neutralized by stomach acid.

The results of a 28-day repeated dose dermal toxicity study of TEPA indicated a systemic toxicity NOEL of 200 mg/kg/day and a dermal toxicity NOEL (local) of 50 mg/kg/day. The dermal LOAEL was 100 mg/kg/day. In addition, in a repeat dose study of TETA administered in drinking water to male and female rats for 90-92 days, the NOEL was 276 mg/kg/day in males and 352 mg/kg/day in females, the highest dose administered with the NIH-31 diet (several diets were used to study the effects of copper deficiency versus toxicity directly to TEPA). In this same study in mice the NOEL was 487 mg/kg/day in males and 551 mg/kg/day in females, the highest dose administered. A lifetime study was conducted via dermal administration in fifty male mice with a solution of 35% TEPA. There were 20 cases of hyperkeratosis, 13 cases of epidermal necrosis and no evidence of dermal hyperplasia.

There were no data available for TEPA for reproductive and developmental toxicity. As a result, data on TETA was used to address these endpoints. TETA data showed no effects on reproductive organs in rats up to 276 mg/kg/day (males) and 352 mg/kg/day (females) and in mice (up to 500 mg/kg/day) when administered in drinking water. TETA was not considered a developmental toxicant via dermal administration in rabbits at maternally toxic doses up to 125 mg/kg/day but showed developmental toxicity in rats at maternally toxic doses of 830 or 1660 mg/kg/day via drinking water. The maternal and fetal toxicity was most likely due to copper deficiency and zinc toxicity at these levels. Subsequent studies where the diet was supplemented with copper resulted in a decrease of fetal abnormalities. There were no standard fertility studies available. However, there were no effects on the gonads observed in a 90-day drinking water study in rats and mice as described above.

In the Ames Salmonella assay, TEPA was found to be positive both with and without metabolic activation. TEPA was

found to increase sister chromatid exchange in CHO cells and was considered positive in a UDS assay using rat hepatocytes. TEPA was not considered genotoxic in the mouse micronucleus assay and had equivocal results in the two dominant lethal assays in Drosophila melanogaster. Again, it is believed that the positive results are based upon TEPA's ability to chelate copper.

Environment

TEPA has the following physical chemical properties: melting point, -30 to –46 °C; boiling point, 20 °C, vapor pressure 1.07 x 10^{-6} hPa at 25 °C; partition coefficient –3.16 at pH 7; and it is completely miscible in water at 20 °C. The lowest acute EC/LC_{50} values of TEPA in fish (96-hr), invertebrates (48-hr) and algae (72-hr) are 310 mg/L, 14.6 mg/L and 2.1 mg/L, respectively. TEPA is not biodegradable (<10% after 28 days) and it should be noted that complexes of TEPA are expected to biodegrade even slower. However, TEPA is not expected to bioconcentrate due to its estimated low log K_{ow} of –3.16 and high water solubility. It should be noted that TEPA is protonated at environmental pH and the log K_{ow} is not a good indicator of the chemical's sorption behavior.

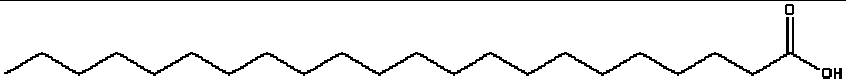
Exposure

TEPA, a synthetic, water soluble amine, is used primarily as a closed system intermediate in the synthesis of other products which are involved in the manufacturing of lubricating oil additives, fuel additives, paints and asphalt adhesives. As of 1998, US production of TETA, TEPA and higher molecular weight materials was 140 million pounds (63,636 tonnes). The source of release to the environment is primarily manufacturing sites. In the US, releases to the environment are anticipated to be small and limited to activities such as product transfer and maintenance operations. These activities could lead to TEPA being potentially released to surface water, air and soil. Based on well-controlled use and release from manufacturing sites, there is a low potential for exposure. In the US, there is no evidence to indicate that TEPA maybe present in consumer products. However, some other OECD member countries (Sweden, France and Denmark) records indicate that there is the possibility of TEPA being present in their consumer products. As a result, it is recommended that each OECD member country evaluate their own exposure scenarios to determine the chemical's priority for further work.

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	112-85-6
Chemical Name	Docosanoic acid
Structural Formula	 $CH_3(CH_2)_{20}COOH$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Oral LD_{50} value of docosanoic acid for rats is greater than 2,000 mg/kg. There are no available data for irritation and sensitization. In an oral study using the OECD combined repeated dose and reproductive/developmental toxicity test [OECD TG 422], docosanoic acid was administered to rats at doses of 0, 100, 300, 1,000 mg/kg/day for at least 42 days. No deaths occurred and also no substance related toxic effects were observed in any parameters. Therefore, the NOAEL is considered to be 1,000 mg/kg/day for both repeated dose toxicity and reproductive/developmental toxicity. The chemical was negative in both a bacterial mutation test [OECD TG 471, 472] and a chromosomal aberration test *in vitro* [OECD TG 473].

Environment

Docosanoic acid is stable in water but inherently biodegradable (OECD TG 301C: 48-56 % (BOD) after 28-day and OECD TG 302C: 79-96% (BOD) after 28 days). It is likely to be easily degraded in air by the reaction with photochemically produced OH radical (half-life time is estimated as 13.7 hours). Fugacity level III calculation shows that the majority of docosanoic acid is likely to be distributed into water and sediment when it is released into water environment.

Acute toxicity values of docosanoic acid on alga (*Selenastrum capricornutum*), aquatic invertebrate (*Daphnia magna*) or fish (*Oryzias latipes*) are greater than its water solubility (0.016 mg/L). The NOEC in a 21-day reproduction test with *Daphnia magna* is also greater than its water solubility. No significant effects are observed in any tests conducted at extremely high concentrations by using dispersant under OECD test guidelines [TG201, 202, 203, 204, or 211]. There is information that some fatty acids with shorter carbon chain caused no mortality at saturated concentration in certain aquatic organisms (gammarus in freshwater; Medaka in seawater condition). Considering from these data and additional information, it is reasonable to assume that docosanoic acid is not toxic to aquatic organisms at the concentration less than its water solubility (0.016 mg/L). A PNEC is not calculated since NOEC values obtained are above the water solubility of the substance.

Exposure

The production volume of docosanoic acid is estimated at 6,440 tonnes (Production; 5,960 tonnes, import; 480

tonnes) in Japan in 1999. Docosanoic acid is produced in two companies in Japan, and used as an intermediate for the production of its metal salts, docosylamine or higher alkyl esters in the chemical industry. The chemical is approved for use as a cosmetic ingredient in Japan. Docosanoic acid naturally occurs as triglyceride in most seed fats, animal milk fats, marine animal oils and so on.

The chemical seems to be released mainly into water from production and use sites after biological treatment.

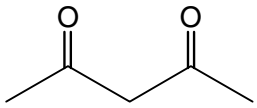
Occupational exposures through inhalation as its vapor or dermal absorption are assumed to be negligible because of the low vapor pressure and low water solubility. While this chemical is produced in a closed system in Japan, workers might be exposed by dust during packing process when the chemical is treated as powder. EHE_{inh} is calculated as 0.71 mg/kg/day (8h operation without protection, body weight; 70 kg, respiratory volume; 1.25 m^3/h). Workers are recommended to wear protective equipment (dust mask) during the work to avoid the exposure by dust. General population is indirectly exposed to this chemical through food consumption, since docosanoic acid exists naturally in various foods.

Docosanoic acid may be permitted for use in cosmetics in some region (e.g. Japan), however, no information is available on whether cosmetic products are available which contain docosaonic acid. Further information in this regard was not requested due to the low hazard profile identified for this substance.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-54-6
Chemical Name	2,4-pentanedione
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In acute toxicity studies the material proved to be moderately toxic after administration by the oral, dermal and inhalation route, respectively:

LD_{50} (oral, rat) = 570/760 mg/kg bw (f/m)
LC_{50} (inhalation, rat) = 5.1 mg/l/4 h (1224 ppm)
LD_{50} (dermal, rabbit) = 790/1,370 mg/kg bw (f/m)

The values obtained show that 2,4-pentanedione has to be regarded harmful by inhalation, in contact with skin and if swallowed. Also, animal studies on the primary irritancy of the substance demonstrated a low, if any irritation potential both to the skin and eyes after single exposure not leading to a classification as a skin and/or eye irritant. After repeated dermal application to rabbits local skin effects have been observed. Human data give a hint to a local irritating effect. Based on the poor data available the sensitising potential of 2,4-pentanedione cannot be evaluated.

In a 14 week repeated dose inhalation toxicity study in rats 2,4-pentanedione exerted substance related effects on hematological parameters, clinical and urinary chemistry at doses of 300 and 650 ppm (1,217 and 2,711 mg/m^3), respectively. On histopathology, no substance related gross lesions were detectable in the organs examined in all dose groups with the exception of different regions in the brain where hemorrhage and neuronal degeneration was observable at a dose of 650 ppm. In this study no pathological findings were made in the reproductive organs of animals of both sexes, especially in the testes of males. Based on reversible hematological, clinical as well as urinary chemical effects in the 300 ppm group and the histopathological findings in the brains and thymus in the 650 ppm group the NOAEL and LOAEL of this study is defined to be 100 ppm (417 mg/m^3) and 650 ppm (2711 mg/m^3), respectively. These doses can be converted to a NOAEL of 144.1 mg/kg bw/d and a LOAEL of 936.7 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250 g/rat. After repeated treatment of rabbits dermally, effects on thymus, spleen and lymph nodes, hemorrhage and neuronal degeneration in several sections of the brain were seen. After administration by the oral route substance related systemic effects were evident in thymus, liver, lungs, kidneys, bladder and lymph nodes.

No mutagenic effects were seen in the Ames test (except slightly mutagenic effect in the *Salmonella typhimurium* strain TA104) and in the HPRT-assay. A positive clastogenic effect in CHO cells was observed in the absence of metabolic activation. All *in vivo* genotoxicity studies conducted in rats and mice by inhalation did neither increase the number of structural or numerical aberrations nor the number of micronuclei. In contrast 2,4-pentanedione was shown to produce statistically significant increases in the incidence of micronucleated PCEs in mice but not in rats after i.p. administration. Concerning effects on germ cells a dominant lethal assay showed slight effects on fertility parameters in the (untreated) pregnant females mated with substance treated males being exposed via the inhalation pathway, which are regarded as a consequence of an unusual low control value. In an *in vivo* mouse spermatogonia assay 2,4-pentanedione did not produce chromosomal aberrations after oral administration to male mice at a dose

close to the MTD. Overall 2,4-pentanedione shows a direct clastogenic potential *in vitro* which is not expressed *in vivo* by the inhalational route.

There is no reproductive toxicity study available, however the investigations of the reproductive organs of a 14-week inhalation study in rats did not show any effects. The reported effects in the dominant lethal tests in rats were evaluated as not induced by the substance. No chromosomal aberrations were observed in spermatogonia of mice. Therefore no further studies are required under the SIDS regarding fertility.

In an inhalation teratogenicity study in female F344 rats the material did not produce teratogenic effects. Fetotoxic effects (reduced fetal weights in male fetuses) were observed at 200 ppm (=834 mg/m^3) without signs of maternal toxicity. In addition, at 400 ppm (= 1,668 mg/m^3) reduced fetal weights in fetuses of both sexes and a consistent pattern of reduced fetal ossification and skeletal variations as well as reduced maternal weight occurs. The NOAEL for maternal toxicity was 200 ppm (=834 mg/m^3 = 288.2 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250g/rat) based on total resorption of litters in two dams and significantly reduced body weight gain in the 400 ppm group only. The NOAEL for developmental toxicity was determined to be 50 ppm (= 209 mg/m^3 = 72.2 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250 g/rat).

Environment

Due to both the vapour pressure and moderate volatility from water of 2,4-pentanedione (9.2 hPa at 20°C and 0.555 Pa x m^3/mol) release to and exposure via the atmosphere constitutes only a minor pathway. The material is readily soluble in water (166 g/l) and according to the log P_{OW} determined (measured: 0.34 and 0.40) no potential for bio- and geoaccumulation exists. According to a Mackay I calculation the target compartment is the hydrosphere (≈ 90 %) followed by air (≈ 10 %). In the atmosphere a half-life for hydroxyl-radical mediated photodegradation of 14 days at a hydroxyl radical concentration of $1.5x10^6$ hydroxyl radicals/cm^3 was calculated. In a MITI I test the substance was found to be readily biodegradable.

Based on the results of acute aquatic toxicity testing the substance has to be regarded as harmful to aquatic organisms which is supported by chronic toxicity tests performed in *Daphnia magna*:

LC_{50} (96 h)	= 60.1 mg/l (*Lepomis macrochirus*)
EC_{50} (48 h)	= 34.4 mg/l (*Daphnia magna*)
IC_{50} (24 h)	> 300 mg/l (green algae, mainly *Scenedesmus sp.*)
LOEL (EC_{16}, 14 d)	= 0.50 mg/l (*Daphnia magna*)
TT (EC_3, 8 d)	= 2.7 mg/l (*Scenedesmus quadricauda*)

From the LOEL of 0.50 mg/l obtained in a chronic toxicity test conducted in *Daphnia magna* a NOEL of 0.25 mg/l was derived yielding a PNEC of 5 µg/l applying a safety factor of 50. The test was performed over a period of only 14 days without analytical monitoring of the substance concentration. Therefore as it cannot be excluded that the NOEC from a 21day test with analytical monitoring is lower and the PNEC has to be regarded as tentative. A high acute/chronic ratio was found for *Daphnia magna*. As the substance is known to be a nerve toxin, also for fish a high acute/chronic ratio can be assumed.

Exposure

2,4-Pentanedione is produced by a German and US-American manufacturer. Worldwide production figures for 2,4-pentanedione exceed 1,000 tons/year for each of the producers and is estimated to be 10,000 t/a. The main use is as a chemical intermediate in the production of pharmaceuticals, dyes and plant protection products, respectively. It is also applied in catalyst systems for the polymerisation of olefins and for the control of curing rates in polyurethane coatings. Other uses are found as gasoline and lubricant additives, driers for varnishes and printers inks and colors. The parent compound is also converted to metal-acetoacetonates, which in turn are used as stabilizers in PVC for instance. No information is known regarding procedures applied by industrial customers. Product register information indicates that products may contain the substance in considerable amounts. Product types are e.g. paints and lacquers, cleaning agents and solvents. Among the products there are several for private use.

NATURE OF FURTHER WORK RECOMMENDED

Environment: The substance is a candidate for further work. As for daphnids a high acute/chronic ratio was found and the substance is known to be a nerve toxin, a high acute/chronic ratio is also assumed for fish. From product registers the use of the substance other than intermediate is evident. Therefore, an exposure assessment, and if then indicated an environmental risk assessment should be performed.

Human Health: The substance is a candidate for further work. In occupational settings where exposure is not controlled and due to information of European product registers exposure to consumers and workers cannot be excluded. As the extent cannot be estimated, a human exposure assessment and, if then indicated, a risk assessment should be performed.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	127-19-5
Chemical Name	N,N-Dimethylacetamide (DMAC)
Structural Formula	$CH_3CON(CH_3)_2$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

DMAC is well-absorbed orally, by inhalation and dermally. There are adequate data with which to evaluate the potential hazard to human health of this compound. DMAC has low toxicity by ingestion: the oral LD 50 ranges from 3000 mg/kg bw to 6000 mg/ Kg in rats and > 5000 mg/Kg bw in rabbits. The chemical is harmful by dermal route and inhalation: dermal LD 50 values were 7500 mg/kg bw in rats, 9600 mg/Kg bw in mice, from 2100 mg/kg bw to 3600 mg/Kg bw in rabbits, but less than 940 mg/ kg bw in guinea pig. Inhalation LC 50 rat was 8.81 mg/l, 1h (˜ 2.2 mg/l, 4h) and LC 50 mouse was 1.47 mg/l, 3.5 h. DMAC is not a skin sensitiser or skin irritant and was only slightly irritating to the eyes. In repeated dose studies (14 days to 2 years) NOAECs of 25 ppm (0.09 mg/l) and higher have been observed in inhalation studies with rats and mice. Effects observed included liver degeneration, some irritation to the respiratory tract and decreased body weight gain. A NOAEL oral of 300 mg/Kg, 24 months, has been observed in oral studies with rats. Observation included kidney and adrenal weights. DMAC does not show mutagenic effects in several *in vitro* and *in vivo* tests. UDS in human diploide fibroblast and a transgenic mouse mutation assay on liver tissue are negative. For the *in vivo* tests two dominant lethal assays with rat (dermal and inhalation) were negative and dominant lethal assays on mouse (dermal, inhalation and i.p.) were negative too. A cytogenetic assay on human lymphocytes from 20 workers who were in contact with DMAC didn't reveal an increase in the frequency of chromosome aberration. DMAC was not carcinogenic in a two year drinking water study and a two year inhalation study in rats and to an 18 months inhalation study in mice. DMAC has been extensively studied for reproductive toxicity properties. Fertility was not affected when male rats had been exposed to up to 386 ppm (1.4 mg/l) in a 43 days inhalation study and in a 10 weeks one-generation inhalation study up to 300 ppm (1.08 mg/l) (females also were exposed). No effects in mice were observed in a sperm abnormalities test with exposures up to 700 ppm (2.52mg/l)for 6 weeks. Developmental toxicity was also investigated: the inhalation study in rats showed no adverse effects at the highest concentration, 300 ppm (1.08 mg/l), other than reduced maternal and fetal weight. The rabbit inhalation study showed a small increase in cardiac malformations at 570 ppm (2.052mg/L), in absence of maternal toxicity signs. The oral studies (rat and rabbit) indicate that high doses can cause both maternal and embryofetal toxicity. In an oral study on rat at 65, 160, 400 mg/kg bw/day the highest dose of DMAC was able to induce specific teratogenic effects such as great vessel malformations and anasarca at maternal toxic levels and the NOEL is 160 mg/kg bw/day. These findings were confirmed by a second oral study on rat performed at the same dose levels, from which a NOEL of 65 mg/kg bw/day can be derived. Due to the observed signs of specific developmental toxicity DMAC has to be considered a developmental toxicant.

Effects seen in the dermal studies (rat and rabbit) occurred at high and generally maternotoxic doses. A recent *in vitro* embryotoxicity study has been performed and embryotoxicity and teratogenic effects were observed at the highest levels. A NOEC was derived, corresponding to an *in vivo* NOEL of 100 ppm as the concentration in the

plasma after the exposure to 100 ppm in air in another study, may be similar to the NOEL observed in this study. Liver impairment was observed in 19 out of 41 workers who had been working from 2 to 10 years in a spinning unit (airborne levels were not reported). Upper respiratory tract, gastric and nervous disturbances were complained. Biological monitoring of workers exposed to DMAC in an acrylic fibre plant was performed: brief threshold limit value-level exposures and chronic low level exposure do not cause hepatotoxic clinical chemistry responses. A retrospective epidemiologic study was undertaken in 571 workers with a 12-months simultaneous exposure to acrylonitrile and no relationship between tumors and DMAC exposure was found. Also dermal absorption and inhalation of DMAC in human volunteers was carried out. They were exposed twice to DMAC for 4 h at intervals of 96 h or above to 6.1 ppm). Mean dermal absorption was estimated to be 40.4% of the total DMAC uptake. DMAC vapour was significantly absorbed through the skin. Biological half lives of urinary MMAC were 9h for skin and 5.6 h for lung respectively.

Environment

Releases of DMAC to the environment are to be expected with waste water (treated), solid wastes (incinerated), exhaust gas (in air by vent), and a residue in the raw acrylic fibres is < 0.5% by weight and in the raw elastane yarns from 0.1% to 3% by weight. DMAC has been tested in aquatic species: alga *Scenedesmus* 72 h -EC50 > 500 mg/l; daphnia 48 h- EC 50 > 500 mg/l, fish acute toxicity 96 h- LD 50 > 500 mg/l. A NOEC for *Daphnia* at 48 h is 1000 mg/l and for *Mysidopsis bahia* a NOEC at 96 h is 320 mg/l. Therefore DMAC is not acutely toxic to aquatic organisms. From the EC50 value for alga *Scenedesmus* of 500 mg/l a $PNEC_{aqua}$ of 0.5 mg/l can be derived by applying an assessment factor of 1000. This factor is justified as long term effect values are not available.

Exposure

The worldwide production volume of Dimethylacetamide in the year 2000 is estimated to be from 50000 to 60000 tons/ year. The substance is mainly used for polymer dissolution in the man-made fibre production industry. It is produced in closed system and processed at the production sites (non dispersive use). DMAC production is limited to the replacement of losses occurring during the production, processing and recovery. DMAC is also used in fine chemical industry. It is not intended to be used by the general public. DMAC is a colourless liquid, completely miscible with water, with a vapour pressure of 1.76 hPa at 20°C. It doesn't hydrolyse and undergoes photochemical degradation with half-life time of 6.1 hours. A bioconcentration factor (BCF) of 0.008, calculated from log octanol-water partition coefficient (log Kow) of –0.77, indicates a low bioaccumulation potential in aquatic species. A low adsorption to soils and sediments can be assumed by a calculated Koc of 9.1. DMAC is inherently biodegradable (77-83 % after 14 days). Distribution MacKay model indicates that considering a release of DMAC into the air, it is likely to be transported in water and soil.

Occupational exposure may occur through dermal contact and vapour inhalation during the use of DMAC. No exposure is envisaged during production and recovery of DMAC as this takes place in a closed system. An air extraction equipment placed above the processing units was adopted to limit any exposure and workers wear solvent-proof gloves during some critical operations, such as fibre spinning, so significant exposure is not expected.

Consumer exposure is negligible as results from migration tests with simulated sweating on textile articles containing residual DMAC (from 0.01% to 0.001%).

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1310-58-3
Chemical Name	Potassium hydroxide
Structural Formula	KOH

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Solid KOH is corrosive. Depending on the concentration, solutions of KOH are non-irritating, irritating or corrosive and they cause direct local effects on the skin, eyes and gastrointestinal tract. Systemic effects are not to be expected. Solutions with concentrations higher than 2% are corrosive, while concentrations of about 0.5 to about 2.0 % are irritating. No studies are available for repeated dose toxicity, *in vivo* genotoxicity, toxicity to reproduction and development.

The reported oral rat LD50 values are 365, 273 and 1230 mg/kg bw/day. Based on the data with other potassium compounds, it could be concluded that potassium has no or a negligible contribution to the toxicity at lethal dose levels of KOH. With KCl, the NOEL in rats for repeated dose toxicity is > 1820 mg/kg bw/day, and > 88-108 mg/kg bw/day in women, and for reproduction/developmental toxicity, > 235 and > 310 mg/kg bw/day for, respectively, mice and rats. With K_2CO_3, the teratogenic NOEL values could be established as > 290 mg/kg bw/day for mice, and > 180 mg/kg bw/day for rats. Under normal handling and use conditions (non-irritating) neither the concentration of potassium in the blood nor the pH of the blood will be increased above normal limits and therefore KOH is not expected to cause systemically toxic levels in the blood. The renal excretion of K^+ can be elevated and the OH^- ion is neutralised by the bicarbonate buffer system in the blood. It can also be stated that the substance will neither reach the foetus nor reach male and female reproductive organs in effective toxic concentrations. Therefore, no risk for reproductive toxicity is expected. An *in vitro* genetic toxicity test indicated no evidence for a mutagenic activity. No mutagenic activity was found for the related substances NaOH (both *in vitro* and *in vivo*) nor KCl and K_2CO_3 (*in vitro).*

Dust formation is unlikely because of the hygroscopic properties. Furthermore KOH has a negligible vapour pressure and is rapidly neutralized in air by carbon dioxide and therefore dust and vapour exposure are not expected.

Based on the available literature, there is a risk for accidental and intentional exposure to solid KOH or to irritating or corrosive solutions of KOH. Most of the ingestion accidents seem to be related with children and seem to occur at home. Accidental skin and eye exposure seems to be less frequently reported than ingestion in the medical literature.

Environment

The hazard of KOH for the environment is caused by the hydroxyl ion (pH effect). For this reason the effect of KOH on the organisms depends on the buffer capacity of the aquatic or terrestrial ecosystem. Also the variation in

acute toxicity for aquatic organisms can be explained for a significant extent by the variation in buffer capacity of the test medium. The LC50 value of acute fish toxicity was in the order of 80 mg/l. It was 880 mg/l for KCl and ranged between 125-189 mg/l for NaOH. The LC50 values of acute invertebrate toxicity for KCl was 660 mg/l (*Daphnia magna*) and 630 mg/l (*Ceriodaphnia dubia*), and for NaOH 40 mg/l (*Ceriodaphnia dubia*). The EC50 algae value (*Nitscheria linearis*) was 1337 mg/l for KCl.

Because the buffer capacity, the pH and the fluctuation of the pH are very specific for a certain ecosystem, it was not considered useful to derive a PNEC. If it is assumed that the upper pH limit for the protection of fish is 9 (according to Directive 78/659/EEC), this limit would be attained with 0.56, 0.86, 4.51 and 8.30 mg/l KOH in, respectively, distilled water, soft water (20 mg/l HCO_3^-), normal hardness water (106 mg/l HCO_3^-) and high hardness water (195 mg/l HCO_3^-). To assess the potential environmental effect of a KOH discharge, the pH change of the receiving water should be calculated or measured and compared with the natural variation of the receiving water. Based on this comparison it should be assessed which amount and pH of the effluent are acceptable under specific local situations.

Some few uses of KOH could result in an emission of KOH leading to a local increase of the pH in the aquatic environment. However, the pH of effluents is normally measured very frequently and can be adapted easily and therefore a significant increase of the pH of the receiving water is not expected. Generally the change in pH of the receiving water should stay within a tolerated range of the pH at the effluent side and for this reason no adverse effects on the aquatic environment are expected due to production or use of KOH, if emissions of waste water are controlled by appropriate pH limits and/or dilutions in relation to the natural pH and buffering capacity of the receiving water.

Aquatic potassium emissions originating from uses of KOH are probably small compared to other sources. It is clear that an environmental hazard assessment of potassium should not only evaluate all natural and anthropogenic sources of potassium but should also evaluate all other ecotoxicity studies (e.g. with potassium salts), which is beyond the scope of this report.

Exposure

Estimated world-wide demand of potassium hydroxide was higher than 1 million tons expressed as KOH 100% in 1994. The global demand is expected to grow with 4.0% per year. KOH is a white and deliquescent solid with a low vapour pressure. It is a strong alkaline substance that dissociates completely in water to potassium and hydroxyl ions.

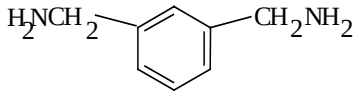
KOH is commercialised as a solid or as solutions with varying concentrations. It has many industrial uses; less than 2% is for wide dispersive use. It is used in paint and varnish removers, drain cleaners, degreasing agents and dairy pipeline cleaners.

NATURE OF FURTHER WORK RECOMMENDED

Environment and Human Health: no further work is recommended if sufficient control measures are in place to avoid significant human and environmental impact, including prevention of accidental exposure.

Due to the corrosivity of the substance, no further studies are required under SIDS programme.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1477-55-0
Chemical Name	1,3-bis(aminomethyl)benzene
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information on toxicokinetics. The toxicity of this chemical is entirely consistent with its corrosiveness at the site of first contact.

Oral LD_{50} of rats was 1090 mg/kg for males and 980 mg/kg for females [OECD TG 401]. The oral LD_{50} of mice was 1180 mg/kg [OECD TG 401]. The inhalation LC_{50} (4h) of rats was 0.8 mg/L for females but it was presumed to be more than 1.42 mg/L for males. The toxicity via oral administration and inhalation was tissue damage in the digestive and respiratory organs, respectively, which are the first contact sites. The chemical is corrosive to rat and mouse skin and a sensitiser in the guinea pig maximisation test.

In the 28-day repeated dose toxicity study [OECD TG 407], the chemical was given to rats by gavage at doses of 0, 10, 40, 150 and 600 mg/kg b.w/day. One male and four females died, and salivation, low locomotor activity and piloerection were noted in the 600 mg/kg group. Furthermore, ulceration, acanthosis with hyperkeratosis and submucosal inflammation were observed in the forestomach. No adverse effects were observed in the 150 mg/kg and the lower dose groups.

A reproductive /developmental toxicity screening test [OECD TG 421] of rats by gavage at 50, 150 and 450 mg/kg b.w/day for at least 41 days resulted in death in one male in the 150 mg/kg group, and three males and one female in the 450 mg/kg group. In almost all 450 mg/kg animals, the same histopathological changes as the above 28-day study were observed in the forestomach. No adverse effects were found at 50 mg/kg b.w/day.

Based on this information, the NOAEL for repeated dose toxicity is considered to be 50 mg/kg b.w/day.

In the above reproductive/developmental toxicity screening test [OECD TG 421] the substance was administered from 14 days before mating to 20 days after mating in males and to day 3 of lactation in females. No adverse effects were observed in terms of copulation, fertility, delivery and nursing of parents, and the viability, body weight and morphology of offsprings. The NOAEL for reproductive/developmental toxicity (F1 offspring) was 450 mg/kg b.w/day.

The chemical was not mutagenic in bacteria [OECD TG 471 & 472]. It induced neither chromosomal aberrations in

mammalian cells *in vitro* [OECD TG 473] nor micronuclei in mouse bone marrow *in vivo* [OECD TG 474].

In clinical observation of workers during the manufacturing process, the chemical appears to act as a gastrointestinal irritant. It has also been shown to cause contact sensitisation reactions in workers at concentrations equal to and below 0.1 mg/m^3 (the occupational threshold limit value in the US).

Environment

The chemical has a log Pow value of 0.18 at 25 °C, a vapour pressure of 0.04 hPa at 25 °C, and a water solubility of > 100 000 mg/L. Fugacity model Mackay level III calculations suggest that the majority of the chemical would distribute to soil if released to soil and/or air compartment(s), and water if released to aquatic compartment.

The chemical is not readily biodegradable (49% after 28 d) or inherently biodegradable (BOD = 22%, TOC = 6% and analysis in HPLC = 21%) and it does not hydrolyse (half-life >1 y at 25 ^{o}C). However, the chemical does not bioaccumulate (BCF < 2.7 at 0.2 mg/L). The chemical will react with carbon dioxide to form the carbamate acid, and will undergo indirect photo-oxidation with hydroxy radicals ($T_{½}$ 5.39 h), and will therefore not persist in the atmosphere.

Acute toxicity data were available for three kinds of fish (Medaka, 96hLC_{50} = 87.6 mg/L; Golden orfe, 96hLC_{50} = 75 mg/L and Rainbow trout, 96hLC_{50} >100 mg/L). In *Daphnia magna*, acute toxicity values of 48hEC_{50} = 15.2 mg/L and 48hEC_{50} = 16 mg/L were reported. The chronic toxicity data for *Daphnia magna* were 6.77 mg/L EC_{50} (21d, reproduction inhibition) and 4.7 mg/L NOEC (21d, reproduction inhibition). The parental toxicity for *Daphnia magna* was 8.4 mg/L 21dLC_{50}. The results in algae were E_bC_{50} = 12 mg/L and NOEC = 6.25 mg/L (*Scenedesumus subspicatus*) and E_bC_{50} = 20.3 mg/L and NOEC (0 to 72 h) = 10.5 mg/L (*Selenastrum capricornutum*).

The predicted no effect concentration (PNEC) of 0.047 mg/L is estimated from the lowest chronic value (NOEC of 4.7mg/L, *D. magna* reproduction), by applying an assessment factor of 100 because two chronic studies are available (that is, in algae and daphnia).

Exposure

Production of the chemical in Japan is ca. 13 000 t/y (1999 – 2000). The chemical is an intermediate in the production of epoxy curing agents, polyamides and polyurethanes. Due to the chemical binding processes that occur during curing, finished products do not contain the chemical. The substance is also not present in the industrial intermediates used in the production of polyamides and polyurethanes, but a few percent is present in the epoxy curing agent. The great majority of the epoxy curing agent is assumed to be used by industrial or professional users. Greater than 99.9% of the substance is used in three categories: polyamide (major), epoxy curing agent, and polyurethane production.

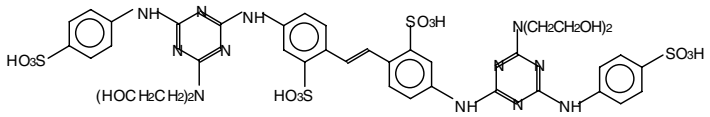
Based on the chemical nature, physico-chemical properties and the annual production amount, a Mackay level III fugacity model calculation shows that the chemical would distribute mainly into water. However, the use as an intermediate indicates that most of the chemical will be consumed in the reaction process. Environmental exposure from manufacture is considered to be negligible, because aqueous waste from plant cleaning is sent to a waste-water treatment plant before release and exhaust gases are sent for incineration.

The manufacture of epoxy resins and other compounds are conducted in closed systems. Occupational exposure limit values are set world-wide as 0.1 mg/m^3 15 min STEL. In a model workshop system, MXDA airborne concentrations varied from 0.064 to 0.229 mg/m^3 without ventilation and 0.018 to 0.051 mg/m^3 with ventilation. The EASE model gave a dermal exposure (non-dispersive use, indirect handling) of much less than 0.1 mg/cm^2/day. Personal protective equipment (vapour masks, goggles, overalls, gloves) is worn during operations such as drum filling. For inhalation exposure, the expected human exposure (inhalation) would be EHEinh =0.0073 mg/kg/day on the highest vapour concentration of 0.051 mg/m^3 in the model workshop system. If absorption occurred through hands and forearms, the calculated EHEder would be 0.03 mg/kg/day.

NATURE OF FURTHER WORK RECOMMENDED

The substance is not a priority for further work in relation to the use of the substance as an intermediate in a closed system.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	16470-24-9
Chemical Name	Fluorescent Brightener 220
Structural Formula	 • 4 Na

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute oral and dermal toxicity is low: oral: LD50 > 15000 mg/kg bw (rat); dermal: LD50 > 2000 mg/kg bw (rat). In the available tests of restricted validity C.I. Fluorescent Brightener 220 is not (after short exposure) or slightly (after prolonged exposure) irritating to the skin and slightly irritating to the eyes. A repeated insult patch test in 103 human volunteers showed no indication of irritation or skin sensitization after application of 0.1% test substance. In a 2-year feeding study in rats there were no adverse effects observed at the highest dose level: NOAEL = 10000 ppm (521 mg/kg bw/day for males; 709 mg/kg bw/day for females). There was no induction of gene mutation in bacteria. There was no induction of cytogenetic effects in an *in vitro* chromosome aberration test in V79 cells, in an *in vivo* chromosome aberration test in spermatogonia (hamster), in a micronucleus test (mouse) and in a dominant lethal test (mouse, OECD TG 478, GLP). A 2-year feeding study in rats did not result in any carcinogenic effects. A 2-generation study in rats showed no evidence of reproduction toxicity (EPA OPPTS 870.3800, GLP): NOAEL = 300 mg/kg bw/day (parental toxicity); NOAEL = 1000 mg/kg bw/day (reproductive performance and offspring toxicity). Two studies revealed no evidence of teratogenicity in rats and rabbits (EPA OPPTS 870.3700, GLP): rat: NOAEL = 1000 mg/kg bw/day (maternal and fetal toxicity); rabbit: NOAEL = 100 mg/kg bw/day (maternal and fetal toxicity).

Environment

C.I. Fluorescent Brightener 220 is a salt with a melting point of > 300 °C. The substance is soluble in water with 377 g/l at 20 °C. In view of the melting point, the vapor pressure is predicted to be low. Nevertheless a log Kow is calculated to be -2.83.

The calculation of a Mackay fugacity model is not appropriate for this substance. From the physico-chemical properties it could be concluded that the sole target compartment for C.I. Fluorescent Brightener 220 is water, as the substance is a salt. However, as a high adsorption to soil was experimentally determined, it has to be assumed that the substance will strongly adsorb also to the sediment compartment as well. The substance is not readily biodegradable. Monitoring data showed the substance to be removed by >75 to >95 % through adsorption from sewage. Direct photolysis is a second elimination process for Fluorescent Brightener 220 in the upper layer of surface waters with t½ in the range of 3.9 to 5.2 hours. Presently, there is no information about photolysis products. The calculation of the indirect photolysis showed a mean t ½ of 1.6 hours for cis- and trans-isomers C.I. Fluorescent

Brightener 220 by OH radicals as well as by ozone. Although measured data on bioaccumulation are lacking, it can be concluded from the ionic nature, that the bioaccumulation potential of C.I. Fluorescent Brightener 220 is not significant via the water phase. However, bioaccumulation from the sediment by benthic organisms cannot be excluded.

According to measured data on soil adsorption Fluorescent Brightener 220 can be regarded as a substance with high geoaccumulation properties, as Koc values up to 10,000 were found.

The acute toxicity has been determined for fish, daphnia and algae as follows:

fish (*Brachydanio rerio*) with a 96 h-LC_0 > 1000 mg/l and a 14 d-NOEC of > 859 mg/l
daphnia (*Daphnia magna*) with a 48 h-EC_0 of >= 113 mg/l and a 24 h-EC_{50} > 1000 mg/l
algae (*Scenedesmus subspicatus*) with a 96 h-EC_{50} > 1000 mg/l.

Chronic toxicity has been tested for Daphnia magna with a 21 d-NOEC of 10 mg/l on reproduction and for algae (*Scenedesmus subspicatus*) with a 96 h-EC_0 of 500 mg/l. A PNECaqua of 0.2 mg/l is derived from the 21 d-NOEC for Daphnia using an assessment factor of 50. For sediment organism no effect values are available. At a screening approach a PNECsed can be estimated via the equilibrium partitioning method. A PNECsed of 4.3 mg/l was derived. Acute toxicity on *Eisenia fetida* was tested in a limit test according to OECD guideline 207. The 14 d-LC50 was > 10,000 mg/kg. With an assessment factor of 1000, a PNECsoil of 10 mg/kg can be derived.

Exposure

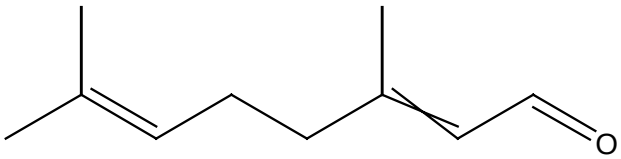
The world production of C.I. Fluorescent Brightener 220 amounts to about 35,000 t/a a.i. by 12 producers. The substance is used as a whitening agent in the paper and textile industry. Recommended concentrations for whitening of paper and textiles are in the range of 0.05 to 0.5 % a.i. at maximum. Due to the high molecular weight of the substance and low releases from products human exposure is assumed to be very low.

Releases into the hydrosphere are expected from production, processing of textiles and paper as well as during paper recycling and cleaning of treated textiles in households (washing out). Releases into the atmosphere may not occur as the substance is a salt. Releases of the terrestrial compartment are expected to occur through application of sewage sludge.

NATURE OF FURTHER WORK RECOMMENDED

No information is available on the toxicity of C.I. Fluorescent Brightener 220 to benthic organisms. Although the substance is not toxic to aquatic organisms the performance of a sediment test is regarded necessary, as it can be assumed that the substance will adsorb to the sediment if released into the hydrosphere. In addition, as the substance is not biodegradable, an accumulation in the sediment may occur. Exposure data from production in the sponsor country show that this life-cycle step will not lead to high water or sediment concentrations. However, there are no information available on the release of fluorescent brightener from processing of paper and textiles as well as from paper recycling and cleaning of treated textiles in households. Therefore, it should be considered to perform a long-term sediment test with the endobenthic organism *Lumbriculus variegatus* or to perform an exposure assessment to clarify the likely impacts on the sediment compartment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	5392-40-5
Chemical Name	Citral
Structural Formula	 $C_{10}H_{16}O$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Citral was rapidly absorbed from the gastro-intestinal tract. Much of an applied dermal dose was lost due to its extreme volatility, but the citral remaining on the skin was fairly well absorbed. Citral was rapidly metabolized and excreted as metabolites. Urine was the major route of elimination.

Acute toxicity of this chemical is low in rodents because the oral or dermal LD_{50} values were more than 1000 mg/kg. This chemical is irritating to skin and not irritating to eyes in rabbits. There is some evidence that this chemical is a human skin sensitizer.

Several repeated dose oral studies show no adverse effect of citral at less than 1,000 mg/kg/day exposure and some histological changes in the nasal cavity or forestomach, the first exposure sites, probably due to irritation, at more than 1,000 mg/kg/day. Male and female F344/N rats received microencapsulated citral in feed at concentrations of 0, 0.63, 1.25, 2.5, 5 and 10% (resultant doses: 0, 142, 285, 570, 1,140 and 2,280 mg/kg/day) for 14 days. Minimal to mild hyperplasia and/or squamous metaplasia of the respiratory epithelium was observed in nasal cavity without inflammatory response at 1,140 and 2,280 mg/kg/day of both sexes. The NOAEL was established at 570 mg/kg/day. In an OECD preliminary reproduction toxicity screening test [TG 421], citral was administered to Crj:CD (SD) rats by gavage at doses of 0, 40, 200 and 1,000 mg/kg/day in males for 46 days and in females for 39-50 days including before and through mating and gestation periods and until day 3 of lactation. Squamous hyperplasia, ulcer and granulation in lamina propria were observed in the forestomach at 1,000 mg/kg/day of both sexes. Therefore, the NOAEL for repeated dose toxicity was 200 mg/kg/day for both sexes.

As for reproductive toxicity in the above preliminary reproductive study, no effects were detected in reproductive ability, organ weights or histopathology of the reproductive organs of both sexes, and delivery or maternal behavior. However, body weights of male and female pups were reduced in the 1000 mg/kg group. Therefore, an oral NOAEL for developmental toxicity was 200 mg/kg/day. In a teratogenicity study, SD pregnant rats were exposed to citral by inhalation for 6 hr/day on gestation days 6-15 at mean concentration of 0, 10 or 34 ppm as vapour, or 68 ppm as an aerosol/vapour mixture. Even in the presence of the maternal effects, no significant teratogenicity was noted at 68 ppm. An inhalation NOAEL of teratogenicity was established at 68 ppm (423 mg/m^3).

Seven bacterial reverse mutation studies indicate negative results with and without metabolic activation. As for non-

bacterial *in vitro* study, two chromosomal aberration results in Chinese hamster cells are negative however one positive result in sister chromatid exchange is given in the same cells. Additionally, two *in vivo* micronucleus tests in rodents indicate negative results. Based on the above information, the genotoxic potential of citral can be considered to be negative.

A NTP study shows that there was no evidence of carcinogenic activity in male/female rats and male mice but some evidence of malignant lymphoma in female mice (up to 4,000 ppm in feed in rats and up to 2,000 ppm in feed in mice).

Dermal application of citral induces prostate hyperplasia with low severity only in some strains of rats. However, the NTP oral carcinogenicity studies in rats and mice found no evidence of lesions (neoplastic or non-neoplastic) in any male reproductive organ, including the prostate. The health significance of the effects seen in the dermal studies in rats is uncertain due to dramatic strain differences and it is noted that the work has primarily been performed in a single laboratory.

Environment

Citral is readily biodegradable (92%, BOD) and its bioaccumulation potential seems to be low based on Log P_{ow} (2.8-3.0). This chemical has been tested in a limited number of aquatic species. For alga (*Selenastrum capricornutum*), 72 h EC_{50} (biomass) is 5 mg/L and 72 h NOEC (biomass) is 3.1 mg/L. For *Daphnia*, acute toxicity of 10 mg/l (24hEC50, immobilization) and 7 mg (48h-EC50, immobilization), and chronic values of 1.0 mg/L (21 d NOEC, reproduction) have been reported. Only the acute toxicity value has been reported for fish, which is 4.1 mg/L (96 h LC_{50}) for *Oryzias latipes.* A PNEC of 0.01 mg/L for the aquatic organisms was calculated from the chronic toxicity value of *Daphnia* using an assessment factor of 100.

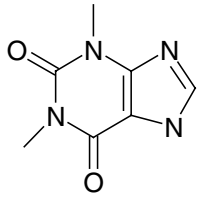
Exposure

Production volume of citral in Japan was 1,200 tonnes in 1990-1999. This chemical is used as a food flavoring and as an intermediate for perfume and vitamin A production. This chemical is a mixture of two geometric isomers, geranial (trans confirmation, approx. 55-70%) and neral (cis confirmation, 35-45%). It is rapidly hydrolyzed at pH 4 (half-life time: Neral: 9.54 days, Geranial: 9.81days) and at pH 9 (half-life time: Neral: 30.1 days, Geranial: 22.8 days), but slowly hydrolyzed at pH 7 (half-life time: Neral: 230 days, Geranial: 106 days). This chemical is classified as "readily biodegradable". A generic fugacity model (Mackey level III) shows that if citral is released to one of the compartments of air, water and soil, it is unlikely to distribute into other compartments. According to a Japanese manufacturer, 1,200 kg/year (estimated) of citral are treated in waste water treatment plants and then released with 5,000 t/year of effluent into a river (flow rate 1.6 $x10^{11}$ t/year). The local predicted environmental concentration (PEC_{local}) is $7.5x10^{-7}$ mg/l, employing a calculation model. The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. The concentration of citral in drinking water is assumed to be less than 7.5 $x10^{-7}$ mg/l. Occupational exposures at production sites may occur by the inhalation and dermal route. The estimated human exposure of a worker who operates the drum filler and does sampling assuming without protective equipment is 0.34 mg/kg/day. However, protective measures i.e. safety glasses and gloves are used during these processes. Therefore, the actual exposure to workers is lower than the estimated value.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	58-55-9
Chemical Name	Theophylline
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Theophylline is moderately toxic after oral uptake and low toxic after dermal and inhalative uptake. LD50, rat (oral): 272 mg/kg bw, LC50, rat (inhalation, aerosol): >6.7 mg/l/4h, LD50, rat (dermal): >2000 mg/kg bw. Main symptoms following exposure are convulsion and accelerated respiration (oral) and irregular and accelerated respiration (inhalation). The undiluted substance was not irritating to the eyes. The substance in a 50% aqueous dilution was not irritating to the skin of rabbits. In repeated dose studies, theophylline was given to rats and mice by feed or by gavage. In rats theophylline caused nephropathy in all fed male rats and a dose-dependent periarteritis in all treated groups. Those effects are discussed to be secondary effects, due to the pharmacological properties (vasodilatation/ -constriction) of methylxanthines. No histo-pathological changes were found in other organs including sex organs of rats and mice. LOAEL: 75 mg/kg bw/d (rat, feed), 37.5 mg/kg bw/d (rat, gavage), LOAEL: 175 mg/kg bw/d (mouse, male, feed), 225 mg/kg bw/d (mouse, female, feed), NOAEL: 75 mg/kg bw/d (mouse, male, gavage), 150 mg/kg bw/d (mouse, female, gavage). Theophylline was not mutagenic or clastogenic in most of the standard *in vitro* tests. Positive results were found only at high, cytotoxic concentrations and without metabolic activations. Theophylline had no mutagenic or clastogenic effects *in vivo*.

In fertility/developmental toxicity studies in mice, the oral administration of theophylline resulted in changes in parental body weight and significant reproductive effects to the offspring (reduced mean number of litters, fewer live pups per litter, decreased live pup weight). No effects were observed in sperm morphology or in the estrous cycle in rats and mice in 14 week studies. LOAEL: 126 mg/kg bw/d. Theophylline was not shown to be teratogenic in CD-1 mice at oral doses up to 396 mg/kg bw/d or in CD-1 rats at oral doses up to 259 mg/kg bw/d. At an oral dose of 218 and 396 mg/kg bw/d, fetotoxicity was observed in rats and mice, respectively, in the presence of maternal toxicity. Intravenous theophylline was fetotoxic and teratogenic in rabbits at maternal toxic doses exceeding the effective therapeutic range (60 mg/kg bw/d i.v.). NOAEL rat maternal/fetotoxicity: 124 mg/kg bw/d, NOAEL rat teratogenicity: 259 mg/kg bw/d. NOAEL mouse maternal/fetotoxicity: 282 mg/kg bw/d, NOAEL mouse teratogenicity: 396 mg/kg bw/d. NOAEL rabbit maternal/fetotoxicity/teratogenicity: 30 mg/kg bw/d. Theophylline showed no carcinogenic activity in rats and mice when tested up to the highest doses (75 mg/kg bw/d rats, female mice and 150 mg/kg bw/d male mice).

In rats theophylline is rapidly and completely absorbed from the digestive tract and distributed to all organs except adipose tissue. It readily crosses the placenta and no blood-brain barrier was observed. Plasma half-life is between

1.2-4 hours in rats and 6-11.5 hours in dogs and strongly dependent on protein binding and dose. Theophylline is metabolized in the liver, mainly by the microsomal system. The metabolites are excreted into the bile and eliminated with the urine. In humans theophylline is readily absorbed after oral intake and distributed in the different body tissues and breast milk. Theophylline is metabolized in the liver and excreted by the kidney. Only 7-12 % is excreted unchanged in the urine. Major metabolites are 1,3-dimethyluric acid (35-55 %), 1-methyluric acid (13-26 %) and 3-methylxanthine (9-18 %). The elimination half-time is 3-11 hours in adults. Signs of intoxication are: headache, gastrointestinal disturbances, hypotension, irritability and insomnia, tachycardia, arrhythmia, cardiac arrest and serious neurological symptoms. Seizures and death have also occurred. Toxicity may be developed at serum levels of 20-30 µg/ml, whereas at levels below 15 µg/ml generally no symptoms were observed. Case-control studies did not show an association between total methylxanthine intake and benign breast disease or breast cancer. No association with congenital abnormalities or stillbirth were seen in studies with females receiving theophylline. In premature infants no effect of theophylline on the development was seen.

Environment

Theophylline has a water solubility in the range of 5.5 to 8.3 g/l, a vapor pressure of $0.7 * 10^{-6}$ Pa and a log Kow of –0.0076. Distribution modelling using Mackay, Level I, indicates that the main target compartment will be water with 99,98%. According to OECD criteria the substance is readily biodegradable. The calculated hydrolysis rate is extremely slow. In the atmosphere theophylline will be indirectly photodegraded by reaction with hydroxyl radicals with a half-life of 20 hours (calculated). Bio- and geoaccumulation is not expected according to the log Kow (-0.0076).

The acute aquatic toxicity has been determined for fish (*Leuciscus idus* LC50(96h) appr. 100 mg/l), for aquatic invertebrates (*Daphnia magna* EC50(48h) 178 mg/l) and for algae (*Scenedesmus subspicatus* EC50(72h) >100 mg/l). Based on these acute toxicity studies theophylline is not considered as hazardous to aquatic organisms. Results from prolonged or chronic studies are not available. Following the EU risk assessment procedure, the PNEC aqua can be calculated to 0.1 mg/l by applying an assessment factor of 1000 on the most sensitive species (*Leuciscus idus* LC50(96h) 100 mg/l).

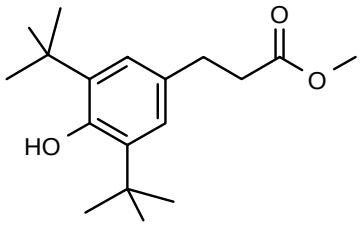
Exposure

Theophylline is produced with a volume of 1,000 to 5,000 tons per year, world-wide, the same level accounting for Germany and Europe. Theophylline is a substance with wide disperse use. It is predominantly used as an antiastmathic drug in the pharma sector (99%). 1% is used in cosmetic applications. Production sites for the technical product: EU (Germany) 1, NAFTA 1, India 1 and China 5. Furthermore theophylline is a naturally occurring substance in plants e.g. in black tea (200 – 400 mg/kg dry weight), coffee (approx. 5 mg/kg in green coffee beans) and cocoa (trace amounts) and therefore is a component in the respective beverages. The use in pharmaceutical applications and also the use in foods will be the predominant way of human exposure and of exposure of the environment. Exposure of workers to theophylline during production is adequately controlled in the industry of the sponsored country. Workplace measurements Germany: 0.1- ca. 0.5 mg/m^3 (8h). At the German production site, process waters with relevant substance quantities are separated and combusted.

NATURE OF FURTHER WORK RECOMMENDED

The substance is currently of low priority of further work. However there is a recommendation for sharing the information on possible aggregated exposure with regulatory agencies responsible for food, pharmaceuticals and cosmetics.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6386-38-5
Chemical Name	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester (Metilox)
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Metilox was of low toxicity in acute toxicity tests, with an oral LD50 value of >5000 mg/kg bw, an inhalation LC50 above 55 mg/m3 and a dermal LD50 of >3000 mg/kg. The substance is not irritating to the skin and eye. No indication for sensitisation due to Metilox was found.

The LOAEL found after repeated oral exposure during a 90 day study was 70 mg/kg bw per day. The liver and thyroid were the target organs, showing hypertrophy. In a reproduction study the NOAEL for parental toxicity was 10 mg/kg bw per day, based on decreased food consumption, decreased body weight gain and liver hypertrophy. No effects on fertility were observed. Effects on pups (decreased litter size, viability and weight) were reported at 250 mg/kg bw per day. The NOAEL for developmental effects is 100 mg/kg bw per day. Metilox is not mutagenic in the Ames test and in the chromosome aberration test *in vitro*.

Environment

Metilox has a low vapour pressure and calculated logPow between 5 and 6. Water solubility is 2.2 mg/L. The substance is hydrolysed to its carboxylic acid. Both Metilox and its hydrolysis product are not or very limited biodegradable and are expected to end up in the sediment. In the 1970s Metilox and degradation products have been monitored in surface water and sediment near a contaminated production site.

At the water solubility limit Metilox was not acutely toxic to fish and daphnids (96-h LC50 5.8 mg/L in fish and 24-h EC50 >100 mg/L in a Daphnia test with the use of a dispersant (nominal concentrations)). For algal growth the 48 h EC50 was 2.3 mg/L (measured concentration). The NOEC in a *Daphnia magna* reproduction study was 0.123 mg/L. Based on this lowest NOEC and applying a safety factor of 50, a PNEC of 2.5 µg/L was derived. The BCF for the main metabolite, Metilox acid, has been determined in carp to be 60-223 (at 50 µg/L) and 121-532 (at 5 µg/L).

Exposure

The production volume of Metilox was 23,500 tonnes in 1992. Greater than 99.8% of the production volume is used as an intermediate in the synthesis of phenolic antioxidants for polymers. Other usages are as an antioxidant in motor oils, hydraulic fluids and lubricants. A very minor part of the production volume is used in fragrances.

During production worker exposure is expected to be very low or negligible, due to the closed production process. Environmental exposure due to release via waste water during cleaning processes and spillage of motor oils may occur.

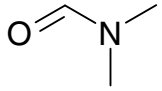
Some consumers may be exposed to very low concentrations of Metilox found in fragrances.

NATURE OF FURTHER WORK RECOMMENDED

There is currently no concern for health.

Based on the available data there is currently no concern for the environment. However local, regional or national exposure information gathering may be considered. If that information indicates significant sediment exposure then the hydrolysis rate of Metilox and effects of Metilox and/or degradation products on sediment dwelling organisms should be investigated.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	68-12-2
Chemical Name	N,N-dimethylformamide
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

N,N-dimethylformamide (DMF) is of low acute toxicity in mammals: LD_{50} rat (oral) 3040 mg/kg bw, LC_{50} rat (inhalative, 4 h) > 5900 mg/m^3, LD_{50} rat (dermal) > 3160 mg/kg bw. Main symptoms following exposure were apathy and staggering (oral) and irregular or intermittent respiration (inhalation). It was irritating to the eyes of rabbits but not irritating to the skin of rabbits and rats.

DMF did not show a sensitizing potential when used as a vehicle in a local lymph node assay. In repeated-dose toxicity studies in rats and mice with chronic exposure over 2 years (rats) or 18 months (mice) and subchronic exposure over 13 weeks by inhalation, or in rats treated by oral administration of DMF (90 day feeding study or administration by gavage for 28 days), the predominant target organ was the liver (NOAEC: chronic inhalation rat: 25 ppm (about 80 mg/m^3), LOAEC: chronic inhalation mouse: 25 ppm (about 80 mg/m^3); NOAEC: subchronic inhalation rat: 100 ppm, mouse: 400 ppm (about 300 mg/m^3 and 1210 mg/m^3 , respectively); NOAEL: rat, 90 days 200 ppm (about 12 mg/kg bw/day), 28 days about 238 mg/kg bw/day). In a 13-week inhalation study with a limited number of Cynomolgus monkeys no treatment-related effects occurred (NOAEC: 500 ppm (about 1500 mg/m^3)).

DMF does not induce chromosome aberrations or gene mutations in various test systems *in vivo* and *in vitro*. In addition, no increased tumor incidence was found in carcinogenicity studies in rats and mice that were exposed to 25, 100 and 400 ppm DMF (about 80, 300, and 1210 mg/m^3) by inhalation for 2 years or 18 months, respectively.

Reproductive toxicity was observed at the presence of some general toxicity in a continuous breeding study in mice, when DMF was administered orally in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day). The maximal tolerated dose for generalized toxicity was 1000 ppm (about 219 mg/kg bw/day) for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index (the latter one only in the high dose group), reduced number of litters, reduced average litter size and for the F1 parental males by effects on prostate weight and epididymal spermatozoa concentration, the latter finding only in the high dose group) and developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) occurred at 4000 ppm and above. At 1000 ppm, reduced pup weights were found in F2 pups. Thus 1000 ppm (about 219 mg/kg bw/day) was the NOAEL for reproductive and developmental toxicity in F0 and F1, and the LOAEL for developmental toxicity in F2.

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral- or dermal

administration) and in mice (oral administration). In rats embryo-/fetotoxicity and teratogenicity were mostly seen at maternally toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

Rabbit: NOAEC (inhalative) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 50 ppm (about 150 mg/m^3); NOAEL (oral, gavage) maternal toxicity and embryo-/fetotoxicity 65 mg/kg bw/day, teratogenicity 44.1 mg/kg bw/day; NOAEL (dermal) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 200 mg/kg bw/day).

In humans, DMF is absorbed by inhalation and through the skin. After high exposures (up to 60 ppm) headaches, abdominal pain, nausea, vomiting, dizziness, elevated liver enzymes, and alcohol intolerance (facial flashing and palpitations) were seen. Case reports of testicular cancer in aircraft repair and leather tannery facilities failed to be confirmed in further studies. Reports of DNA and chromosomal damage in peripheral lymphocytes of subjects exposed to DMF either failed to take into account smoking as a confounder or coexposure to other chemicals.

With respect to the metabolism of DMF the following conclusion can be drawn: DMF is readily absorbed via all exposure routes. N-hydroxymethyl-N-methylformamide is the main urinary metabolite and to a minor extent, but with greater toxicological relevance the metabolite mono-N-methylformamide (MMF) occurs which may partially be conjugated to glutathione forming S-methylcarbamoylglutathione. The GSH and its sequel adducts (S-methylcarbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) seem to be responsible for developmental toxic effects.

At higher doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precedes the GSH binding.

Persons who repeatedly inhaled DMF excreted the mercapturic acid at levels of ~ 13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours.

Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause a severe alcohol intolerance.

Environment

N,N-dimethylformamide (DMF) is a colorless liquid, which is miscible with water in all proportions and has a vapour pressure of 3.5 hPa (at 20°C). The log Kow was measured to –0.85 (at 25°C).

Distribution modelling using Mackay Level I indicates water to be the main target compartment for DMF (98.7%). In the atmosphere DMF is indirectly photodegraded by reacting with hydroxyl radicals with $t_{1/2}$ = 2 hours. According to OECD criteria the substance is readily biodegradable. Hydrolysis is not expected under environmental conditions. Bioconcentration factor in fish was measured to 0.3 – 1.2.

In short term tests with fish, daphnids and algae DMF showed an acute toxicity EC/LC50 >100 mg/l. Hence DMF is not regarded as harmful to aquatic organisms. In the following the lowest valid EC/LC50 data of different aquatic species are summarized:

Lepomis macrochirus: LC50(96h) = 7100 mg/l
Daphnia magna: EC50(48h) > 100 mg/l; EC50(48h) = 15700 mg/l
Scenedesmus subspicatus: EC10 and EC50(96h) > 1000 mg/l (biomass and growth rate).

Long term reproduction studies with *Daphnia magna* resulted in NOECs of 1140 mg/l (28 days) and 1500 mg/l (21 d).

Applying an assessment factor of 50 on the lowest available NOEC of 1140 mg/l a $PNEC_{aqua}$ = 22.8 mg/l can be

derived according to the EU risk assessment procedure.

Exposure

In Germany 50,000 to 100,000 t DMF were produced in 2000 at BASF AG, Ludwigshafen. Further producers are located in Belgium, Korea, Japan, Spain and USA. The total production volume in the EU (including Germany) is in the range of 50,000 to 100,000 t/a. In Asia, the production volume is 100,000 to 500,000 tonnes per year and in North America it is 50,000 to 100,000 tonnes per year. DMF is predominately used as a solvent in synthesis of fine chemicals, in polyacrylonitrile fibre production, polyurethane coating and in the electronics industry. The remaining is split into various applications like varnishing, surface coating, polyamide coating, absorbents, cleaners and extractants. In addition, DMF is also used as a solvent in crop protection agents.

Releases into the environment may occur during production of DMF and during its use as solvent or cleaning agent. In 1991 the maximum annual release of DMF into the hydrosphere from production and processing in pre-unification Germany was estimated to 352 t. Approximately 9000 t/a were emitted into the atmosphere. More recent data about environmental releases are not available. Releases into the terrestrial compartment may occur from use of DMF as solvent in plant protection products. However, this release is not quantifiable.

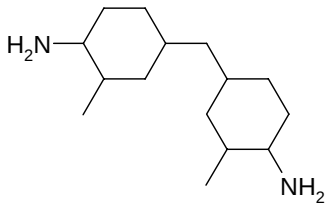
Product register information indicates that there are several products that contain the substance in significant amounts (up to 100 %). The product types are solvents, intermediates, paints, lacquers and varnishes. Among the products there are some products for private use. Therefore consumer and occupational exposure can not be excluded. Exposure to workers during production is well controlled in the industry of the sponsor country (Germany).

NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. In occupational settings where exposure is not controlled and, due to information of European product registers, exposure to consumers and workers cannot be excluded. As the extent of exposure cannot be estimated and the substance is a developmental toxicant, a human exposure and if then indicated a risk assessment should be performed.

Environment: Concerning the aquatic compartment, DMF is of low concern due to the low toxicity to aquatic organisms, the low bioaccumulation potential and the classification as readily biodegradable. However, high releases of DMF into the atmosphere are described in the BUA report from 1991. Although the substance has a half-life in the atmosphere of 2 hours, these very high emissions may pose a local problem in the vicinity of point sources. In addition releases into the soil result from the use of the substance in plant protection products. Therefore, exposure data gathering should be performed. Depending on the exposure information further information on toxicity to terrestrial organisms may be required, for example a plant fumigation test.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6864-37-5
Chemical Name	2,2'-dimethyl-4,4'methylenebis(cyclohexylamine)
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In humans (epoxy resins production workers) scleroderma-like skin changes have been described revealing 2,2'dimethyl-4,4'methylenebis(cyclohexylamine) as most probable causative agent. In DMD production workers unspecific skin changes, but no scleroderma-like symptoms were seen. DMD is harmful via the oral route and toxic via the dermal and inhalation route:

LD_{50} rat (oral): > 320 < 460 mg/kg bw, symptoms: unspecific;
LC_{50} rat (inhalation, liquid aerosol): 420 mg/m^3/4h, symptoms: irritation of the airways;
LD_{50} rabbit (dermal): > 200 < 400 mg/kg bw, symptoms: cyanosis, necrotic changes at the test site.

The substance is highly corrosive to skin (full thickness necrosis after 3 minutes of exposure) and may cause severe damage to eyes. In the guinea pig maximization test the substance showed no sensitizing effect. In a well conducted rat 90-day inhalation study (OECD TG 413) body weight development was impaired, local irritative effects observed for the skin and upper airways (nasal mucosa) and target organ toxicity indicative of a mild anemic effect as well as effects on the liver, testes and kidneys were seen at 48 mg/m^3. No histopathological correlate was found with respect to increased absolute lung weights. At 12 mg/m^3 the only effect seen was an increase in GPT levels in males. The NOAEC was 2 mg/m^3.

In a subchronic oral toxicity study with rats (OECD TG 408), the animals were exposed to 0, 2.5, 12 and 60 mg/kg bw/day by gavage over 3 months. Liver, white and red blood cells, kidneys, adrenal glands and heart were the target organs for toxic effect showing also histopathological alterations. At the high dose level (60 mg/kg bw/day) body weight development/food consumption were clearly impaired and the general state of health was poor. The absolute testes weight was decreased and an atrophy of the seminiferous tubuli and a reduced content of the seminal vesicle were noted. These changes were interpreted as consequence of the marked impairment on body weight. While the toxic effects at the mid dose of 12 mg/kg bw/day were generally less pronounced, a NOAEL was achieved at 2.5 mg/kg bw/day.

The substance showed no genotoxic effects in the Ames test (OECD TG 471), cytogenetic assay with CHO cells

(OECD TG 473) and HGPRT assay (OECD TG 476) when tested up to the cyto-/bacteriotoxic range.

In rat 90-day oral and inhalation studies the substance showed no direct adverse effects to the male and female reproductive organs (testes, ovaries and uterus examined). The observed effects on testes being a secondary non-specific consequence of the severe systemic toxicity (e.g. decrease in body weight) seen at the same dose level. A fertility study is not required under SIDS due to the existence of good 90 day repeated dose toxicity studies with histopathological evaluation of the sex organs.

In a developmental toxicity study (OECD TG 414) the test substance (0, 5, 15 or 45 mg/kg bw/day) was administered from day 6 to 19 post-coitum orally by gavage to rats. The NOAEL for maternal toxicity was 5 mg/kg bw/day. Slight fetotoxicity (retardation of ossification of skull bones) without teratogenicity was observed at 45 mg/kg bw/day, together with severely reduced body weight of the dams. The NOAEL for developmental toxicity was 15 mg/kg bw/day.

Environment

2,2'-dimethyl-4,4'methylenebis(cyclohexylamine) has a water solubility of 3.6 g/l, a vapour pressure of 0.08 Pa and a measured log Kow of 2.51. However, due to the Lewis base character of the substance the experimental determination of the log Kow is inaccurate.

From the physico-chemical properties the hydrosphere is identified as target compartment for the substance. According to OECD criteria the substance is not biodegradable even with adapted inoculum (OECD TG 302B <1 % after 28 days) and can only be poorly eliminated in sewage water treatment plants. Due to the chemical structure of 2,2'-dimethyl-4,4'methylenebis(cyclohexylamine) hydrolysis is not likely to occur under environmental conditions. In the atmosphere the substance is quickly degraded by photochemical attack (half life =3.1 hours). The log K_{OC} was calculated to 3.26. It has to be considered however, that as a basic compound cyclohexylamine can additionally be bound to the soil by ion exchange. The following aquatic effects concentrations are available:

Leuciscus idus: LC_{50} (96 h) > 22 < 46 mg/l,
Daphnia magna: EC_{50} (48h) = 15.2 mg/l,
Scenedesmus subspicatus: ErC_{50} (72 h) > 5 mg/l; EbC_{50} (72 h) = 2.1 mg/l

With these data the substance is considered as toxic to aquatic organisms. With an assessment factor of 1000 a PNECaqua of 2.1 µg/l can be derived. Results from prolonged or chronic studies are not available. No data are available on terrestrial organisms.

Exposure

The global production volume of 2,2'-dimethyl-4,4'methylenebis(cyclohexylamine) (DMD) in 2000 amounts to 1000 – 5000 t. The total volume was produced in Germany by one company. The substance is mainly used as a hardener in epoxy resins and polyamides. No relevant releases to the environment could be identified. The exposure of workers at the manufacturing and processing site is controlled.

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended unless information regarding significant exposure becomes available.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	71-36-3
Chemical Name	n-butyl alcohol
Structural Formula	CH_3-CH_2-CH_2-CH_2OH

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Data from butyl acetate (BAc) toxicity studies have been included in the assessment of n-butanol (BA). Data from BAc is useful when assessing the hazards associated with the systemic toxicity of BA exposure due to the rapid and complete hydrolysis of BAc to BA *in vivo*. Exposure to BAc via dermal, inhalation, and water or dietary administration results in the rapid appearance of BA in the systemic circulation. Since exposure to either BAc or BA results in systemic exposure to BA, systemic toxicity data from studies that administer BAc are useful in identifying hazards associated with BA exposure. Endpoints of BAc toxicity that are associated with direct contact-mediated effects (e.g. eye, skin, and respiratory tract irritation) cannot be extrapolated from BA data due to the difference in physical-chemical properties of the two materials.

Human Health

n-Butyl alcohol (BA) was only slightly toxic to experimental animals following acute oral, dermal, or inhalation exposure. The acute oral LD_{50} values for female rats ranged from 790 to 4360 mg/kg. Different strains of rat were used in each of four studies, which may account for the variability. Oral LD_{50} values for mice, rabbits, hamsters, dogs, and male rats all fell within the same range. The rat inhalation LC_0 of 8000 ppm (24000 mg/m^3) indicates very low inhalation toxicity (no lethality at 8000 ppm). The rabbit dermal LD_{50} was 3402 mg/kg, indicating that BA can penetrate the skin, but not very readily. Animal experiments and human experience indicate that BA is, at most, moderately irritating to the skin, but it is a severe eye irritant. These effects are most likely due to BA's localized defatting and drying characteristics. Although no animal data are available, human studies and experience show that BA is not likely to be a skin sensitizer. A recent *in vivo* toxicokinetics study confirmed the rapid metabolism of n-butyl acetate (BAc) to BA. Hydrolysis of BAc in blood and brain was estimated to be 99 percent complete within 2.7 minutes (elimination $t_{½}$ = 0.41 minute). Thus, organisms exposed to BAc can experience appreciable tissue concentrations of BA. In this way, the results of toxicity studies with BAc can be used as supplemental, surrogate data to provide information on the toxicity of BA. A thirteen-week, subchronic exposure to BAc, the metabolic precursor of BA, produced transient hypoactivity (during exposure only) at 1500 and 3000 ppm (7185 and 14370 mg/m^3) along with decreased body weight and food consumption, but no post exposure neurotoxicity even at 3000 ppm. A concurrent subchronic neurotoxicity study under the same exposure conditions showed no evidence of cumulative neurotoxicity based upon functional observational battery endpoints, quantitative motor activity, neuropathology and scheduled-controlled operant behavior endpoints. A no observable effect level (NOAEL) of 500 ppm (2395 mg/m^3) was reported for systemic effects in rats, and a NOAEL of 3000 ppm (14370 mg/m^3) was reported for post exposure neurotoxicity in rats. Several studies indicate that BA is not a reproductive toxicant. Female rats exposed to 6000 ppm (18000 mg/m^3) BA throughout gestation and male rats exposed to 6000 ppm (18000 mg/m^3) BA for six weeks prior to mating showed no effects on fertility or pregnancy rate. Male rats given BA at 533 mg/kg/day for 5 days had no testicular toxicity. BA produced only mild fetotoxicity and developmental

alterations at or near the maternally toxic (even lethal) dose of 8000 ppm (24000 mg/m^3) throughout gestation. An entire battery of negative *in vitro* tests and a negative *in vivo* micronucleus test indicate that BA is not genotoxic. The median odor threshold for BA (0.17 ppm) is well below the lowest nasal irritation threshold in humans (289 ppm), allowing warning of possible chemical exposure prior to nasal irritation occurring. Human studies are complicated by the odor characteristics of the material, as the odor threshold is well below the levels at which irritation is observed.

Environment

BA's vapor pressure is 0.56 kPa at 20^{0}C, water solubility is 77 g/L at 20^{0}C and a Log K_{ow} is 0.88. Based on level III fugacity modeling, BA will partition 83.5% in air, 5.9% in soil, 10.6% in water, <0.1% in suspended solids, and <0.1% in biota and in sediment. BA degrades in air by reaction with hydroxyl radicals, having a half-life in air of 1.2 to 2.3 days. The volatilization half-life for BA in water is estimated to be 2.4 hours for streams, 3.9 hours for rivers and 126 days for lakes. BA exhibits low toxicity to fish, amphibians and aquatic invertebrates, plants, algae, bacteria and protozoans. However, some algal species are sensitive to BA. Acute toxicity to aquatic life may occur at concentrations greater than 500 mg/l. BA is classified as "readily biodegradable" under aerobic conditions. The octanol:water partitioning coefficient (log K_{ow}) for BA ranges from 0.88 to 0.97, and the calculated bioconcentration factor (BCF) is 3. These data indicate that BA has a low potential to bioaccumulate. BA is expected to migrate readily through soil to groundwater and not to sorb to soil particles.

Exposure

BA is used primarily as an industrial intermediate in the production of ethers and butyl ether acetates, pharmaceuticals, polymers and plastics. BA is used to a lesser extent as a solvent, reactant/diluent and component in consumer (nail polish formulations, rubber cement and safety glass) and industrial products. Production in the US is estimated at 784,000 tonnes, 575,000 tonnes in Western Europe and 225,000 tonnes in Japan. In regards to physical hazards of the chemical, it has a flammable range of 1.4 – 11.2 volume % in air (14,000 – 112,000 ppm) and a flash point of 98^{0}F (37^{0}C). In the US, due to the physical chemical properties of BA, workplace exposure during manufacture and use as industrial intermediate is limited by closed processing. For the same reasons, exposure is not anticipated during the formulation of butyl alcohol into various products as a solvent. Inhalation and dermal exposure can occur during industrial and commercial application of products containing butyl alcohol, such as lacquers and other coatings. Use in consumer products is limited, but is a possible source of exposure. Releases to the environment are primarily from solvent use. Butyl alcohol occurs naturally in foods.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7447-40-7
Chemical Name	Potassium chloride
Structural Formula	K-Cl

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Potassium chloride is an essential constituent of the body for intracellular osmotic pressure and buffering, cell permeability, acid-base balance, muscle contraction and nerve function.

Acute oral toxicity of KCl in mammals is low (LD50 = 3020 mg/kg bw). In humans, acute oral toxicity is rare because large single doses induce nausea and vomiting, and because KCl is rapidly excreted in the absence of any pre-existing kidney damage. Usual therapeutic doses of potassium for oral solution-adults are 1.5-3 g/day to prevent depletion, and 3-7.5 g/day for replacement. For repeated dose toxicity, a NOAEL at 1820 mg/kg bw/day in rats, and a NOAEL > 80 mmol KCl/day (approx. 85 mg/kg bw/day) in humans can be retained. A threshold concentration for skin irritancy of 60 % was seen when KCl in aqueous solution was in contact with skin of human volunteers. The threshold concentration when applied to broken skin was 5 %.

No gene mutations were reported in bacterial tests, with and without metabolic activation. However, high concentrations of KCl showed positive results in a range of genotoxic screening assays using mammalian cells in culture. The action of KCl in culture seems to be an indirect effect associated with an increased osmotic pressure and concentration. Therefore KCl, do not have any direct relevance in the intact body were such concentrations can not occur. Further studies using *in vivo* systems are not considered necessary under SIDS.

No evidence of treatment-related carcinogenicity was observed in rats administered up to 1820 mg KCl/kg body weight/day through the food in a 2 year study.

A developmental study revealed no foetotoxic or teratogenic effects of KCl in doses up to 235 mg/kg/day (mice) and 310 mg/kg/day (rats). No fertility study has been located. Based on the extensive amount of knowledge on KCl intake, regulation and effects in the human body, and on a worst case exposure estimate (see Exposure), no further testing of fertility is considered required under SIDS.

Gastro-intestinal irritant effects in humans caused by KCl administrated orally have been reported at doses from about 31 mg/kg bw/day. One epidemiological investigation among potash miners disclosed no evidence of predisposition of underground miners to any of the diseases evaluated, including lung cancer.

Environment

KCl as inorganic salt is not subjected to further degradation processes in the environment. In water, potassium

chloride is highly water soluble, and readily undergoes dissociation. In soil, transport/leaching of potassium and chloride is affected by the clay minerals (type and content), pH, and organic matter.

In short-term acute toxicity tests with fish, daphnia and algae the following results were found (lowest test result values): *Ictalurus punctulus* 48h-LC50 = 720 mg/l; *Daphnia magna*: 48h-LC50 = 177 mg/l; *Nitzschia linearis:* 120 h-EC50 = 1337 mg/l. A chronic reproductive test with the invertebrate Daphnia magna gave a LOEC of 101 mg/l. All the studies compiled on the acute and chronic aquatic toxicity were > 100 mg/L. Thus it is concluded that KCl is not hazardous to freshwater organisms. Taking into considerations the background concentrations of KCl in seawater (380 mg/l K^+ and 19,000 mg/l Cl^-), it is concluded that there is no reason for further investigations of KCl on marine species. The low concern for the environment is supported by the absence of a bioaccumulation potential for the substance.

In plants, potassium is one of the three major nutrients and chloride is an essential micronutrient. The potassium requirement for optimal plant growth is in the range 2-5 % of the plant dry weight of vegetative parts. In most plant species the Cl requirement for optimal growth is in the range of 0.2-0.4 mg/g dry matter.

Potassium in plants is important for the osmotic and ionic regulation, plays a key role in the water homeostasis, and is closely connected with processes involved in the protein synthesis. In higher plants, potassium affects photosynthesis at various levels. Cl is also essential for the photosynthesis in plants, and has important functions in the osmotic regulation. An adequate supply of potassium and chloride in plants tends to improve the plant's resistance towards several diseases.

Exposure

World-wide production figures for KCl exceed 1 million metric tons/year. Virtually all commercial KCl is extracted from natural sources of the substance. More than 90 % of the total KCl consumption is used for fertilizer production. Production of potassium hydroxide accounts for more than 90 % of the non-fertilizer or industrial uses of KCl. Other non-fertilizer uses of KCl include food/foodstuff additives, supplement of animal feed, pharmaceutical products, laboratory chemicals, deicing agents and photo chemicals.

KCl is ubiquitous in the environment, occurring in minerals, soil and sediments, and natural waters. KCl is also present as a major and essential constituent in animals and plants. The main human exposure to KCl is the normal dietary intake (2-4 g K and 3.5-9 g Cl), and indirect exposure via the environment (drinking water).

Specific occupational exposure limits (OELs) and actual exposure levels in the mining, refining, fertilizer and other industries have not been found. Assuming 100 % body retention breathing from a working atmosphere containing 10 mg/m^3 KCl (in accordance with the TWA value for "Particulates Not Otherwise Classified), a worker's daily inhalation dose for KCl was calculated to 140 mg (worst case).

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	74-83-9
Chemical Name	Methyl bromide
Structural Formula	CH_3Br

RECOMMENDATIONS

The chemical is currently of low priority for further work in the SIDS program as it is subject to with-drawl under international activity (Montreal Protocol).

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Metabolism studies with radiolabeled methyl bromide show that it is rapidly metabolized and excreted. The primary route of excretion is exhalation as CO2 with lesser amount of radioactivity excreted in the urine and feces. Tissue distribution upon inhalation exposure showed that the liver contained the highest levels of radiolabel with appreciable amounts found in the lungs, nasal turbinates and kidneys. Upon oral or intraperitoneal injection, the liver was also the main organ for appreciable radiolabel with lesser amounts seen in the kidneys, testes, lung, heart, stomach and spleen.

Methyl Bromide (bromomethane) exhibits moderate acute toxicity by the oral and inhalation routes. The oral LD 50 in rats ranged from 104 to 214 mg/kg. Toxicity by the inhalation route is both time and concentration dependent. In mice, LC 50 values ranged from 1700 ppm (6,630 mg/m^3) for a 30 minute exposure to 405 ppm (1,575 mg/m^3) for a 4-hour exposure. Similarly in rats, the LC_{50} for a 30-minute exposure was reported as 2833 ppm (11,049 mg/m^3) while that for an 8-hour exposure was 302 ppm (1,178 mg/m^3). In repeated dose studies (4 weeks to 6 months duration) NOAELs of 5 – 33 ppm (20 - 129 mg/m^3) have been observed in inhalation studies using rats, mice, rabbits and dogs. Effects observed included decreased body weight, neurobehavioral changes and hematologic and clinical chemistry effects. Neurotoxic effects seen in experimental animals have included decreased locomotor activity, hyperactivity, depression, lethargy, ataxia, gait disturbances, tremor and convulsions. Methyl bromide was evaluated in 4 inhalation developmental toxicity studies (1 in rats, 3 in rabbits). No developmental effects were reported in these studies at exposure concentrations up to 70 ppm (273 mg/m^3) in both rats and rabbits. In one rabbit study, equivocal fetal effects were seen at a maternally toxic concentration of 80 ppm (312 mg/m^3). In a reproductive study by the inhalation route, no effects on reproductive performance were seen at exposure concentrations up to 90 ppm (351 mg/m^3). Neonate effects were limited to reduced body weights at day 28 post partum in F2 pups at 30 and 90 ppm (117 and 351 mg/m^3). The weight-of-evidence for all genetic toxicity testing indicates that methyl bromide is genotoxic, inducing gene mutations, chromosome mutations, DNA effects and other genotoxic effects both *in vitro* and *in vivo.* However, long-term and reproductive tests *in vivo* show no evidence of carcinogenic response. Methyl bromide is not considered to have produced heritable effects as no such effects were seen in reproductive studies in rats, or developmental studies in rats or rabbits at methyl bromide concentrations that did not induce maternal toxicity. This conclusion is further supported by negative results seen in the dominant lethal study in male rats.

In long-term inhalation bioassays, there were no statistically significant increases in tumors in rats exposed to concentrations up to 90 ppm (351 mg/m^3) for 29 months and mice exposed to concentrations up to 100 ppm (390

mg/m^3) for 2 years. The primary histological changes in both species were degeneration and hyperplasia of the nasal olfactory epithelium. Further, no evidence of oncogenicity was seen in a two-year dietary study in rats in which the animals were fed microencapsulated methyl bromide in order to maintain dietary concentrations.

Human exposure to methyl bromide may occur through inhalation of the gas or inadvertent contact with the liquid. The primary effects of methyl bromide in humans are on the nervous system, lung, nasal mucosa, kidney, eye, and skin. Effects on the central nervous system include blurred vision, mental confusion, numbness, tremors, and speech defects. Topical exposure can cause skin irritation, burns, and eye injury. Exposure to high levels of methyl bromide causes pulmonary edema. Central nervous depression with respiratory paralysis and/or circulatory failure is the immediate cause of death generally preceded by convulsions and coma.

Environment

Although methyl bromide is very soluble in water (16.1 g/L at 25^0C), its high vapor pressure (1893 kPa) , log K_{ow} (1.94 at 25^0C) and log K_{oc} ranging from 2.1 to 2.2 in various soil types indicates a low tendency to absorb to soils causing it to rapidly evaporate from either water or soil. Methyl bromide has a half-life in air estimated between 0.3 and 1.6 years. The primary degradation is due to photolysis. In soils, projected half-lives are in the range of 0.2 to 0.5 days. In water, a half-life of 3 hours was calculated for a model river, this half-life relates to loss due to evaporation. As a result of evaporative transfer, abiotic and biotic processes are insignificant for methyl bromide due to the short residence time. Methyl bromide does not accumulate in aquatic species based on an estimated bioconcentration factor of 4.7 calculated from an octanol/water partition coefficient of 1.19. Rainbow trout and daphnid acute toxicity studies were conducted under static conditions with no headspace over the water column. A number of studies in several fish species indicate that methyl bromide causes acute lethality at concentrations of 0.7 to 20 mg/L. The most reliable 96-hour LC50 based on measured concentrations in the trout was 3.9 mg/l with NOECs of 1.9 and 2.9 mg/l for clinical signs and mortality, respectively. In daphnids, tests under similar conditions, the 48-hour LC50 for mortality and immobilization was 2.6 mg/l. Two studies have been reported in the literature for aquatic plants with a 48h-EC50 of 5 and 3.2 mg/l. A number of chronic studies in aquatic organisms are available, however, none were considered reliable to provide definitive results.

Exposure

In the United States, processing of the chemical is done in closed systems and is a chemical intermediate and a fumigant. In 1990, worldwide consumption of methyl bromide was reported to be 67,000 tonnes or approximately 74,000 US tons. In 1987, combined US production and import totaled 23,000 to 24,000 tonnes or approximately 26,000 US tons. Methyl bromide is used as a fumigant inside dwellings, office buildings, warehouses, silos, mills, vaults, ships and freight cars to control fungi, nematodes, insects and rats. Methyl bromide is also used outdoors as a fumigant, usually under gas-proof sheeting to control pests in soil and orchards. Soil fumigation consumes the bulk of methyl bromide production. In the US methyl bromide may only be applied and used by professional, certified applicators. Primary exposure would be via the inhalation route under occupational scenarios. Since methyl bromide is a gas at room temperature and dissipates rapidly from fumigation sites, non-occupational exposure to low residual amounts may occur to persons living in areas of methyl bromide fumigation. Most countries strictly regulate the application and handling of methyl bromide during fumigation operations to limit and protect the workers and public. Dermal exposure can result from direct contact to liquid methyl bromide through accidental splashing or contact with contaminated clothing.

Recent monitoring studies in areas of high fumigation activity and coinciding with the time periods of fumigation showed ambient air concentrations of methyl bromide in the mean range of 0.099 to 7.68 ppb. Occupational exposures to methyl bromide in various types of soil fumigation show mean exposures ranging from 2 to 605 ppb.

Methyl bromide is highly regulated in various OECD countries based on its hazard data and use information. Under the Montreal Protocol, methyl bromide is considered to be an ozone depleting substance (ODS) and it has been agreed that a phase out of the consumption and production of this chemical is to occur by the year 2005 for industrialized countries. However, in order to satisfy the needs of developing countries, a decreasing level of production is authorized until 2010. Currently there are two exemptions to the 2005 phase out; they are: quarantine and pre-shipment exemption (= 18% of the uses); and critical and emergency exemptions. It should also be noted

that under the Protocol, the amount of methyl bromide used as feedstock in the manufacture of other chemicals is not considered as production. It is anticipated that methyl bromide will be further investigated by individual OECD member countries participating in the Montreal Protocol. As a result, it does not appear that further work will be necessary in the SIDS Program regarding the collection of exposure or release data from use, as the need for this information is required to be investigated for "exemptions" from the phase out.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-01-4
Chemical Name	Vinyl Chloride
Structural Formula	CH_2=CHCl

RECOMMENDATIONS

This chemical is currently of low priority for further work in the SIDS Program as human exposures are controlled due to the chemical's genotoxicity and cancer hazard and based upon OECD risk reduction measures.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The primary route of exposure for vinyl chloride is by inhalation. Vinyl chloride is rapidly and well absorbed following inhalation or oral exposure, and is bioactivated by the liver. The acute toxicity (rat oral LD_{50} >4000 mg/kg; rat and mouse inhalation LC_{50} 390,000 mg/m^3 and 294,000 mg/m^3 respectively) is low. Anesthetic effects have been reported in humans at levels of 12000 ppm (30,720 mg/m^3 for a five minute exposure period. The NOAEL for inhalation exposure to rats, rabbits, guinea pigs or dogs is 50 ppm (128 mg/m^3) for 6 months. For oral repeated dose, the critical target organ is the liver (liver cell polymorphism) with a lifetime NOAEL in the rat of 0.13 mg/kg/day. Vinyl chloride (and/or its metabolites) produces DNA adducts and has been positive in gene mutation and chromosomal aberration assays. Chromosomal aberrations have also been observed in peripheral lymphocytes of exposed workers in some studies. Long term exposure in experimental animals and humans causes liver cancer (angiosarcoma). Vinyl chloride is a known human carcinogen. Cancer of the lymphopoietic system, connective tissues, and soft tissue have been associated with vinyl chloride exposure in some studies, but not others. In a combined reproductive/developmental study in rats the NOAEL for reproductive/developmental effects was 1,100 ppm (2816 mg/m^3), the highest dose tested. Human studies have not linked vinyl chloride exposure with negative reproductive outcomes.

Environment

Vinyl Chloride has a vapor pressure of 3330 hPa at 20^{0}C, a water solubility value of 1.1 g/l at 20^{0}C and a log P_{ow} of 1.58 at 22^{0}C. In the soil and water microorganism study, vinyl chloride was biodegraded at 30% after 40 days and 99% after 108 days, and has a low bioaccumulation potential. Environmental releases of vinyl chloride are almost exclusively to the air compartment. Fugacity modeling indicates that of the vinyl chloride released >99% will remain in the air compartment. The dominant removal process in the atmosphere is photoxidation with a calculated half-life of 2.2 – 2.7 days. The 96 hour LC_{50} ranges from 210 to > 1000mg/l for fish (four studies). The estimated QSAR value for algae EC_{50} (96hr) is 118 mg/L and the LC_{50} (48 hr) for daphnia is 196 mg/L. Toxic concentrations of vinyl chloride are not expected to be reached in aquatic systems based on low emissions, low bioaccumulation potential and high volatility.

Exposure

Vinyl chloride is a gas, which is manufactured in closed systems as an industrial intermediate - mainly for the production of polyvinyl chloride (PVC) and vinyl copolymers. North American production capacity in 1999 was

about 8.344 million metric tons and global capacity was 30.022 million metric tons. Workplace exposure is tightly controlled in the U.S. and other OECD countries. The most likely route for consumer and environmental exposure is inhalation of residual vinyl chloride monomer (VCM) present in PVC products, however, residual monomer levels in these products are highly regulated and tightly controlled to very low levels. Such products include food packaging, medical devices, PVC pipe, wire coatings, automotive interiors, exterior siding, interior vinyl floors, wall and furniture coverings, and toys. Vinyl chloride is present in the air near production facilities generally at levels <0.1 mg/m^3, and in ground water generally below the 0.001 ppm detection limit.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-38-7
Chemical Name	1,1-Difluoroethylene or vinylidene fluoride
Structural Formula	$F_2C=CH_2$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Metabolic/kinetic studies with vinylidene fluoride (VF2) in rats and mice indicate that during inhalational exposure, VF2 reaches a maximum level in blood at 15 minutes. Some metabolism takes place in the liver. It has been hypothesized that some fluoroacetic acid may be formed during metabolisation of VF2, which in turn may interfere with the citric acid cycle. However, mammalian toxicity study results do not indicate that this leads to structural or functional pathological changes.

Acute toxicity of VF2 is low with 1 hr LC00 of 200,000 ppm (524,000 mg/m^3) in rats. Only slight CNS effects were noted at very high concentrations (80% in air). Cardiac sensitization studies were negative. Several inhalation exposure studies have been conducted in rats and mice exposed 6h/d, 5d/week for 13 weeks. No target organs were consistently identified although effects on the kidney, spleen and testes were reported in various studies. In rats and mice the LOEC of 500 ppm (13,100 mg/m^3) was identified, based on body, organ weight and clinical chemistry changes in the absence of histopathological changes. A NOEC of 250 ppm (6,550 mg/m3) was identified in rats. At 40,000 - 50,000 ppm (104,8000 – 131,000 mg/m^3) effects on the nasal epithelium were noted in rats.

In chronic toxicity/carcinogenicity inhalation studies, rats and mice were exposed 6 h/d, 5d/week for 24 and 18 months, respectively at concentrations up to 10,000 ppm (26,200 mg/m^3). Neoplastic findings were comparable in control and treated animals. An earlier 52 week study in rats exposed orally to VF2 indicated increased lipomas/liposarcomas. However, this study was performed according to a protocol with significant deviations from currently prescribed guidelines and was reported in insufficient detail for proper evaluation. In genotoxicity studies, VF2 has shown some activity in bacterial assays, but was negative in the *in vitro* chromosomal aberration and gene mutation study in mammalian cells. *In vivo*, VF2 was negative in a mouse micronucleus and Drosophila SLRL test. Thus there is no evidence of genotoxicity *in vivo*. Overall, the results suggest that VF2 does not present a genotoxic hazard to man.

VF2 did not induce teratogenic or embryofetal toxicity effects in developmental toxicity studies in rats exposed up to 10,000 ppm during gestation days 6 –15. The NOEL for reproductive effects is $\geq$ 7000 ppm (18,340 mg/m^3) in rat studies.

Environment

VF2 is a gas at ambient temperatures and atmospheric pressure. Emissions will only occur during production and processing of VF2 and will partition nearly exclusively to air (>99%). Its low log P_{ow} does not indicate any significant bioaccumulative potential. In air, VF2 will be degraded by reaction with hydroxyl radicals. A half-life of

3.3 days has been calculated. Likely primary products resulting from the tropospheric degradation of VF2 are COF_2 and formaldehyde. Fluorogyloxal (CFOCHO) may also be a product of the degradation of VF2. The ultimate degradation products are formaldehyde, HF and CO2.

No biodegradation studies in water have been performed for VF2, however, related gaseous materials (tetrafluoroethane, pentafluoroethane, difluoromethane, 1-chloro-1,1-difluorethane, vinylidine chloride) generally showed < 10% degradation indicating that transformation to metabolites in soil or the water compartment may be considered very low. Based on these analogous substances, VF2 is not expected to be readily biodegradable and testing is not recommended. Due to specific physico-chemical properties of VF2 its production and use pattern, and its nearly exclusive partitioning to air, no aquatic toxicity testing has been performed. Using QSAR, the LC50 (96 hr) for fish is 245 mg/L, the daphnia LC50 (48 hr) is 250 mg/L and the green algae EC50 (96 hr) is 149 mg/L.

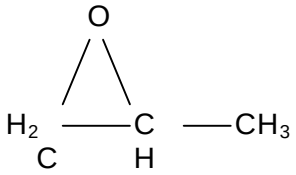
Exposure

VF2 is almost exclusively used as a monomer for the production of fluoropolymers (polyvinylidene flouride) and as copolymer with hexafluoropropylene and chlorotrifluoroethylene. In the United States, production is performed in closed systems and is anticipated to be representative of global production methods based on the chemicals physical chemical properties. Global production in 1999 was approximately 33,000 tonnes (72,600,000 pounds). The emissions of VF2 come exclusively from production and processing installations of VF2. The segment of the population exposed directly or indirectly to VF2 is very limited: workers during production and processing. Consumers manipulating goods made of VF2 (polymers) are not exposed to VF2. Possible emissions during production and processing are low and lead to very low atmospheric concentrations. VF2 is not expected to be released to water systems but in case of emissions will totally partition to air. It will not partition to the water from the air. VF2 is a flammable gas at ambient temperature (limits 4.7 % to 25.1%). Its flammability constitutes its most important physical danger.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-56-9
Chemical Name	Methyl oxirane (Propylene oxide)
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The human health effects database meets the requirements for the SIDS data package. Propylene oxide is extremely flammable. Hazardous polymerisation may occur when in contact with highly active catalytic sources or changes of neutrality (e.g. in contact with acids, bases, oxidising materials).

PO is rapidly absorbed into the tissues and metabolised via conjugation with glutathione and hydrolysis. At high doses saturation of the metabolic process for elimination is assumed. Haemoglobin and DNA adduct formation has been observed in several animal tissues following inhalation exposure, including nasal mucosa, trachea, lung, liver, brain and testes. The presence of kidney adducts have not been investigated in the inhalation experiments. PO is harmful to human health following single exposure via inhalation, ingestion or contact. No reliable human data are available. In experimental animals, acute toxicity oral LD50 values are 520 - 950 mg/kg; dermal LD50s values are 1250mg/kg and 950 mg/kg; inhalation 4 hour LC50 values are about 4000 ppm in the rat and 1740 ppm in the mouse. Signs of respiratory tract irritation were observed.

PO may cause local irritation on contact with the skin and eyes. PO has demonstrated some potential to cause skin sensitisation and it is plausible that it could bind to tissue proteins and elicit an immunological response. There is no data available on respiratory sensitisation. Repeated inhalation exposure produces irritation of the nasal epithelium, with marginal effects at 30 ppm and pronounced epithelial damage at 100 ppm and above. Neurotoxicity was observed in experimental animals exposed to 1500 ppm for 7 weeks, although no such effects were observed in rats exposed to 300 ppm for 24 weeks. Repeated oral administration caused gastric irritation, with microscopic changes such as reactive changes in the squamous epithelium of the stomach at the lowest dose tested, 15 mg/kg. Target tissues are the sites of the initial contact.

Propylene oxide is a direct acting mutagen in a wide variety of standard *in vitro* test systems and genotoxic in somatic cells *in vivo*. There is no evidence for propylene oxide induced heritable mutations in germ cells from dominant lethal tests in rats and mice. Given that propylene oxide is a direct-acting mutagen that might reach the germ cells (DNA adducts seen in the testes) the possibility for PO inducing heritable mutations in germ cells cannot be discounted.

PO is a respiratory tract carcinogen in animals. Repeated gavage induced forestomach carcinoma in rats. At present, the relative contribution to the carcinogenic process made by irritation, consequential proliferative response and genotoxicity is unclear.

There is no evidence for reproductive and developmental toxicity at non-maternally toxic dose levels from animal studies.

Environment

The environmental effects database meets the requirements for the SIDS data package.

Short-term toxicity data are available for fish, daphnia and algae, but there are no long-term studies. Fish appear to be the most sensitive organisms, with the lowest 96h LC_{50} value of 52 mg/l for rainbow trout, *Oncorhynchus mykiss*. The only reported test on aquatic invertebrates was conducted on *Daphnia magna*, 48-hour EC_{50} 350 mg/l. A single algal test is available, with 96h EC50 240 mg/l, NOEC 100 mg/l based on growth (*Selenastrum capricornutum)*. A PNEC of 52 µg/l was derived from the acute fish toxicity data, using an assessment factor of 1000 according to the EU technical guidance. There are no data on sediment organisms, so the equilibrium partitioning method was used to obtain a PNEC of 43.2 µg/kg for sediment. There are some data on effects on soil from fumigation experiments using high exposure levels. These demonstrate that propylene oxide sterilises soil. However, these results could not be used to derive a NOEC. The equilibrium partitioning method was used to derive a PNEC for soil of 16.5 µg/kg. Data relating to terrestrial plants are also available. The germination and growth of wheat and alfalfa were retarded by 50-60% in propylene oxide-treated soil (initial concentration 32 and 68 g propylene oxide /kg dry weight).

Propylene oxide is not considered to be important as a cause of photochemical air pollution. Although some of the potential products of propylene oxide breakdown in the atmosphere have relatively high photochemical ozone creation potentials, they are unlikely to be formed at a rate that could give rise to local air pollution problems.

Exposure

The annual world production of propylene oxide (PO) was 3.5 million tonnes in 1990 with an increasing trend. Production in the European Union (EU) is estimated as 1.45 million tonnes, with 1.5 million tonnes used. There are at least 7 EU producers and an estimated 150-300 user plants within the EU. Propylene oxide has two main use areas: as a monomer in polymer production (polyols, used in polyurethane production and other areas) and as an intermediate (for propylene glycol, propylene glycol ethers, butanediol). Direct uses include use as a stabiliser (e.g. in dichloromethane and other hydrocarbons), fumigation of foodstuffs (in the USA) and as a solvent in the preparation of samples for electronmicroscopy. Propylene oxide is not used as a food fumigant in the EU and this has not been addressed in the accompanying risk assessment. Release of propylene oxide to water and air compartments could arise from production and processing, and there is possible release to air arising from direct use.

In the EU, during manufacture and use as an intermediate PO is mainly used in closed systems and there is a potential for occupational exposure to occur via inhalation or contact during breaches of the system. The potential for exposure is controlled to as low as is reasonably practicable. This includes use of enclosed sampling systems, dry break coupling systems for transfer of PO to or from rail and road tankers, magnetic delivery pumps, systems for purging and testing process lines before breaching, use of PPE and the monitoring and control of fugitive emissions. PO is used as an intermediate in the manufacture of consumer products. Because of the reactivity of PO and subsequent dilution in consumer products, consumer exposure to residual PO in consumer products (foodstuffs, medicinal products, and hydraulic brake fluids for cars) is considered to be extremely low. Human exposure indirectly via the environment is primarily via inhalation and is extremely low.

Propylene oxide is a liquid, with a melting point of -112.16°C, boiling point of 34°C, vapour pressure 60 kPa at 20°C, water solubility 400 g/l and octanol-water partition coefficient (log Kow) 0.055. The half-life in air is estimated as 32 days. The substance hydrolyses in water, with a half-life at neutral pH of 22 days. The hydrolysis product is propylene glycol which is readily degradable. The biodegradation data shows variable results; it has been

interpreted as showing inherent biodegradability but with ready biodegradation in wastewater treatment plants where bacterial populations are acclimated. Propylene oxide is not very volatile from water (a Henry's Law constant of 12.4 Pa m^3 $mole^{-1}$ has been assumed) and has a high water solubility. It is unlikely to bioaccumulate, since the predicted log BCF is -0.65. Propylene oxide will not be sorbed strongly to organic matter (predicted Log Koc = 1.05).

NATURE OF FURTHER WORK RECOMMENDED

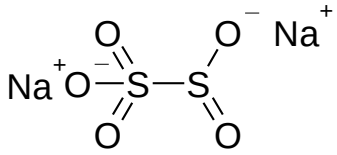
Sufficient information exists to address hazard classification for all SIDS endpoints and for other non-SIDS endpoints. However, the chemical is a candidate for further work as follows:

National or regional exposure information gathering and risk assessment may need to be considered where there is potential for exposure.

If significant soil exposure is likely, for example from fumigant use, it may be necessary to refine the PNEC for soil and soil toxicity testing may be required. It is noted that in the USA use as a fumigant is well controlled.

No thresholds have been identified below which there would be no concern for human health for the endpoints of mutagenicity and carcinogenicity (based on an existing regional risk assessment for Europe). In the EU, further risk reduction was not considered necessary as the industry currently maintains occupational exposures to be as low as is reasonably practicable (further information available from SIDS dossier). This conclusion is valid so long as industry continue to implement new procedures to reduce exposures when possible. It is noted that in the USA the minor fumigant use is highly controlled and regulated. Further risk reduction is not necessary for consumers or for exposures via the environment where exposure is extremely low. Due to insufficient information on skin sensitisation, a risk assessment was not conducted for this endpoint. Due to the concerns for mutagenicity and carcinogenicity (outlined above) further testing for this endpoint would not affect the risk assessment or management outcomes.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7681-57-4
Chemical Name	Disodium disulphite
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Disodium disulphite is rapidly eliminated as sulphate in humans and dogs. When sulphite is present in the tissues in sufficiently high concentrations, it may be metabolized to inorganic thiosulphate that is then excreted in the urine. The acute toxicity of oral LD_{50} in rats is 1,540 mg/kg bw. In decedents, toxicity was observed to the stomach and liver, and the gastro-intestinal tract was filled with blood. For repeated dose toxicity, disodium disulphite was given to rats through diet for 30 to 104 weeks. The predominant effect was the induction of stomach lesions due to local irritation and was characterized as forestomach and glandular stomach hyperplasias and inflammation. There were no signs of local toxicity (stomach irritation) at ca. 217 mg/kg bw/day, and the lowest dose where this effect occurred was ca. 454 mg/kg bw/day as actual intake dose [NOAEL for local (stomach irritation), rats, oral feed : ca. 217 mg/kg bw/day]. From the same dietary study in rats, the NOAEL for systemic effects was the highest dose tested (942 mg/kg bw/day).

The results of genotoxic tests *in vitro* are equivocal but there is no evidence that disodium disulphite is genotoxic *in vivo*. It was not carcinogenic in rats that received disodium disulphite via feed for 104 weeks. No reproduction toxicity of disodium disulphite was observed for a period of up to 2 years and over three generations (NOAEL, fertility, oral feed: ca. 942 mg/kg bw/day). No developmental toxicity and teratogenic effects appeared in rats or rabbits at the highest dose tested (NOAEL 110 and 123 mg/kg bw/day, respectively).

This chemical is not irritating to the skin, but irritating to the eyes. In humans, urticaria and asthma with itching, edema, rhinitis, and nasal congestion were reported. An immunological pathogenesis of these reactions is still not clear. In a non-guideline study, no indication of skin sensitization for guinea pig was observed. In a few cases allergic contact dermatitis as well as positive patch-testing was observed. With respect to wide spread use, it is not considered as a skin sensitizer. Disodium disulphite is unlikely to induce respiratory sensitization but may enhance symptoms of asthma in sensitive individuals. Given the wide-spread use, the number of cases is considered to be low.

Environment

Boiling point, melting point and vapour pressure are not relevant for disodium disulphite. Also, testing for the endpoint of biodegradability, is not appropriate due the chemical not being an organic chemical. Bioaccumulation is

not expected. For the boiling point, decomposition occurred at 150 °C to form sulfur dioxide. This chemical will be mainly transported to the water compartment when released to environmental compartments since it is highly water soluble (470 g/L at 20℃). The low K_{OC} (2.447) indicates that disodium disulphite is so mobile in soil that it may not stay in the terrestrial compartment. Instead it has a potential to leach into the groundwater.

The chemical has been tested in a limited number of aquatic species. In an acute toxicity test with fish, the 96 hr-LC_{50} was >100 mg/L. For algae, the 72 hr-EC_{50} was 48.1 mg/L. For daphnids, the acute 48 hr-EC_{50} was 88.76 mg/L, and the chronic 21day-NOEC was >10 mg/L. Therefore, a PNEC of 0.1 mg/L for aquatic organisms was obtained from the chronic NOEC for daphnids using an assessment factor of 100.

Exposure

In 1999, estimates for the world market of sodium salts of sulphites, without China and the Russian Federation, amounted to approx. 330,000 tonnes/ year. These are distributed as follows : 20,000 tonnes in Germany, 60,000 tonnes in the rest of Europe and 250,000 tonnes in the rest of the world. Disodium disulphite is a basic chemical and used in chemical synthesis. Exposure to consumer may occur, but the extent of this exposure is unknown. There is a potential for exposure to the respiratory tract, skin and eyes during manufacture or formulation of the chemical into products.

In Korea, the total production of disodium disulphite was about 3,200 tonnes/year in 1998. The chemical is used in tanning agents, food additives, bleaching agents, photography and reducing agents but the amount for each use pattern is not available. There is no exposure data for the environment and humans at the present time.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-10-7
Chemical Name	2-Propenoic acid (Acrylic acid)
Structural Formula	$C_3H_4O_2$

RECOMMENDATIONS

The chemical is a candidate for further work (environment and consumer).
Risk reduction measures are recommended for the workers.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acrylic acid is absorbed via the lungs in animals and humans, absorption via the oral and dermal routes of exposure is demonstrated. In animals with solely nasal respiration, it is resorbed at the nasal mucosa. The extent of absorption depends on pH and solvent with direct dependence on substance concentration. In mice acrylic acid is rapidly and completely metabolised mainly in liver and kidney via the normal catabolic pathways of beta-oxidation. Elimination preferably occurs as carbon dioxide.

Pure acrylic acid is a very reactive chemical and accordingly exhibits severe corrosive properties in contact with biological material. Thus, acrylic acid causes acute harmful effects by oral and dermal exposure. Oral LD50 values for rats cover a range from 140 up to 1400 mg/kg bw depending on the concentration of the test substance. An oral LD50 of 1350 mg/kg bw was detected for male rats with a 10% aqueous solution of acrylic acid (pH 2.5) thus indicating that corrosive effects are not caused by the pH of the test substance. A dermal LD50 of 640 mg/kg bw was determined for rabbits (with undiluted acrylic acid). Acute inhalation toxicity is low because acrylic acid interacts with humidity of the air prior to reaching the depth of the respiratory tract. LC50 values of 3.6 to >5.1 mg/l/4 hours have been determined.

Workplace data demonstrate that acrylic acid causes skin corrosion and irritation of the respiratory tract in humans. In tests with rabbits the pure acid caused severe burns to skin and eyes. Severe ocular damage caused by acrylic acid cannot be avoided by neutralizing the acid.

Pure acrylic acid does not show skin sensitizing properties in animal sensitization tests. However, skin sensitization was observed in humans. This was attributed to oligomeric impurities in the raw material. Respiratory sensitization has not been observed in humans.

Repeated oral and inhalation exposure of acrylic acid to rats and mice resulted in dose related severe effects. Gavage on 90 days revealed dose-dependent mortality, irritation and ulceration of the stomach, and renal tubular necrosis in rats (LOAEL 150 mg/kg bw/d). No specific toxic effects were noted in subchronic and chronic drinking water studies. Reduced palatability (decreased water consumption) and unspecific signs of toxicity (decreased food consumption, body weight gain) at dosages >2000 ppm (100 mg/kg bw/d in male rats, 150 mg/kg bw/d in females) were observed. In a 90-day inhalation study, acrylic acid induced degenerative lesions on the olfactory mucosa in mice at 5 ppm (0.015 mg/l) and in rats at 75 ppm (0.221 mg/l). Mice seemed to be more sensitive than rats, thus a LOAEC of 5 ppm (0.015 mg/l) was derived for local effects. Long term dermal exposure at concentrations >1 % resulted in skin irritation.

Acrylic acid did not induce gene mutations in Salmonella or CHO cells (HPRT locus) but was clearly positive in the mouse lymphoma assay and in the *in vitro* chromosomal aberration test. In the mouse lymphoma assay small colonies were induced preferentially, thus the mutagenic potential of acrylic acid seems to be limited to clastogenicity. *In vivo*, acrylic acid did not induce mutagenic effects in either rat bone marrow cells or mouse germ cells after oral administration.

There is no evidence that acrylic acid administered orally to rats or applied dermally to mice is carcinogenic. There are no cancer data available with respect to human exposure.

In oral studies on rats no effects on reproductive function (fertility) were observed. Some signs of postnatal developmental toxicity (retarded body weight gain of the pups) were seen following exposure of the parental generation at dose levels that led to reduced food intake and weight gain in the dams. No gross abnormalities were observed in the offspring. No prenatal developmental toxicity was observed in rats and rabbits following inhalation exposure.

Environment

AA is fully miscible in water, has a vapour pressure of 3.8 hPa, and a log Pow of 0.46. The environmental behaviour of AA is determined by its range of 40 - 156 hours atmospheric half life and very low volatility. AA is readily biodegradable. Hydrolysis is not significant at all tested pHs (3, 7, 11). The average Kp value of 1.0 l/kg indicates no relevant adsorption onto sediment or soil. Based on the physico-chemical properties of AA, hydrosphere and to a much lower extent air are the preferred target compartments for distribution and neither relevant bioaccumulation nor geoaccumulation are expected. In waste water treatment plants (WWTPs) 87.3 % of the substance are estimated to be removed entirely by biodegradation.

For fish, three valid results from acute tests are currently available. *Oncorhynchus mykiss* was found to be most sensitive, the recorded 96h-LC50 is 27 mg/l. For invertebrates, acute and long-term studies on *Daphnia magna* had been conducted. A 48h-EC50 of 47 mg/l and a 21d NOEC of 7 mg/l was obtained. Among four algae toxicity tests, the results of two independent guideline studies with *Scenedesmus subspicatus*, point particularly at specific algal sensitivity to AA. Derived from growth rate, the reported 72h-EC50 is 0.13 mg/l and the 72h-EC10 is 0.03 mg/l, respectively.

The Predicted No Effect Concentration (PNEC) is derived from the lowest valid effect concentration, i.e. 30 µg/l in an algae test. Although long-term test results are available from only two trophic levels, an assessment factor of 10 can be chosen because of the comparatively high toxicity of AA to algae. PNECaqua = 3 µg/l.

The derivation of a PNEC for microorganisms is based on results from tests on cell multiplication inhibition with protozoa and bacteria. For three protozoa tests NOEC values between 0.9 mg/l and 41 mg/l are reported, for a bacterial test with activated sludge a 30min-NOEC of 100 mg/l is reported. Applying an assessment factor of 1 for the protozoan species, the PNECmicroorganisms is set at 0.9 mg/l for municipal plants. For industrial plants, a PNEC of 10 mg/l is derived, applying an assessment factor of 10 to the result with activated sludge.

It is not possible to derive a PNEC for the atmospheric compartment due to the lack of experimental data.

Only one test on effects to terrestrial organisms is available. A respiration inhibition test with natural soil microflora revealed a 28d-NOEC of 100 mg/kg bw. With an assessment factor of 1,000 a PNECsoil of 0.1 mg/kg would result.

Exposure

In the European Union acrylic acid (hereafter referred to as AA) is produced and isolated as chemical intermediate. According to industry statements the total EU production capacity is estimated at 830,000 t/a for 1997/1998. The market trend is quite dynamic during the last decade with apparent annual growth rates about 5 %.

AA is either processed directly into a polyacrylate or polymerised via the intermediate stage of an acrylate ester.

Furthermore, acrylic acid is used as an ingredient and occurs as residual monomer in consumer products like adhesives, paints, binding agents and printing inks. Among the homo- and copolymerisates of AA, superabsorber polymers (SAP) are the most expansive use.

About half of the 830 000 t/a crude AA is processed to purified (glacial) AA, which is further processed both on-site (captive use) and by external downstream users. The other half of crude AA is transformed into various acrylate esters at the production sites. 99% of the acrylate esters are n-butyl, ethyl, methyl and 2-ethylhexyl acrylates, of which butyl acrylate predominates quantitatively. Identical to glacial AA, these acrylic esters serve as commercial products, which are further processed both on-site and by external downstream users.

Releases of AA into the environment are to be expected during production and processing mainly via waste water and less amounts via exhaust gases. Regarding the formulation step, relevant releases may possibly occur during formulation of polymer dispersions. Residual monomeric AA-contents, which are the basis for release estimations from different polymeric products, are reported to range between 0.0002 and 0.2 %. From the use of grouting agents containing magnesium diacrylate, releases of AA to the hydrosphere occur via drainage water. Direct releases to agricultural or natural soil are not expected from the current use pattern.

Occupational exposure occurs during production and further processing and during manufacture and use of adhesives.

NATURE OF FURTHER WORK RECOMMENDED

This substance is agreed in the European Union Risk Assessment Programme under Regulation EEC/793/93, with the following conclusions:

Environment:

There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account:

Acrylic acid (AA) represents, based on the present data configuration, a potential risk to the local aquatic environment from wet polymerisation processes including wet production of SAP (super absorber polymers) by downstream users of monomeric AA (default calculations and three known sites).

Although an improvement of the data configuration (i.e. effluent measurements and/or site specific data on flow rates for the whole range of relevant sites) may in principle be possible, it is judged to be unlikely that representative monitoring data from the downstream users can be obtained sufficiently complete with reasonable expenditure of time and money. For certain known SAP production sites and wet polymerisation sites, regular effluent concentrations up to >> 100 mg/l AA have been reported. These data indicate that high effluent concentrations cannot be excluded, if certain types of process engineering are applied. On the other hand, application of waste water reutilization / recycling systems is known to warrant zero emission to hydrosphere at a number of downstream user sites which are processing about 50 % of AA used externally for SAP production and about 12 % of AA used externally in wet polymerisation processes. Measures to be applied for limiting the risk to the local aquatic environment are supposed to be also protective for municipal waste water treatment plants.

During the use of a grouting agent containing magnesium diacrylate high concentrations of AA are released via the drainage water. The exposure assessment was based on measured effluent concentrations at a tunnel construction site. Quantitative extrapolation to other construction sites seems difficult, but similar conditions might be anticipated. Dependent on the local circumstances appropriate measures have to be chosen.

Acrylic acid (AA) represents, based on the present data configuration, a potential risk to municipal waste water treatment plants for the downstream use scenarios of SAP production (default calculation and highest site specific PECwwtp) and wet polymerisation (default calculation and two known sites). However, possible further testing to

refine the data configuration is postponed, since risk reduction measures necessary to remove concern for surface water will also cover the protection of municipal waste water treatment plants.

Human Health:

Consumer: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Worker: There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The occupational risk assessment comes to the conclusion that additional risk reduction measures are necessary for inhalation exposure in several scenarios. The relevant toxicological endpoints via inhalation are irritation and repeated dose toxicity (local and systemic effects).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-20-9
Chemical Name	Methylacetate
Structural Formula	CH_3-C(=O)-O-CH_3

RECOMMENDATIONS

The chemical is currently of low priority for further work (environment and consumer).
Risk reduction measures are recommended for the workers.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Methyl acetate is absorbed via the lungs in animals and humans, absorption via the oral route is demonstrated. After absorption the substance undergoes hydrolysis to methanol and acetic acid. From the available *in vitro* data it may be anticipated that the half-life of methyl acetate in blood ranges between 2 and 4 hours. Immediately after stopping a 6-hours-inhalation exposure to rats (2000 ppm, 6.04 mg/l) blood concentrations below the limit of quantification (< 4.6 mg/l) were determined indicating rapid hydrolysis and high clearance of the substance. Thus, a low systemic availability of methyl acetate can be assumed. The main metabolite methanol is metabolized to formic acid. Formate is introduced into C1-metabolism after activation by reacting with tetrahydrofolate. Humans as well as monkeys are more sensitive to methanol poisoning compared with rats because of a lower tetrahydrofolate content in liver. Therefore, the interspecies differences in the metabolism are considered mainly of concern at dose levels leading to acute toxicity.

Methyl acetate is of low acute toxicity (rats LD50 oral: 6482 mg/kg bw, dermal: > 2000 mg/kg bw, LC50: > 49 mg/l/4h). After oral application and after inhalation animals showed narcotic symptoms, spasms, dyspnea and vomiting. Inhalation of vapors in addition caused irritation of eyes and upper respiratory tract. The narcotic concentrations for mice and cats are 34 mg/l and 56 mg/l, respectively. In humans accidental inhalation of vapors caused severe headache and considerable somnolence.

Methyl acetate causes only weak skin irritation in humans and in rabbits. Eye irritation, however, was strong but reversible within 7 days. Exposure to methyl acetate vapors causes irritation to eyes and respiratory tract of humans. Taking into account the long experience with human exposure, methyl acetate is not supposed to exhibit skin sensitizing properties. No relevant human or animal data are available.

A 28-day inhalation study on rats revealed degeneration/necrosis of the olfactory mucosa (nose) at a methyl acetate concentration of 2000 ppm (6.04 mg/l). In addition, diureses, minimal liver cell dysfunction, adrenal weight increase, and reduces serum cholesterol concentrations are observed. The NOAEC both for local and systemic effects was identified at 350 ppm (1.06 mg/l). No repeated dose studies are available for the oral and dermal route. In a study on cats, inhalation exposure for 5 days to about 20 mg/l methyl acetate resulted in increased hemoglobin and erythrocyte levels, transient leukocytosis, eye irritation and moderate CNS depression.

Methyl acetate showed negative results in a bacterial mutation test and a rat bone marrow micronucleus test. Furthermore, the hydrolysis products methanol and acetic acid do not reveal evidence for a mutagenic potential.

No data are known which give relevant concern on cancerogenicity following methyl acetate exposure, although in methanol studies on rats and mice an increased incidence of lung adenoma/adenomatosis was seen in high dose male rats only.

No data are available on the reproductive toxicity of methyl acetate itself. However, due to the rapid hydrolysis of the compound hazards with respect to reproduction can be assessed on the toxicological properties of the immediate metabolites. No indications of a fetotoxic or teratogenic potential of acetic acid are found, whereas embryo-/fetotoxic and teratogenic effects were demonstrated for methanol in rodents at high, maternally toxic concentrations. A NOEC/fertility for methanol of 1000 ppm (1.3 mg/l) was derived from a 2-generation inhalation study with rats. Assuming an immediate degradation of methyl acetate to methanol at a molar ratio of 1, this value corresponds to a NOAEC/fertility of about 3.0 mg methyl acetate/l. A NOAEC/developmental toxicity for methanol of 1000 ppm (1.3 mg/l) was derived from studies with mice and rats corresponding to a NOAEC/developmental toxicity of about 3.0 mg methyl acetate/l.

Environment

Methylacetate has a water solubility of 250 -295 g/l, a vapor pressure of 217 hPa and a log Kow of 0.18. According to the physico-chemical properties the target compartment for this substance are the atmosphere (69.3 %) and the hydrosphere (30.7 %). Methylacetate is stable in neutral solution. The substance is classified as "readily biodegradable". There is no considerable potential for bio- or geoaccumulation. An atmospheric half-life of 50.4 days was calculated for methylacetate.

The following results from ecotoxicity tests with aquatic species are available:

In a short-term test with fish a 96h LC_{50} of 320 mg/l was found for *Pimephales promelas*. For invertebrates an acute study on *Daphnia magna* had been conducted. A 48 h EC_{50} of 1027 mg/l was found. In a study with *Scenedesmus subspicatus* no effects could be observed after 72 h at a concentration of 120 mg/l. Long-term toxicity tests with fish and invertebrates are not available. With an assessment factor of 1000 a PNEC of 320 µg/l is determined.

Exposure

The production volume of methylacetate in the EU was ca. 30,000 t/a in 1993. Methylacetate is used as intermediate in chemical synthesis for the production of vitamins and crop protection agents. The chemical is also used as a solvent in paints and lacquers, in household chemicals and in adhesives. In Germany, approximately 70 % of the methylacetate is used as solvent, about 10 % is used as intermediate and the remainder 20 % are exported for the production of sweeteners. No information on the use pattern of the substance in the EU is available. However, it is assumed that the use pattern for Germany is also applicable to the EU.

Releases into the hydrosphere and atmosphere are expected from production, processing and use as solvent. Exposure of the terrestrial compartment is expected due to deposition from the atmosphere.

Workers are exposed during production and further processing, use of formulations (paints, adhesives, cleansers) and few other uses (flooring works, use of cosmetics).

NATURE OF FURTHER WORK RECOMMENDED

This substance has been agreed in the European Union Risk Assessment Program under Regulation EEC/793/93 with the following conclusion:

Environment:

There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

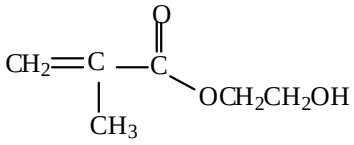
Human Health:

Consumer: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Worker: There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The occupational risk assessment comes to the conclusion that additional risk reduction measures are necessary for inhalation exposure in several scenarios. The relevant toxicological endpoints via inhalation are irritation, repeated dose toxicity (local and systemic effects) and developmental toxicity.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	868-77-9
Chemical Name	2-hydroxyethyl methacrylate
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute toxicity of hydroxyethylmethacrylate (HEMA) is low (Oral LD50 > 4000 mg/kg; Dermal LD50 > 3000 mg/kg). HEMA is not more than slightly irritating to skin, and moderately irritating to eyes. HEMA is hydrolyzed to methacrylic acid and ethylene glycol. While other acrylates and methacrylates have been shown to cause nasal lesions on inhalation after hydrolysis to Methacrylic Acid (MAA) (discussed in SIAM 11), this effect has not been observed for HEMA.

The effects of repeated oral administration to CRJ CD(SD) rats of HEMA were shown in a combined repeat dose developmental reproductive screening assay (OECD TG 422) at concentrations of 30, 100, 300, and 1000 mg/kg/day. In males, systemic toxicity was seen only at the highest dose level, 1000 mg/kg/day, after 49 day of treatment. These signs included salivation, suppression of body weight gain, decreased feed consumption, increased relative liver weights, decreased triglycerides and increased K, Cl, or inorganic phosphorous. Relative kidney weights were increased at 100 mg/kg/day or higher. Findings related to renal histopathology were found only at 1000 mg/kg/day, the high (limit) dose group, of mild severity. One of 12 animals in this group died.

In females, HEMA was administered from 14 day prior to mating through the 3rd day of lactation. Six of the 12 animals died in the high dose group, 1000 mg/kg/day. Agonal effects or general weakness preceded death. There was suppression of body weight gain, decreased feed consumption, increased absolute and relative kidney weights, and neutrophilic cellular infiltration in the renal papillae and medulla. Histopathologic changes included a slightly softened spinal cord of one animal of those dying. The NOAEL for repeat dose toxicity in males and females was 30 mg/kg/day. The LOAEL was 100 mg/kg/day, which showed only an increased relative kidney weight (females).

This chemical was not mutagenic in bacteria but was clastogenic and induced polyploidy in mammalian cells *in vitro*. It, however, did not induce micronuclei in rat bone marrow up to the maximum tolerated dose. Based on the weight of evidence, it could be concluded that the chemical was not genotoxic *in vivo*, as it did not induce micronuclei in bone marrow.

In the six surviving females of in the above-mentioned OECD TG 422 assay, HEMA produced no sign of reproductive or developmental toxicity up to 1000 mg/kg/day, the limit dose. Thus, the NOAEL was 1000 mg/kg/day for both reproduction (both sexes, adults) and developmental (offspring) toxicity.

Animal studies suggest HEMA is a weak skin sensitizer in guinea pigs giving variable (mixed) results depending on the protocol. Positive reactions were shown only with injection of Freund's adjuvant but not by topical application alone. Whether or not this chemical induces skin sensitization in humans is equivocal; mixed results are reported in the literature on dental clients. Based on human patch test results, HEMA has sensitizing properties and HEMA has potential for cross-reaction with other (meth)acrylates.

Environment

HEMA is readily biodegradable (OECD 301C; BOD: 92-100 % after 14 days), and has a low bioaccumulation potential based on the Log Pow (0.42). Abiotically this chemical is stable at pH 4 and 7, whereas it is hydrolyzed at pH 9 with a half-life of 10.9 days.

This chemical has been tested in a limited number of aquatic species including algae, daphnid and fish. The toxicity (growth inhibition: OECD TG 201) to algae (*Selenastrum capricornutum*) was 345 mg/L for 72 h-EC50 and 160 mg/L for 72 h-NOEC. The acute (immobility: OECD TG 202) and chronic toxicity results (reproduction: OECD TG 202) for *Daphnia magna* were 380 mg/L (48 h-EC50), 90.1 mg/L (21d-EC50), 24.1 mg/L (21d-NOEC), respectively. The acute LC50 (96 h: OECD TG 203) was 227 mg/L for fish (*Pimephales promelas*) while the prolonged toxicity (14 d: OECD TG 204) for fish (*Medaka; Oryzias latipes*) was >100 mg/L. An assessment factor of 100 was used to calculate the predicted no-effect concentration (PNEC) of 0.241 mg/L for aquatic organisms because two chronic data (daphnid and algae) were available.

Exposure

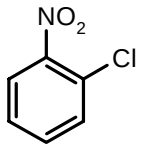
In 1999, the production volume of HEMA was reported as approximately 15,000 t/year in Japan and 42,000 t/year world-wide. HEMA is used industrially as a monomer for synthesis of polymers, and for dental prosthetics. It is also used in geotechnical grouting in construction work. Fugacity modeling (Mackay level III) predicts that HEMA released to water unlikely will migrate into other compartments. HEMA is readily biodegradable and not persistent in the water phase. On the other hand, when this chemical is released to air, it will be transported to soil and water compartment to a certain extent.

HEMA is produced in a fully-closed system and workplace exposures during production are controlled. Occupational and non-occupational inhalation exposures to HEMA are considered to be low based on its physicochemical properties (low vapour pressure) and use patterns. Occupational and environmental exposure to HEMA and environmental exposure to MAA may occur when HEMA is used in geotechnical grouting operations. The only known consumer exposure to HEMA in its monomeric form is through use in the dental profession. Low levels of residual, unpolymerized HEMA may be contained in consumer products. Migration of residual monomer from the polymer matrix in articles is expected to be low. Nevertheless, the possibility of consumer exposure cannot be excluded.

NATURE OF FURTHER WORK RECOMMENDED

This is not a priority for further work in relation to exposure assessment regarding the use of this substance as a chemical intermediate in closed systems or in controlled occupational settings. Note the recommendations from SIAM 11 with respect to methacrylic acid (CAS Nr. 79-41-4) and the EU risk reduction activity on geotechnical grouting.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-73-3
Chemical Name	1-Chloro-2-nitrobenzene
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

After single oral application 1-chloro-2-nitrobenzene is toxic to moderate toxic (LD_{50}, oral: rat, male: 144, 251or 560 mg/kg bw; rat, female: 263 mg/kg bw); the acute inhalative and dermal toxicity is moderate (LC_{50}, rat: 3200 mg/m^3 (= 495 ppm, vapor/aerosol mixture); LD_{50}, dermal, rat: female: 1320 mg/kg bw, male: 655 mg/kg bw; LD_{50}, dermal, rabbit: 400 mg/kg bw (male: 455 mg/kg bw, female: 355 mg/kg bw): Cyanotic appearance was the predominant symptom for all routes of application.

The documentation of the available studies on skin irritation is incomplete in one case and in two other cases the test substance was applied undissolved or respectively diluted. However, the studies gave no evidence of a skin irritating potential. 1-Chloro-2-nitrobenzene caused slight irritation effects to the eyes of rabbits, which were reversible within 24 hours. Due to the limited and poor quality information available regarding skin sensitization, it cannot be concluded whether or not the chemical has a sensitizing activity.

Target organs of repeated dose toxicity in rats and mice are blood, liver, kidney and spleen with methemogobinaemia as the most sensitive parameter. The repeated dose toxicity was examined in rats and in mice for a period of 13 weeks via whole body inhalation. The NOAEL in rats was not achieved, the LOAEL is 1.1 ppm (7 mg/m³). In mice, increased liver and kidney weights were observed even at 1.1 ppm and respectively 2.3 ppm. The NOAEL for histopathological injury in mice is 4.5 ppm (28.8 mg/m³). In a subacute feeding study with mice the NOAEL was 50 ppm (males: 16 mg/kg bw/day; females: 24 mg/kg bw/day).

1-Chloro-2-nitrobenzene showed weak mutagenic activity in bacterial test systems but not in mammalian cell test systems *in vitro*. It was not mutagenic in *Drosophila melanogaster*. In mammalian cells *in vitro*, it showed weak clastogenic activity. The substance induced increased rates of Sister Chromatid Exchanges, whereas the biological relevance of this effect is not yet clear. Intraperitoneal injection into mice resulted in DNA damage in the liver and kidney. The inconsistent results of the available genotoxic studies are typical for nitroaromatics. As a whole 1-chloro-2-nitrobenzene is suspected of being genotoxic, at least a weak clastogen.

1-Chloro-2-nitrobenzene induced tumours in different organs of rats and in the liver of mice. Based on the available studies, which have methodological deficiencies, there is a concern for a carcinogenic potential of 1-chloro-2-nitrobenzene. Following inhalative exposure of F344/N rats and B6C3F1 mice for 13 weeks, only in males 1-

chloro-2-nitrobenzene affects the reproductive organs. Performance of a specific study on toxicity to reproduction (NTP continuous breeding protocol) reveals that 1-chloro-2-nitrobenzene was without reproductive toxicity in a different mice strain following oral treatment by gavage despite of significant changes in liver and spleen weight and despite of elevated methaemoglobin levels. Thus, the NOAEL $_{fertility}$ in Swiss CD-1 mice after oral application is 160 mg/kg bw/day whereas the dams showed general toxicity effects at this concentration. Because 1-choro-2-nitrobenzene affected the reproductive organs in systemic toxic doses in male rats and in males of one strain of mice after subchronic inhalation there is a concern for a reproductive toxicity potential, even if an impairment of reproduction after oral administration in males of a second strain of mice could not be detected.

Developmental toxicity was examined by two studies with Sprague-Dawley rats which have methodology deficiencies. In one study, due to high mortality rate at the highest dose level, only two doses could be evaluated. NOAEL $_{maternal\ toxicity}$ is 25 mg/kg bw/day, a NOAEL $_{developmental\ toxicity}$ could not be conclusively derived since there was an increase in the number of litters exhibiting specific skeletal variations. In the second study only one dose was applied: NOAEL $_{developmental\ toxicity}$ is 100 mg/kg bw/day, a NOAEL maternal toxicity could not be derived. Based on the available studies the overall conclusion is, that there is no indication of developmental toxicity, although there are some limitations within the studies.

Environment

1-Chloro-2-nitrobenzene has a melting point of 32 °C, a solubility in water of 441 mg/l at 20 °C, and a vapour pressure of 4.0 Pa at 20°C. The log Kow was measured to 2.24.

According to Mackay fugacity model level I the main target compartments for 1-chloro-2-nitrobenzene are water (65.4 %) followed by air (32.9 %). 1-Chloro-2-nitrobenzene shows no ready biodegradation in aquatic compartments (OECD 301 C: 8.2% after 14d) but under the conditions of industrial waste water treatment plants removal to > 95 % was observed at one production/processing site. However, this elimination cannot be transferred to other sewage treatment plants. Special tests showed adapted cultures to be able to degrade 1-chloro-2-nitrobenzene in a cometabolic pathway. Bioconcentration factors determined for fish were in the range of 7.0 – 22.3 and thus indicate no significant bioaccumulation potential of 1-chloro-2-nitrobenzene. A calculated Koc suggests the substance to have a medium geoaccumulation potential. In the atmosphere the substance is photodegradable indirectly with a calculated half-life of 187 d.

The acute toxicity has been determined for: fish (*Cyprinus carpio*) with a 96 h-LC_{50} of 25.5 mg/l; daphnia (*Daphnia magna*) with a 24 h-$EC_{50}$of 12 mg/l and a 48 h-EC_{50} of 23.9 mg/l, and *Daphnia carinata* with a 48 h-EC_{50} of 21.3 mg/l; algae (*Chlorella pyrenoidosa*) with a 96 h-EbC_{50} of 6.9 mg/l. With another alga species (*Secendesmus subspicatus*) a 48h-ErC50 of 75 mg/l and a 48h-ErC10 of 19 mg/l was found.

Chronic toxicity has been tested for *Daphnia magna* with a 21 d-NOEC of 3 mg/l on reproduction (measured concentration) and for fish (*Pimephales promelas*) in an Early Life Stage Test with a 33 d-NOEC of 0.264 mg/l concerning the endpoint normal larvae (measured concentration). A PNECaqua of 0.026 mg/l is derived using an assessment factor of 10.

In a test with terrestrial plants a 14 d-EC50 in the range of 3.2 - 10 mg/kg soil dry weight was determined for Lactuca sativa regarding the endpoint of growth. APNECsoil of 3.2 µg/kg bw was derived from this value using an assessment factor of 1000.

Exposure

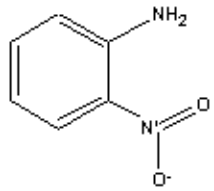
About 111,800 t/a 1-chloro-2-nitrobenzene are produced by about 30 producers world wide. 1-Chloro-2-nitrobenzene is a basic chemical which is processed chemically to other intermediates in different fields of application. There is currently no information that there is consumer use.

NATURE OF FURTHER WORK RECOMMENDED

Human Health: The substance is a candidate for further work. Due to possible hazards (haemotoxicity, reproductive toxicity, genotoxicty, and carcinogenicity) the exposure situation in occupational settings and consumer settings should be clarified and, if then indicated, a risk assessment should be performed.

Environment: The substance is a candidate for further work. Environmental exposure at the sponsor company is adequately controlled. However, as there are no information on environmental releases from other production / processing sites, exposure assessment should be conducted and, if then indicated, a risk assessment may need to be considered. This is justified because the substance is not readily biodegradable and has a PNECaqua of 26 µg/l.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-74-4
Chemical Name	2-nitroaniline
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The results of the published studies on 2-nitroaniline did not show significant increases of methemoglobin in animals except in the inhalation study. This difference with other isomers or inducers seems to be due to the difference of chemical reactivity of the nitro substitution in position 2 compared to other substitutions. 2-Nitroaniline is metabolised *in vitro* by rabbit liver microsomes to 4-amino-3-nitrophenol. 2-nitroaniline has been shown to have an oral LD50 value of 1838 mg/kg b/w in the rat, this is the only acute effect noted. It is not irritating to skin and to the eyes, and not sensitising. In oral repeated administration a NOEL of 50 mg/kg bw/day was determined from a 9 weeks study. The major treatment-related effects are clinical signs, but not methemoglobinemia, and weight loss. In a vapour inhalation 28 day assay a NOAEL was determined at 10 mg/m^3 in rats, due to slight methemoglobinemia and haematological effects seen at 90 mg/m^3.

2-nitroaniline was shown to be non-mutagenic in relevant bacterial studies. Nonetheless, a weak mutagenic influence was reported in some studies in which tests were performed on *S. typhimurium* strains TA98 and TA1538 in presence of Hamster S9 mix or with Flavin Mononucleotide activation. Investigations of general interaction with DNA on bacteria (*E. coli*) yielded negative results, as well as *in vitro* UDS tests and *in vivo* clastogenicity tests (micronucleus i.p.) or test on the alkaline elution behaviour of the DNA. In conclusion, 2-nitroaniline is not mutagenic.

In reproduction and developmental toxicological studies, the substance caused neither teratogenic nor fertility effects, but did cause developmental effects due to pups lethality at 450 mg/kg bw /day where a maternal body weight decrease occurred. The NOAEL for developmental effects was 150 mg/kg bw/day and the maternal NOAEL was set at 50 mg /kg bw in a study according to OECD TG 422.

Environment

2-nitroaniline has been found to be non-biodegradable, even in high inoculum concentration conditions. It therefore can be considered as persistent. The highest bioconcentration factor in fish was observed to be 8, leading to the conclusion that 2-nitroaniline does not significantly bioaccumulate.

The most valid and lowest E(L)C 50 found were a LC 50 (96 hours) in *Brachydanio rerio* of 19.5 mg/l, an EC 50 (24 hours) in *Daphnia magna* of 8.3 mg/l and an EC50 (growth rate, 72 hours) in *Selenastrum capricornutum* was > 100 mg/l. The lowest result is the EC 50 (24 hours) in *Daphnia magna*. Using an extrapolation factor of 1000, a PNEC of 0.008 mg/l can be estimated for the aquatic compartment.

Exposure

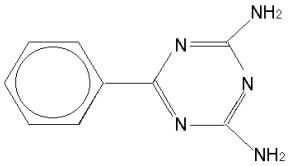
Estimated worldwide production of 2-nitroaniline is 20000 to 25000 tonnes/year. The production in the E.U. was 1000 to 5000 tonnes / year in 2000 in a unique site. The use in this region is non-dispersive, as an intermediate for synthesis in chemical industry. No other use could be documented in the EU. Nevertheless, the use in metal working fluids (<10%) and dyes (<1%) which can represent about 10% of the production volume were reported but not confirmed. 2-nitroaniline is an orange massive solid at room temperature, commercialised as flakes, or melted above 71 °C. It has a low vapour pressure at room temperature (0.00368 hPa at 25 °C) which reaches 1.33 hPa at 104 °C. So when melted, a potential exposure is possible by inhalation.

The water solubility of 2-nitroaniline is 1170 mg/l at 20 °C and the measured log Pow is 1.85. Anilines are known to make covalent bonds to humic acids. Therefore 2-nitroaniline will distribute as such mainly to the water compartment in the environment, but could be covalently bound to sediments.

NATURE OF FURTHER WORK RECOMMENDED

Human Health and Environment: The recommendation that this substance is not a priority for further work is based on the use of this substance exclusively as an intermediate in a closed system.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	91-76-9
Chemical Name	2,4-diamino-6-phenyl-1,3,5-triazine
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics and metabolism of this substance. The oral LD_{50} of rats was 933 mg/kg for males and 1231 mg/kg for females [OECD TG 401]. The major toxicity was edema in the forestomach. The LC_{50} value in the acute inhalation toxicity was 2.932 mg/L (4 hr, rat) [OECD TG 403]. This substance was not irritating to the skin in rabbits [OECD TG 404] and mildly irritating to the eyes in rabbits. There is no information on skin sensitization.

In the OECD combined repeat dose and reproductive/developmental toxicity screening test by gavage [OECD TG 422], this substance was given at 0, 4, 20 and 100 mg/kg/day to rats for at least 39 days. One male and one female rat died and the body weight gain was decreased in the 100 mg/kg group. Hematological and blood chemical examination showed decreases in the erythrocyte counts and hematocrit values with increased reticulocyte counts, and increases of GOT, GPT and total bilirubin with centrilobular hypertrophy of hepatocyte in the 100 mg/kg group. The severity of these changes, however, were toxicologically not significant or adaptive changes, except for the increase in reticulocyte count whose significance was equivocal. The NOAEL in this study was considered as 20 mg/kg/day.

In the 90-day feeding study of rats at 0, 1.9, 19.0, and 173.0 mg/kg/day [OECD TG 408], the body weight gain was decreased in the high dose group. In the histopathological examination, centrilobular hepatocyte enlargement, an increased severity of extramedullary hemopoiesis in the spleen and hemosiderin pigment accumulation in the kidneys and the spleen, hypertrophy and vacuolation of adrenal zona glomerulosa cells, and degeneration of pancreatic exocrine cells together with associated inflammatory cell infiltrates were observed in the high dose group. At the mid dose, the severity of hemosiderin pigment accumulation in the spleen was also increased moderately in males. This change in the spleen was considered not to be an adverse effect because no other changes were observed at this dose level. Therefore, the NOAEL in this study was considered to be 19 mg/kg/day.

On basis of these two studies, the NOAEL for repeated dose toxicity was considered to be 20 mg/kg/day.

For genotoxicity of this substance, there were two Ames tests, three non-bacterial *in vitro* studies, and two genotoxic *in vivo* studies reported. This substance was not mutagenic in bacteria [OECD TG 471 & 472]. It induced

chromosomal aberration in CHL/IU cells with and without an exogenous metabolic activation system even under the soluble concentrations. It also gave a positive response in the human lymphocyte test [OECD TG 473] and the mouse lymphoma TK assay [OECD TG 476] but only under the insoluble dose levels. The cytogenetic effect observed in *in vitro* assays however, could not be reproduced in the micronucleus tests *in vivo* [OECD TG 474]. Based on the weight of evidence, it could be concluded that this substance was not genotoxic *in vivo*.

For carcinogenicity, two dietary studies using male rats and male/female mice for 18 months showed no tumorigenic activity of this substance. However, these studies were considered to be insufficient for assessment of the carcinogenicity because of insufficient testing protocol compared to current test guidelines.

In the OECD combined repeat dose and reproductive/developmental (one generation) toxicity screening test [OECD TG 422], this substance was given for 49 days from 14 days before mating in males and from 14 days before mating to day 3 of lactation in females. At 100 mg/kg, one female died in gestation and another female was not impregnated. Birth index was decreased with increase in stillborns at 100 mg/kg. All pups of two dams at 20 mg/kg and seven dams at 100 mg/kg died due to the lack of nursing activity, and the viability index on day 4 after birth was consequently decreased in these groups. The body weights of pups were also decreased at birth and at day 4 of lactation in the 100 mg/kg group. The decrease of litter size observed at 100 mg/kg seems to be the chemical-induced effect although it is not statistically significant. No malformations or variations were observed in the pups.

From these results, the parental NOAEL of reproductive toxicity was considered to be 100 mg/kg/day for males, and 4 mg/kg/day for females, based on the lack of nursing activity, and the NOAEL of developmental toxicity was considered to be 20 mg/kg/day, based on the decrease of birth index and body weight of pups.

Environment

This substance (2,4-diamino-6-phenyl-1,3,5-triazine) is slightly soluble in water (320 mg/L at 25°C). The vapour pressure of this substance is estimated as very low (1.6×10^{-5}Pa at 25°C). This substance would be released into the aquatic environment from waste water, and distributed almost entirely in the water compartment from the calculation using the fugacity model [Mackey level III]. Although this substance is stable in water biotically and abiotically, this substance has a low potential of bioaccumulation based on BCF = 6.4, estimated from log Pow = 1.38.

In acute toxicity to aquatic species, the toxicity to algae [OECD TG 201] was 53.7 mg/L for EC50 (72 hr, *Selenastrum capricornutum*, biomass) and the toxicity to daphnids [OECD TG 202] was 52.0 mg/L for EC50 (48 hr, *Daphnia magna*, immobility). The toxicity to fish [other method] was 99 mg/L for LC_{50} (48 hr, *Leuciscus idus* (L.)).

In chronic toxicity to aquatic species, the toxicity to daphnids [OECD TG 211] was 1.91 mg/L for NOEC (21 day, *Daphnia magna*, reproduction). The toxicity to algae [OECD TG 201] was 24.4 mg/L for NOEC (72 hr, *Selenastrum capricornutum*, biomass).

PNEC = 0.0191 mg/L for the aquatic organisms was calculated from the 21 day – NOEC (1.91 mg/L) for *Daphnia magna* using an assessment factor of 100, because two chronic data (*Daphnia magna* and alga) were available.

Exposure

Production volume of this substance (2,4-diamino-6-phenyl-1,3,5-triazine or benzoguanamine) is estimated 3,000 t/y in Japan and 5,000 t/y world-wide in 2000. The producing countries are Japan, Germany and the People's Republic of China. This substance can be produced in closed systems. The main use is as an intermediate in benzoguanamine-formaldehyde resins whose applications are coatings, paints, thermosetting resins and others. In the case of coatings, the resins are used as outside and/or inside coatings of cans for storing foods and beverages.

The fugacity model suggests that if released from air or soil, the majority of this substance would distribute into the water and soil. It would not distribute into the air and soil from water. From the uses and properties of this substance, estimated exposures are considered in the following three scenarios. The effects are as follows:

(1) Occupational exposure scenario: inhalation of dust without breathing protection in the factory;
Dust level was 0.25 mg/m^3 by measurement at the packing workplace;
EHEinh = 0.027 mg/kg/day and EHEder = 1.7 mg/kg/day (estimate).

In Japan, this substance has been manufactured since 1964, and no persons handling or contacting this substance have experienced any adverse symptoms regarding skin or respiratory organs.

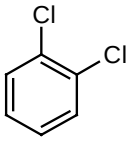
(2) Environmental exposure scenario: emission to aquatic compartment from waste water;
PEClocal water = 0.0176 mg/L (calculation).

(3) Consumer use exposure scenario: intake through migration from can coating of benzoguanamine-formaldehyde resins for storing foods and beverages;
EHE for consumer use was calculated as 0.076 mg/kg/day at the worst scenario based on the migration tests.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-50-1
Chemical Name	1,2-Dichlorobenzene
Structural Formula	

RECOMMENDATIONS

Health: The chemical is not a candidate for further work.
Environment: The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,2-Dichlorobenzene has been shown to cause eye and respiratory irritation in humans at exposure levels above 100 ppm. Skin irritation has been observed following dermal application in humans and animals.

1,2-Dichlorobenzene is absorbed via the oral route. Absorption via the dermal or inhalation routes is poorly characterized. Inhalation is expected to be the major route for human exposure. The available toxicological data indicate that metabolic profiles and effects from 1,2-dichlorobenzene exposure are similar in rats, mice and humans. Animal studies with rats and mice have shown 1,2-dichlorobenzene to induce acute hepatotoxic effects. The LD_{50} for a single oral exposure to 1,2-dichlorobenzene for the rat ranges from 1516 to 2138 mg/kg bw. The LC_{100} for the rat is ≤ 977 ppm (5.9 mg/L) for a 10 hour exposure. During a 4 hour exposure, 1 of 20 rats died at 941 ppm (5.6 mg/L). In humans, the acute effects of 1,2-dichlorobenzene by ingestion or inhalation are reported to be headache, nausea, vomiting, vertigo, malaise and unconsciousness.

Several oral studies of rats and mice ranging from 10 days to 2 years duration indicate that the adverse effects include increases in liver and kidney weights and hepatotoxicity. From these repeat dose studies, the NOAEL for non-neoplastic effects was 60 mg/kg bw, while the LOAEL was 120 mg/kg bw due to increased renal tubular regeneration in male mice.

In several microbial organisms and mammalian systems, 1,2-dichlorobenzene tested negative *in vitro*. However, it did induce sister chromatid exchanges in Chinese Hamster ovary cells and increased mutation frequency in mouse lymphoma cells, both in the presence of metabolic activation. 1,2-dichlorobenzene was negative in several *in vivo* mammalian tests, except one of two micronuclei assays in mouse bone marrow was positive. In a two-year oral study in rats and mice, 1,2-dichlorobenzene was considered not to be carcinogenic (maximum dose of 120 mg/kg bw). In an inhalation 2-generation reproduction study in rats, no fertility effects were observed and reduced pup weight during lactation occurred at doses toxic to adults. The NOAEL and LOAEL (kidney and liver effects) for adult rats were 50 (0.3 mg/L) and 150 ppm (0.6 mg/L) respectively. In developmental studies in rats and rabbits, developmental effects were only seen in rats at maternally toxic doses (400 ppm, 2.4 mg/L). No human epidemiological studies have been conducted.

Environment

1,2-Dichlorobenzene has a water solubility of 155.8 mg/L; vapour pressure of 0.196 kPa; and Log Kow of 3.4. It is expected to partition mainly to the atmospheric compartment where its primary removal mechanism will be through reaction with hydroxyl radicals (half life <50 days). Where released to either soil or water compartments, a major removal mechanism being volatilisation up into the surrounding atmosphere. However, adsorption to sediment may also be a major fate process. Biodegradation studies (generally following non-standard procedures) show 1,2-dichlorobenzene to be biodegradable under aerobic conditions where bacterial populations have been acclimatised to the chemical. However, where bacterial populations are not acclimatised, the chemical can not be regarded as ready biodegradable. The chemical is not degraded under anaerobic conditions. 1,2-Dichlorobenzene has a high potential for bioconcentration in the fatty tissue of aquatic species with BCFs based on lipid content up to 8710 for fish, and 28840 for a crab species. However, depuration from exposed organisms is expected to be rapid once exposure ceases.

1,2-Dichlorobenzene has been tested on a wide range of aquatic organisms under acute exposure, although chronic data are scarce. Results for fish ranged from 96 h LC50=1.58 mg/L for rainbow trout to 57 mg/L for fathead minnow. Both acute and chronic toxicity to aquatic invertebrates were obtained with two results showing high acute toxicity, namely EC50's of 0.78 mg/L and 0.66 mg/L to *Daphnia* and *Ceriodaphnia* respectively. Results from exposure to algae showed EC50 values in the 1-100 mg/L range for 1,2-dichlorobenzene. Toxicity to micro-organisms can be considered slight.

Although the major compartment expected to be exposed to 1,2-dichlorobenzene is the atmosphere, there are no ecotoxicity results available for organisms exposed through the gas phase. The chlorine substituents on the chemical suggest a potential for effects on stratospheric ozone. However, the chemical is unlikely to persist long enough to escape the troposphere, although it may persist long enough to undergo long range atmospheric transport.

While there are a large number of acute data covering all trophic levels, chronic data are scarce. Therefore, an assessment factor of 100 has been chosen. The result used for determining the PNEC was the lowest chronic value obtained, i.e. 21 d NOEC = 0.63 mg/L for *Daphnia magna*. The $PNEC_{aquatic}$ was therefore determined to be 6.3 µg/L.

Exposure

1,2-Dichlorobenzene is manufactured in Europe, the USA, Canada, Mexico and China. Production figures were reported to be approximately 16,500 tonnes for Western Europe in 1983 and approximately 23,680 tonnes produced by the USA in 1984. More recent data indicates that in 1999 production in the Western World was 54,000 tonnes, with the predominant uses being chemical synthesis and use as a solvent.

The main industrial use of 1,2-dichlorobenzene in Australia is as a solvent with approximately 86% used in the agricultural sector for wool branding products. The chemical is also used as an automotive and marine degreaser/decarboniser and in industrial paint strippers, industrial deodorants and a small amount in a single pharmaceutical preparation.

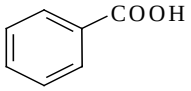
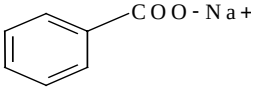
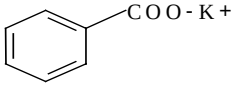
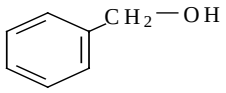
Occupational exposure to 1,2-dichlorobenzene can occur during manufacture and end use, with inhalation the major route of exposure. Potential for consumer exposure from the use of products and human exposure via the environment is expected to be low.

NATURE OF FURTHER WORK RECOMMENDED

Environment: 1,2-Dichlorobenzene is toxic and bioconcentrates. Additionally, it may be considered persistent due to its lack of biodegradation where microbial communities are not acclimatised. Member countries may wish to undertake a more in-depth exposure analysis and if then indicated, a risk assessment may be considered.

SIDS INITIAL ASSESSMENT PROFILE

Benzoates Category

CAS No.	65-85-0	532-32-1	582-25-2	100-51-6
Chemical Name	Benzoic acid	Sodium benzoate	Potassium benzoate	Benzyl alcohol
Structural Formula				

RECOMMENDATIONS

The chemicals are currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

The benzyl alcohol, benzoic acid and its sodium and potassium salt can be considered as a single category regarding human health, as they are all rapidly metabolised and excreted via a common pathway within 24hrs. Systemic toxic effects of similar nature (e.g. liver kidney) were observed. However with the benzoic acid and its salts at higher doses than the benzyl alcohol. For environmental effects the category is less clear, however all are readily biodegradable, non-bioaccumulative and acute toxicity values are similar. For human health all exposure routes are possible, despite benzoic acid and its salts are solids and benzyl alcohol is a liquid. For workers it will mainly be by inhalation and by skin, whereas for consumers it will mainly be oral and dermal.

Human Health

The compounds exhibit low acute toxicity as for the oral and dermal route the LD50 values are > 2000 mg/kg bw except for benzyl alcohol that needs to be considered as harmful by oral route in view of an oral LD50 of 1610 mg/kg bw. The 4 hrs inhalation exposure of benzyl alcohol or benzoic acid at 4 and 12 mg/l as aerosol/dust respectively gave no mortality, showing low acute toxicity by inhalation for these compounds.

Benzoic acid and benzyl alcohol are slightly irritating to the skin, while sodium benzoate was not skin irritating. No data are available for potassium benzoate but it is also expected not to be skin irritating. Benzoic acid and benzyl alcohol are irritating to the eye and sodium benzoate was only slightly irritating to the eye. No data are available for potassium benzoate but it is expected also to be only slightly irritating to the eye.

The available studies for benzoic acid gave no indication for a sensitizing effect in animals, however occasionally very low positive reactions were recorded with humans (dermatological patients) in patch test. The same occurs for sodium benzoate. It has been suggested that the very low positive reactions are a non-immunologic contact urticaria. Benzyl alcohol gave positive and negative results in animals. Benzyl alcohol also demonstrated a maximum incidence of sensitization of only 1% in human patch

testing. Over several decades no sensitization with these compounds has been seen among workers.
For benzoic acid repeated dose oral toxicity studies give a NOAEL of 800 mg/kg/day. For the salts values > 1000 mg/kg/day are obtained. At higher doses increased mortality, reduced weight gain, liver and kidney effects were observed.

For benzyl alcohol the long-term studies indicate a NOAEL $\geq$ 400 mg/kg bw/d for rats and $\geq$ 200 mg/kg bw/d for mice. At higher doses effects on bodyweights, lesions in the brains, thymus, skeletal muscle and kidney were observed. It should be taken into account that administration in these studies was by gavage route, at witch saturation of metabolic pathways is likely to occur. It can be concluded that benzoic acid and its salts exhibit very low repeated dose toxicity. Benzyl alcohol exhibits low repeated dose toxicity.

All chemicals showed no mutagenic activity in *in vitro* Ames tests. Various results were obtained with other *in vitro* genotoxicity assays. Sodium benzoate and benzyl alcohol showed no genotoxicity *in vivo.* While some mixed and/or equivocal *in vitro* chromosomal/chromatid responses have been observed, no genotoxicity was observed in the *in vivo* cytogenetic, micronucleus, or other assays. The weight of the evidence of the *in vitro* and *in vivo* genotoxicity data indicates that these chemicals are not mutagenic or clastogenic. They also are not carcinogenic in long-term carcinogenicity studies.

In a 4-generation study with benzoic acid no effects on reproduction were seen (NOAEL > 750 mg/kg). No compound related effects on reproductive organs (gross and histopatology examination) could be found in the (sub) chronic studies in rats and mice with benzyl acetate, benzyl alcohol, benzaldehyde, sodium benzoate and supports a non-reprotoxic potential of these compounds. In addition, data from reprotoxicity studies on benzyl acetate (NOAEL >2000 mg/kg bw/d; rats and mice) and benzaldehyde (tested only up to 5 mg/kg bw; rats) support the non-reprotoxicity of benzyl alcohol and benzoic acid and its salts.

In rats for sodium benzoate dosed via food during the entire gestation developmental effects occurred only in the presence of marked maternal toxicity (reduced food intake and decreased body weight) (NOAEL = 1400 mg/kg bw). NOEL: 300 mg/kg bw (hamsters); 250 mg/kg bw (rabbits); 175 mg/kg bw (CD-1 mice). For hamster, rabbit and mice no higher doses (all by gavage) were tested and no maternal toxicity was observed. For benzyl alcohol: NOAEL= 550 mg/kg bw (gavage; CD-1 mice). LOAEL = 750 mg/kg bw (gavage mice). In this study maternal toxicity was observed e.g. increased mortality, reduced body weight and clinical toxicology. Benzyl acetate: NOEL = 500 mg/kg bw (gavage rats). No maternal toxicity was observed.

Environment

From the data (fish, daphnia, algae, bacteria) it is obvious that neutralization of the pH greatly reduces (up to one order of magnitude) the acute toxicity of benzoic acid. This is also supported by the lower toxicity observed with the sodium benzoate. Under environmental relevant conditions therefore the acute toxicity of benzoic acid, sodium benzoate and potassium benzoate for all four trophic levels is > 100 mg/l. Under environmental relevant conditions the acute toxicity of benzyl alcohol for fish, daphnia and bacteria is > 100mg/l. For algae, an EC 50 3hrs of 95 mg/l is reported. Under environmental relevant conditions, benzoic acid and its salts have very low acute toxicity, whereas benzyl alcohol has low to moderate acute toxicity.

Exposure

Worldwide production capacity of benzoic acid is estimated at 700 kt. The major outlet (75%) for benzoic acid is as a chemical intermediate in the production of phenol, which in turn is mainly used to produce caprolactam. The next largest outlet is as a feedstock for sodium benzoate (10%) and chemical synthesis of plasticizers (5%).

Worldwide production capacity of sodium benzoate is estimated at 100 kt. The major outlet for sodiumbenzoate is as preservative in food and beverages (60%). Second most important market is cooling liquids (10%). The main function of sodium benzoate in most applications is as preservative.

Worldwide production capacity of potassium benzoate is estimated at 7Kt. It is used as a preservative in nonalcoholic beverages.

Worldwide production capacity of benzyl alcohol is estimated at 50 kt. Major use for benzyl alcohol is as curing agent in epoxy coatings (30%), where it becomes chemically bounded after reaction. Other important uses include the use as a solvent in low concentrations in waterborne coatings (10%) and use in paint strippers (10%) and chemical intermediate for synthesis for benzyl esters that are used in the flavor and fragrance industry (10%). The use in paint strippers is limited to uses in industrial settings.

Benzyl alcohol, benzoic acid and its sodium and potassium salt are decades also used in pharmaceuticals, cosmetics and/or food. Consumer exposure in these specific applications are controlled by the fact that, for all these applications, specific regulatory frameworks (regional and/or national) with authorization/approval procedures and specific advisory bodies exist (*inter alia*: the US FDA, WHO JECFA, EU SCF, etc), including, on a regular basis, reevaluation of approvals, hazardous properties and factual exposures. According to information from products registers, uses that are not specifically regulated include uses of the substances in different kinds of products e.g. paints, varnishes solvents, cleaning and washing agents, photochemicals and antifreeze agents.

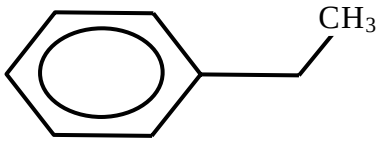
Benzoic acid is a white solid, with a solubility in water of 2.9 g/l and with a vapour pressure of 0.0011 hPa at 20 °C. The log octanol/water partition coefficient was measured to 1.88; the Henry coefficient = 0.0046-0.022 $Pa*m^3/mol$; and the pKa = 4.2. Sodium benzoate and potassium benzoate are white solids, with solubility in water of 556 g/l and with a vapour pressure of <0.0011 hPa at 20 °C. The log octanol/water partition coefficient were measured to –2.269. Benzyl alcohol is a colorless liquid, with a solubility in water of 40 g/l and with a vapour pressure of 0.13 hPa at 20°C. The log octanol/water partition coefficient was measured to 1.1.

The distribution modeling according to Mackay Level III indicates soil and water to be the favored compartments for the chemicals. However, physical chemical properties and use patterns indicate water to be the main compartment for these substances. None are expected to hydrolyze. All are readily biodegradable. None has bioaccumulative potential.

NATURE OF FURTHER WORK RECOMMENDED

Regarding all the information provided, the substances have low priority for further work.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-41-4
Chemical Name	Ethylbenzene
Structural Formula	

RECOMMENDATIONS

The chemical is a low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Ethylbenzene is readily absorbed following inhalation, oral, and dermal exposures, distributed throughout the body, and excreted primarily through urine. There are two different metabolic pathways for ethylbenzene with the primary pathway being the α-oxidation of ethylbenzene to 1-phenylethanol, mostly as the R-enantiomer. The pattern of urinary metabolite excretion varies with different mammalian species. In humans, ethylbenzene is excreted in the urine as mandelic acid and phenylgloxylic acids; whereas rats and rabbits excrete hippuric acid and phenaceturic acid as the main metabolites. Ethylbenzene can induce liver enzymes and hence its own metabolism as well as the metabolism of other substances. Ethylbenzene has a low order of acute toxicity by the oral, dermal or inhalation routes of exposure. Studies in rabbits indicate that ethylbenzene is irritating to the skin and eyes. There are numerous repeat dose studies available in a variety of species, these include: rats, mice, rabbits, guinea pig and rhesus monkeys. In a 13 week inhalation repeat-dose study in male and female rats, mild body weight or organ weight (kidney, liver, lung) effects occurred at doses $\geq$250 ppm without any accompanying histopathological or clinical chemistry changes, as a result these findings were not considered toxicologically significant. In chronic toxicity/carcinogenicity studies, both rats and mice were exposed via inhalation to 0, 75, 250 or 750 ppm for 104 weeks. In rats, the kidney was the target organ of toxicity, with renal tubular hyperplasia noted in both males and females at the 750 ppm level only. In mice, the liver and lung were the principal target organs of toxicity. In male mice at 750 ppm, lung toxicity was described as alveolar epithelial metaplasia, and liver toxicity was described as hepatocellular syncitial alteration, hypertrophy and mild necrosis; this was accompanied by increased follicular cell hyperplasia in the thyroid. As a result the NOAEL in male mice was determined to be 250 ppm. In female mice, the 750 ppm dose group had an increased incidence of eosinophilic foci in the liver (44% vs 10% in the controls) and an increased incidence in follicular cell hyperplasia in the thyroid gland. In addition, female mice exposed to 250 ppm and 750 ppm had an increase in hyperplasia of the pituitary gland. As a result, the NOAEL for female mice was 75 ppm. Hearing loss has been reported in rats (but not guinea pigs) exposed to relatively high exposures *(400 ppm and greater)* of ethylbenzene. Ethylbenzene was negative in bacterial gene mutation tests and in a yeast assay on mitotic recombination. In mouse lymphoma assays, positive responses were only observed at doses with excess cytotoxicity. No clear conclusion can be drawn from the chromosomal aberration tests *in vitro*. A single *in vitro* micronucleus test without S-9 mix was positive. An *in vitro* SCE test was clearly negative with and without S-9 mix. With *in vivo* tests, negative findings were obtained in micronucleus tests and in a mouse liver UDS test. In studies conducted by the U.S. National Toxicology Program, inhalation of ethylbenzene at 750 ppm resulted in increased lung tumors in male mice, liver tumors in female mice, and increased kidney tumors in male and female rats. No increase in tumors

was reported at 75 or 250 ppm. Ethylbenzene is considered to be an animal carcinogen, however, the relevance of these findings to humans is currently unknown. Although no reproductive toxicity studies have been conducted on ethylbenzene, repeated-dose studies indicate that the reproductive organs are not a target for ethylbenzene toxicity. Furthermore, in the 13-week NTP studies with rats and mice, no effects were observed for sperm, testicular morphology, spermatid counts, sperm motility, caudal or epididymal weights, or length of estrous cycle. Developmental toxicity studies have been conducted in the rabbit and rat with developmental effects (14% increase in incidence in pups with supernumerary ribs) observed in the rat only at 1,000 ppm ethylbenzene. Maternal effects in the dams at this dose consisted of increases in liver (approximately 22%), kidney (approximately 10%), and spleen (approximately 10%) weights in the absence of histopathology changes.

Environment

Ethylbenzene has the following physical chemical properties: molecular weight, 106.2; Log Kow, 3.15; water solubility, 169 mg/l at 25^0C ; vapor Pressure, 1270 Pa (1.27 kPa); melting point, -95C; Henry's Law Constant, 798.1 Pa.m3/mol. Ethylbenzene partitions to air from water and soil, and is degraded in air. Ethylbenzene is volatile and when released will quickly vaporize. Photodegradation is the primary route of removal in the environment. Photodegradation is estimated with a half-life of 1 day. Ethylbenzene is considered inherently biodegradable and removal from water occurs primarily by evaporation but in the summer biodegradation plays a key role in the removal process. Level I and Level III fugacity modeling indicate that partitioning is primarily to the air compartment, 98 and 96%, respectively. Ethylbenzene is inherently biodegradable in water and in soil under aerobic conditions, and not rapidly biodegradable in anaerobic conditions. Ethylbenzene is expected to be moderately adsorbed to soil. In acute aquatic toxicity testing LC_{50} values range approximately between 1 and 10 mg/l. In acute aquatic fish tests (fresh water species), the 96-hr LC_{50} for *Pimphales promelas* and *Oncorhynchus mykiss* are 12.1 and 4.2 mg/L, respectively. Data are available in the saltwater species *Menidia menidia* and give results within the same range as for the fresh water species with a 96-hr LC_{50} = 5.1 mg/L. In fresh water invertebrate species *Daphnia magna* and *Ceriodaphia dubia*, 48-hr LC_{50} values were 1.81 and 3.2 mg/L, respectively. Additional data is available in the saltwater species *Crangon franciscorium* (96-hr LC_{50} = 0.49 mg/L) and *Mysidopsis bahia* (96-hr LC_{50} = 2.6 mg/L). In 96-hr algal toxicity testing, results indicate that ethylbenzene inhibits algae growth in *Selanastrum capricornatum* at 3.6 mg/L and in *Skeletonema costatum* at 7.7 mg/L. Based on measured data, ethylbenzene is not expected to bioaccumulate (BCF 1.1 – 15).

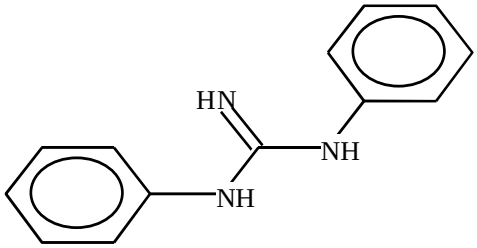
Exposure

Ethylbenzene is an industrial chemical that is primarily produced and further reacted to make styrene in a closed continuous process; thus, occupational exposures are expected to be very low. In addition, ethylbenzene occurs in crude oil and as a component of mixed xylenes, which is used in gasoline or as a solvent. Emissions and exposures from solvent use are not well characterized. Ethylbenzene has been detected in urban and rural air and water samples at ppt to low ppb concentrations. Exposure to the general population is possible through extremely low ambient air concentrations, primarily due to gasoline and automobile emissions.

NATURE OF FURTHER WORK RECOMMENDED

Regional and national exposure and risk assessments are ongoing. This chemical is a substance of the 1st EU Priority List. An in-depth risk assessment will be performed within the framework of the EU Risk Assessment Programme under Regulation 793/93. This chemical is also to undergo review in the US Voluntary Children's Chemical Evaluation Programme and additional testing of reproductive toxicity (two generation study), adult neurotoxicity, and immunotoxicity is planned.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	102-06-7
Chemical Name	1,3-Diphenylguanidine
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,3-Diphenylguanidine is absorbed rapidly after oral uptake but only slowly after dermal application. The substance is metabolised quickly and eliminated in the urine and faeces. No information is available on the mode of action.

1,3-Diphenylguanidine has an acute oral LD50 of 350-460 mg/kg b.w. for the rat. By dermal route, the dermal LD0 is > 2,000 mg/kg b.w. in the rabbit. After oral administration, the symptoms were normally of a nervous character, but post mortem examination revealed liver effects (dark colour) and severe irritation of the gastro-intestinal tract.
Sub-chronic (90-day) feeding studies in rats have shown an increase in mortality rate at 181 mg/kg bw/d, and a decrease in body weight gain (>10%) and food consumption (>12%) at 32 mg/kg bw/d and above. In a 90-day feeding study in mice, a decrease in body weight gain (>7%) was seen at 114 mg/kg bw/d and above. Decreases in rat body weight gain are considered to be due to the poor palatability of 1,3-diphenylguanidine. No treatment related effects were seen on organs, haematological and clinical-chemistry parameters, or urinalysis. Thus, from this data, a NOAEL of 17 mg/kg bw/d was determined in the rat for decreases in body weight gain and food consumption.

1,3-Diphenylguanidine gave negative results in numerous Ames and *in vitro* mammalian cell assays. An equivocal response was observed in a single Ames test, along with a positive result in a host mediated mutagenicity assay that was not reproducible. *In vivo*, negative results were seen in a (oral) rat bone marrow cytogenetic test and a (oral) mouse micronucleus assay. Thus, the data indicate 1,3-diphenylguanidine is not genotoxic.

The only available carcinogenicity studies are of insufficient rigour to determine whether or not DPG is carcinogenic.

1,3-Diphenylguanidine, with a purity of 97.7% to 99.9%, representative of the industrial product, did not affect the fertility of male mice when administered by gavage up to the maximal tested dose level of 16 mg/kg/d. In addition to the results of the feeding sub-chronic studies on the rat and mouse, special studies for recognising reproductive toxic effects were also performed. Comparisons of the parameter changes with the results of tests with feed withdrawal infer that the effects observed in the 1,3-diphenylguanidine-treated animals in high concentration groups

are a result of the poor general state of health (malnutrition, exhaustion) of the animals and not a direct toxic effect on the reproductive organs. Very conservative NOAELs, based on the effects on the reproductive organs, secondary to malnutrition and exhaustion, can be established at 32 mg/kg bw/d for rats and from 16 to 114 mg/kg bw/d for mice.

In female rats and mice foetotoxic, but not teratogenic, effects were seen after gavage administration of maternotoxic doses. In the rat study, based on a decrease of the maternal body weight gain at 25 mg/kg bw and above, and a decrease of the foetal body weight at 50 mg/kg bw, the NOEL was given as 5 mg/kg bw for the dams and 25 mg/kg bw for the foetuses. In the mouse study the NOEL was given as 4 mg/kg bw for the dams based on a decrease of mean number of implants and > 10 mg/kg bw for the foetuses. 1,3-Diphenylguanidine is irritating to the eye and non-irritating to the skin. Human cases have shown that contact dermatitis patients, for whom a rubber intolerance was often present, occasionally reacted positively to 1,3-diphenylguanidine in the patch test. Taken into account the negative Guinea pig maximisation assay, it can be infer that the positive reactions observed in human patients with contact dermatitis reflected cross-reactions rather than a direct sensitising effect of 1,3-diphenyl guanidine. In man, earlier and unconfirmed studies described the following symptoms after workplace exposures to 1,3-diphenylguanidine: eye and mucous membrane irritation, gastric and bilious complaints and disturbed liver metabolism.

Environment

1,3-Diphenylguanidine has three forms: unionised, primarily protonated and secondarily protonated. The pKa at which the first protonation occurs is 10.12 while the pKa for the second protonation is unknown and as this will be less than 10.12 it is not known whether this state will be reached at normal environmental pHs between 6 and 8. This leads to problems in determining the environmental fate of the substance.

Due to the relatively high solubility (approx. 0.5 g/l) at environmental pHs (6 to 9), low octanol water partition coefficient (<3) and low volatility of 1,3-diphenylguanidine the substance is not expected to adsorb to sediment and will mainly be present in the aqueous phase although, due to the positive charge of the ionised form of the molecule, adsorption to material with a high capacity for ion exchange (e.g. clay) may occur. Although not readily biodegradable, the substance has been shown to mineralise rapidly in the presence of adapted micro-organisms. A bioconcentration test on fish provided a BCF of <20 (LOQ). Based on the above the substance can be considered inherently biodegradable while bioaccumulation in biota is not expected for this substance.

1,3-Diphenylguanidine has been shown to be toxic to fish and algae and harmful to daphnia in several acute studies (fish : 96 h LC50 = 4.2-11 mg/l; algae : 72 h EC50 = 7.5 mg/l; 96 h EC50 = 1.7 mg/l; daphnid : 24 h EC50 = 73.6 mg/l; 48 h EC50 = 17mg/l).

The PNEC can be determined using the NOECs from the algae (0.3 mg/l) and daphnid chronic 21 d (0.6 mg/l) studies (excluding the EbC50 results), by applying an uncertainty factor of 50. The resulting PNEC would be 6 µg/l.

A terrestrial plant study conducted on monocotyledons and dicotyledons did not show a high level of concern for DPG in these species (*Brassica rapa*: EC50 = 358 mg/kg; *Avena sativa*: EC50 = 1169 mg/kg). In an avian study performed on three species of song bird at a limit concentration of 100 mg/kg, no effects were observed.

Exposure

1,3-Diphenylguanidine is a solid with a melting Point in the region of 147-150°C. Its boiling point is greater than 200°C. Vapour pressure is relatively low (1.74×10^{-7} kPa at 20°) and solubility in water varies greatly with the pH of the medium from 475 mg/l at pH 7 and 20^{o} C, to 519 g/l at strongly acid pH and 20°C. At higher pHs the solubility does not appear to decrease significantly. The change in solubility is due to the ionisation state of the substance. There are two protonation steps. The log pKa of the first protonation occurs at 10.12 but the second is unknown. The log Kow is measured as 1.69 but the pH of test is unknown. Probably this result relates to the protonated molecule but whether in cationic or di-cationic form not known. A calculated value is 2.9

The expected production volume of 1,3-Diphenylguanidine in year 2000 is 2400 tonnes/year in Europe, 2400 tonnes/year in the USA, an amount of 5300 tonnes/year for Asia and 11100 tonnes per year for the world.

1,3-Diphenylguanidine is used as a primary accelerator in vulcanisation of rubber, as secondary accelerator for sulfur-containing compounds such as thiazoles, sulfenamides and thiurams and as a minor use as a primary material for standardising acids.

Depending on the specific application, the concentration of 1,3-diphenylguanidine used in the production of rubber compounds may vary from 0.25% to 2.0% by weight.

1,3-Diphenylguanidine can be absorbed into the body by inhalation. Accidental exposure can occur by ingestion or contact with the eyes. Dermal exposure is probably minimal due to the low skin penetration.

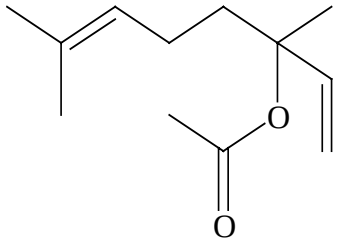
NATURE OF FURTHER WORK RECOMMENDED

Human health: The substance is a candidate for further work (post-SIDS) due to the high toxicity profile. In occupational settings where exposure is not controlled, exposure to workers cannot be excluded. As the extend cannot be estimated, a human exposure assessment and, if then indicated, a risk assessment should be performed.

Environment: Based on current information no clear conclusion can be drawn. While the fate properties suggest that the substance will not bioaccumulate in the environment and that degradation will occur, the PNEC, be it based on flora or fauna is relatively low and the downstream use is such that the substance is likely to be found (within or outside polymer matrix) in the environment mainly due to abrasion from car tyres.

In the absence of knowledge on the leaching behaviour of the substance from abraded rubber compounds, further work to provide a reasonable estimate of the environmental concentration is considered necessary.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	115-95-7
Chemical Name	Linalyl acetate
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Linalyl acetate is of very low acute toxicity to mammals, the acute oral LD_{50} is >13,360 mg/kg, while the inhalation LC_{50} is >2740 mg/m^3. Linalyl acetate has no or a very low potential to irritate the human skin. No information on possible eye irritation is available. Based on the use of linalyl acetate in cosmetics (constituent of perfumes) it is doubted that the substance has significant sensitising properties.

Linalyl acetate is an ester that is expected to be hydrolysed to linalool and acetic acid in the gastro-intestinal tract. The main effects of the hydrolysis product, linalool (72.9%), in a 28-day oral rat study were increased liver and kidney weight, thickened liver lobes and pale areas on the kidneys and in females only hepatocellular cytoplasmic vacuolisation. Other findings were related to local irritation of the gastro-intestinal tract. Based on the effects on liver and kidney a NOAEL of 160 mg/kg bw/d was derived for linalool (equivalent to 148 mg/kg bw/d linalyl acetate). In this study no effects on male and female gonads were found.

Linalool (72.9%) was tested in a reproduction screening test (non-OECD). The NOAEL for maternal toxicity based on clinical signs and effects on body weight and food consumption was 500 mg/kg bw/d for linalool (equivalent to 464 mg/kg bw/d linalyl acetate). The NOAEL on reproduction toxicity and developmental toxicity is 500 mg/kg bw/d (equivalent to 464 mg/kg bw/d linalyl acetate) based on the decreased litter size at birth and pup morbidity/mortality thereafter.

Linalyl acetate does not induce gene mutations or chromosomal effects *in vitro.*

Environment

Linalyl acetate is a liquid with a vapour pressure of 0.61 Pa (at 25ºC), a water solubility of 30 mg/L and a Log K_{ow} of 3.9 (measured). It has a calculated half-life for photo-oxidation of 1.1 hours.

Linalyl acetate will partition primarily to water (Mackay level III modelling). In a hydrolysis study linalyl acetate

was found to disappear from the test medium within 2.4 hours at pH 4, 7 and 9 (at 50°C) ($t_{1/2}$ < 24 hours at 20°C). Hydrolysis products are linalool and acetic acid.

Linalyl acetate is readily biodegradable. Based on the log K_{ow} a BCF of 412 was calculated. Linalyl acetate has potential for sorption to soil (predicted log Koc 2.9), however, in view of the rapid hydrolysis of the substance it is unlikely that significant uptake or sorption may occur.

Linalyl acetate is toxic to fish and daphnia. All values are based on measurements of the parent compound, which is expected to hydrolyse very quickly. The 96-hour LC_{50} in fish is 11 mg/L. The 48-hour EC_{50} for daphnia is 6.2 mg/L. In a test with algae (*Scenedesmus subspicatus*, 72-hours exposure), a reduction of biomass was seen at 1.2 mg/L and above. The 72-hour E_bC_{50} was 4.2 mg/L, the E_rC_{50} was 16 mg/L).

The EC_{50} for the inhibition of micro-organisms is 415 mg/L (ethanol was used as dispersant).

Exposure

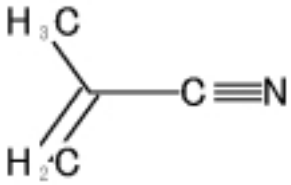
The market for linalyl acetate is 1000-5000 tonnes. It is used as an intermediate and can be found in consumer products as soaps, cleaning products, cosmetics (perfume), oil paint and extracts. Linalyl acetate is a food additive. Foodstuffs contain between 1.9 (soft drinks) and 13 ppm (chewing gum) linalyl acetate.

There is a potential for occupational exposure. Consumers may be exposed orally and dermally. There is potential exposure to the aquatic compartment arising from the production/formulation and consumer use of this substance.

NATURE OF FURTHER WORK RECOMMENDED

No further work recommended, because this molecule hydrolyzes rapidly.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	126-98-7
Chemical Name	Methyl Acrylonitrile
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Methylacrylonitrile was readily absorbed through the gastrointestinal tract. It distributed to all tissues, but the potential for bioaccumulation was minimal. The main excretion route was expired air as carbon dioxide, which was saturable with increased dose. Metabolism and excretion of this chemical depend on the dosing vehicle and the species/strain.

There are definite species differences in the acute toxicity. The oral LD_{50} was 64~240 mg/kg b.w. for rats, 17 mg/kg b.w. for mice, 16 mg/kg b.w. for rabbits and 3.8~4.9 mg/kg b.w. for gerbils. Clinical signs were decrease in locomotor activity, adoption of a prone and/or lateral position, and hyperpnea. Inhalation LC_{50} of rats was also obviously higher than that of mice and rabbits although all these were reported in 1968. Clinical signs by inhalation were unconsciousness and tonic-clonic convulsions. This chemical is mildly irritating to skin and eyes in rabbits**.** In a human voluntary study, this chemical was also slightly irritating to respiratory tracts and eyes (even at 2 ppm (6 mg/m^3) for 10 minutes). There is no available data on skin sensitization.

Six oral and four inhalation repeated dose toxicity studies including two oral carcinogenic studies are available. Anemia and histopathological changes in olfactory epithelium and bone marrow were observed in rat oral studies. In addition, rats and mice at the higher doses showed clinical signs such as lethargy, tremors and convulsions. In NTP 13-week studies, various effects including death were observed at 42.9 mg/kg b.w./day and more in rats, and at 8.6 mg/kg b.w./day in mice, showing significant species differences of the repeated dose toxicity. From a 2-year carcinogenicity study [NTP], the NOAEL for oral repeated dose toxicity was considered to be 7.14 mg/kg b.w./day for rats and 4.29 mg/kg b.w./day for mice. For inhalation exposure (90 days), the NOAEL was reported as 19.3 ppm (57.9 mg/m^3) for rats and 8.8 ppm (26.4 mg/m^3) for dogs although the data quality was not sufficient.

This chemical was not mutagenic with and without an exogenous metabolic activation system in a bacterial test [OECD TG 471], while the cytogenetic effect was judged to be positive because of increases in mammalian cultured cells with structural chromosomal aberrations and polyploidy with an exogenous metabolic activation [OECD TG 473]. However, micronucleus tests by intraperitoneal injection to rats and mice or by gavage to mice showed negative results [NTP]. Therefore, a weight of evidence suggests that methylacrylonitrile may not be genotoxic *in vivo.*

In 2-year gavage studies [NTP], this chemical did not cause any neoplastic changes in rats (up to 21.4 mg/kg b.w./day) and mice (up to 4.29 mg/kg b.w./day). Therefore, methylacrylonitrile was considered not to be carcinogenic in rodents.

In an OECD combined study, there were no effects of this chemical on reproductive/developmental parameters even at the highest dose of 30 mg/kg b.w. In a two-generation study in rats, methylacrylonitrile did not affect the reproductive performance of both sexes, but induced a decrease of epididymal sperm density in the second generation at 20 mg/kg b.w. At higher doses in rats (40 to 100 mg/kg b.w.), prolonged estrous cycles were observed in an oral 13-week study and the pregnancy was not kept in an oral developmental study. In another developmental study in rats, there were no effects on fetal development up to 50 mg/kg b.w. by oral administration. Based on these results, the oral NOAEL for reproductive/developmental toxicity in rats was considered to be 7 mg/kg b.w./day. On the other hand, there was a decrease in the male/female ratio of fetuses/litter at a dose of 5 mg/kg b.w. in rabbits and a decreased body weight of fetuses was observed at 100 ppm by inhalation, probably due to maternal toxicity. The NOAEL for developmental toxicity was 3 mg/kg b.w. in rabbits by oral administration, and 50 ppm in rats by inhalation. This chemical is not a teratogen.

Environment

Methyl Acrylonitrile is readily biodegradable and its bioaccumulation potential seems to be low based on its Log P_{ow} (0.68). In the air, this chemical is expected to be photodegraded ($T_{1/2}$=about 46 hours). Hydrolysis is not expected to occur. A generic level III fugacity model shows that if methylacrylonitrile is released to one of the compartments of air, water and soil, it is unlikely to distribute into other compartments.

Regarding the acute aquatic toxicity of this substance, the algal ErC50 of 25.3 and EbC50 of 15.1 mg/L are the lowest values among available data on species from three trophic levels.

Chronic toxicity NOEC values of 10 (growth rate) and 1.0 (biomass) mg/L for algae are reported. The NOEC for daphnids is 2.20 mg/L for reproduction.

Exposure

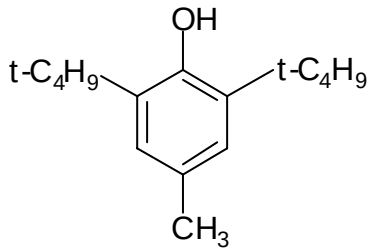
Methylacrylonitrile is a colorless liquid with acrid odor, which is soluble in water (29 g/L at 25 °C). Its vapour pressure is 8.5 x 10^3 Pa at 20° C. The production volume of methyl acrylonitrile in Japan was about 20,000 tonnes in 1998.

This chemical is used as an intermediate in the preparation of methacryllic derivatives, and polymers. Exposure to this chemical via inhalation and dermal routes may be possible during handling of quality control samples, and tank lorry filling. Estimated exposure concentration for these operations is 10-50 ppm by EASE model, and $EHE_{inh+der}$ was 1.3 mg/kg·bw/day at the production site. A TLV (TWA) of 1 ppm has been adopted in several countries.

NATURE OF FURTHER WORK RECOMMENDED

This chemical is currently not a candidate for further work unless there is significant exposure.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	128-37-0
Chemical Name	2,6-di-tert.-butyl-p-cresol (BHT) Butylated Hydroxytoluene
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

BHT is of low acute toxicity. BHT caused acute toxic effects in mammalians but there were no specific clinical symptoms. In rats, the oral LD_{50} was > 2930 mg/kg bw, the LD_{50} after dermal exposure was > 2000 mg/kg bw. It was slightly irritating to the skin and eyes of rabbits.

On chronic oral exposure of rats, liver and thyroid are the main targets. Doses above 25 mg/kg bw/day BHT resulted in thyroid hyperactivity, enlargement of the liver, induction of several liver enzymes. 25 mg/kg bw/day BHT can be considered as NOAEL for chronic exposure. The haemorrhagic effects of high repeated doses of BHT seen in certain strains of mice and rats, but not in other species, may be related to its ability to interact with prothrombin and vitamin K.

BHT showed no potential to cause point mutations in several bacterial and mammalian *in vitro* test systems.

Overall, the available studies demonstrate that BHT has no clastogenic activity *in vitro* or *in vivo*. Most *in vitro* chromosome aberration assays were negative as were sister chromatid exchange assays and DNA damage and repair assays. *In vivo*, micronucleus assays with mice, cytogenetic assays with rats and mice, dominant lethal assays with rats and mice, and the heritable translocation assay with mice were also negative.

BHT is not a genotoxic carcinogen. Carcinogenic effects observed in one long-term study with rats probably were caused by the specific study conditions. However, it cannot be completely ruled out that the hepatotoxic effects caused by high and chronic doses of BHT may result in persistent cell proliferation, which is known as a possible mechanism of non-genotoxic carcinogens. In addition, depending on the application regime, BHT may exert either anticarcinogenic or tumour-promoting activity at relatively high doses. For the possible carcinogenic and tumour-promoting effect of BHT, a threshold level of 100 mg/kg bw/day can be assumed. At this dose, no increase in the incidence of liver carcinoma, but a slight increase in liver adenoma were observed after chronic exposure starting *in utero* as a worst case scenario.

The only effects on reproduction were lower numbers of litters of ten or more pups at birth at doses of 100 mg/kg bw/day and above. The NOAEL was 25 mg/kg bw/day.

From studies with mice and rats there is no evidence of teratogenic effects of BHT. During pregnancy BHT had maternal effects on mice above oral doses of 240 mg/kg bw/day. The NOEL for developmental toxicity was 800 mg/kg bw day.

Despite of being in wide dispersive use as ingredient of various products for many years only very few cases of allergic reaction in humans after dermal exposure or oral intake have been described. For the use of BHT as antioxidant in foodstuff an acceptable daily intake (ADI) of 0 - 0.3 mg/kg bw/day has been established.

Environment

BHT has a melting point of ca. 70 °C, a water solubility in the range of 0.6-1.1 mg/l (20-25 °C), a density of 1.03 g/cm³, and a vapor pressure of 1.1 Pa (20 °C). The measured log Kow is determined to be 5.1.

According to a Mackay Level I model calculation, the main target compartment for BHT is air (79-87 %), followed by soil (6.1-10.2 %) and sediment (5.7-9.5 %). Due to the instability of BHT in aqueous solution the estimations reflect a tendency for BHT distribution among environmental compartments. BHT is relatively unstable under environmental conditions. Extent and products of decomposition are dependent on several factors like irradiation, pH, temperature, moisture, presence of soil and soil microorganisms, and oxygen content. In air BHT is indirectly photodegradable by hydroxyl radicals with $t_{1/2}$ = 7.0 hours. In aqueous solution BHT is decomposed in natural sunlight with irradiation (ca. 75 %) and without (ca. 40 %), forming different, partly unidentified metabolites. BHT is also not stable in soil. Within one day of incubation 63-82 % of BHT were decomposed in non-sterilized and 25-35 % in sterilized soils. A mineralization up to 30 % was observed under non-sterilized conditions. Depending on the exposure pathways, the compartments air, hydrosphere and soil can be environmental target compartments for this substance and its metabolites. BHT is not readily biodegradable in water according to a modified MITI-I test (4.5 % degradation after 28 days). A wide range of bioconcentration factors (BCF) was found in different experiments. Bioconcentration factors (BCF) in the range of 230-2500 have been determined for fish after 56 days. The BCF values determined after a 28 days exposure period in a model ecosystem with soil were 2-17 for fish, 30 for snails and 38 for algae. It can be assumed that BHT has a moderate to high bioaccumulation potential in aquatic species.

For the toxicity of BHT on aquatic species reliable experimental results from tests with fish, daphnia, and algae are available. Only those effect values are considered for the assessment that did not exceed the low water solubility of BHT (0.6 - 1.1 mg/l) and were based on measured concentrations. The lowest reliable acute toxicity values are:

fish (*Brachydanio rerio*): 96h LC0 ≥ 0.57 mg/l;
invertebrates (*Daphnia magna*): 48h EC0 ≥ 0.17 mg/l;
algae (*Scenedesmus subspicatus*): 72h E_rC_8 = 0.4 mg/l. This value can be used as a NOEC.

In a 21 days reproduction test with *Daphnia magna* a NOEC = 0.07 mg/l was determined. Using an assessment factor of 50,a PNECaqua = 0.0014 mg/l is derived from this long term NOEC.

Exposure

In 2000, the world production capacity of BHT amounts to about 62,000 t/a by more than 20 producers. BHT is a registered antioxydant, licenced for food products, animal feed, cosmetics, and packaging material. It is also used in petroleum products, synthetic rubbers, plastics, elastomers, oils, waxes, soaps, paints, and inks.

Releases into the environment may occur during production of BHT as well as during its use in different applications as stabilizer and during the use of the products that contain the substance. A significant release into the environment is expected from migration of BHT onto the surface of products containing the substance.

NATURE OF FURTHER WORK RECOMMENDED

Environment: The substance is a candidate for further work. Releases into the environment during use of BHT and from products containing the substance have to be assumed but are not quantifiable. In the environment, BHT is rapidly decomposed forming several, partly unidentified, metabolites. BHT is not readily biodegradable, a moderate to high bioaccumulation potential has to be assumed. The NOEC from the long-term toxicity to daphnids was 0.07 mg/l, resulting in a PNEC of 0.0014 mg/l. Therefore, the performance of an environmental risk assessment is recommended. Especially the questions concerning exposure, bioaccumulation as well as toxicity of the metabolites should be clarified.

Human Health: No recommendation for further work, because all SIDS endpoints are adequately covered and because exposure is controlled in occupational settings.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1310-73-2
Chemical Name	Sodium hydroxide
Structural Formula	NaOH

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Solid NaOH is corrosive. Depending on the concentration, solutions of NaOH are non-irritating, irritating or corrosive and they cause direct local effects on the skin, eyes and gastrointestinal tracts. Based on human data concentrations of 0.5-4.0 % were irritating to the skin, while a concentration of 8.0 % was corrosive for the skin of animals. Eye irritation data are available for animals. The non-irritant level was 0.2-1.0 %, while the corrosive concentration was 1.2 % or higher. A study with human volunteers did not indicate a skin sensitisation potential of sodium hydroxide. This is supported by the extensive human experience.

The acute toxicity of sodium hydroxide depends on the physical form (solid or solution), the concentration and dose. Lethality has been reported for animals at oral doses of 240 and 400 mg/kg bw. Fatal ingestion and fatal dermal exposure has been reported for humans.

No valid animal data are available on repeated dose toxicity studies by oral, dermal, inhalation or by other routes for NaOH. However, under normal handling and use conditions (non-irritating) neither the concentration of sodium in the blood nor the pH of the blood will be increased and therefore NaOH is not expected to be systemically available in the body. It can be stated that the substance will neither reach the foetus nor reach male and female reproductive organs, which shows that there is no risk for developmental toxicity and no risk for toxicity to reproduction. Both *in vitro* and *in vivo* genetic toxicity tests indicated no evidence for a mutagenic activity.

Based on the available literature, there is a risk for accidental and intentional exposure to solid NaOH or to irritating or corrosive solutions of NaOH. Most of the ingestion accidents seem to be related with children and seem to occur at home. Accidental skin and eye exposure seem to be less frequently reported than ingestion in the medical literature. Dust formation is unlikely because of hygroscopic properties. Furthermore NaOH has a negligible vapour pressure and is rapidly neutralized in air by carbon dioxide and therefore dust and vapour exposure are not expected.

Environment

The hazard of NaOH for the environment is caused by the hydroxyl ion (pH effect). For this reason the effect of NaOH on the organisms depends on the buffer capacity of the aquatic or terrestrial ecosystem. Also the variation in acute toxicity for aquatic organisms can be explained for a significant extent by the variation in buffer capacity of the test medium. LC50 values of acute toxicity tests with aquatic organisms ranged between 33 and 189 mg/l.

Because the buffer capacity, the pH and the fluctuation of the pH are very specific for a certain ecosystem it was not considered useful to derive a PNEC or a $PNEC_{added}$. To assess the potential environmental effect of an NaOH discharge, the pH change of the receiving water should be calculated or measured. The change in pH should be compared with the natural variation in pH of the receiving water and based on this comparison it should be assessed if the pH change is acceptable.

The use of NaOH could potentially result in an emission of NaOH and it could locally increase the pH in the aquatic environment. However, the pH of effluents is normally measured very frequently and can be adapted easily and therefore a significant increase of the pH of the receiving water is not expected. If emissions of waste water are controlled by appropriate pH limits and/or dilutions in relation to the natural pH and buffering capacity of the receiving water, adverse effects on the aquatic environment are not expected due to production or use of NaOH.

Aquatic sodium emissions originating from uses of NaOH are probably small compared to other sources. It is clear that an environmental hazard assessment of sodium should not only evaluate all natural and anthropogenic sources of sodium but should also evaluate all other ecotoxicity studies with sodium salts, which is beyond the scope of this report.

Exposure

Estimated worldwide demand of sodium hydroxide was 44 million tonnes expressed as NaOH 100% in 1999. The global demand is expected to grow with 3.1% per year.

NaOH is commercialised as a solid or as solutions with varying concentrations. NaOH solidifies at 20 °C if the concentration is higher than 52 % (by weight), which can be considered the maximum water solubility at 20 °C. NaOH has many industrial uses but it has also wide dispersive use. It is used for example for cleaning, disinfection, wood treatment and to make soap at home, but many other uses could exist.

NATURE OF FURTHER WORK RECOMMENDED

Environment and human health: no further work is recommended if sufficient control measures are in place to avoid significant human and environmental impact, including prevention of accidental exposure.

Due to the corrosivity of the substance, no further studies are required under the SIDS programme.

In the EU a risk assessment will be performed according to Council Regulation 793/93.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	141-78-6
Chemical Name	Ethyl acetate
Structural Formula	CH_3-COO-CH_2-CH_3

RECOMMENDATIONS

The chemical is currently of low priority for further work

SUMMARY CONCLUSIONS OF THE SIAR

Analog Justification

No data on ethyl acetate is available for the developmental toxicity endpoint. As a result, data from ethyl acetate's metabolite, ethanol is being used to complete this endpoint, as ethyl acetate is rapidly converted to ethanol. Pharmacokinetic studies have demonstrated an elimination half-life for ethyl acetate of 33-37 seconds in blood *in vivo*. The rapid appearance of the ethanol metabolite due to hydrolysis allows the use of studies conducted directly with ethanol to be used in systemic hazard identification for ethyl acetate. In addition, supporting data from ethanol has been presented for the repeat dose and reproductive toxicity endpoints.

Human Health

Ethyl acetate is readily absorbed and rapidly hydrolyzed in mammals to acetic acid and ethanol. Ethyl acetate exhibits low acute toxicity by the oral, inhalation, and dermal routes. The oral LD_{50} ranges from 4,100 mg/kg in mice to 7650 mg/kg in rabbits. Inhalation LC_{50} values for vapor exposures in rats and mice range from the lowest value of 33.5 mg/l (2hr exposure) to the highest reported value of 200 mg/l (1hr exposure). A single dermal LD_{50} value is reported as above 18,000 mg/kg. In addition to the standard acute inhalation study, a functional observational battery and motor activity test was conducted prior to exposure and after a 6hr exposure at 7 and 14 days at doses of 600 (2.25 mg/l), 3000 (11.25 mg/l) and 6000 ppm (22.5 mg/l). A NOEL for systemic effects was not determined based upon transient decrease in body weights at all doses. At 3000 ppm (11.25 mg/l) decreases in motor activity were observed in both male and female rats and in the functional battery, sedation effects were observed at 3000 ppm (11.25 mg/l). The NOEL for neurotoxicity was 600 ppm with a LOEL (sedation) being 3000 ppm (11.25 mg/l). In addition, acute effects were observed in a 90-day study which resulted in a diminished response to delivery of an alterting stimuli at 750 ppm (3 mg/l) in which this response was attributed to ethyl acetate's acute sedative properties. The LOAEL from this study in rate would be 750 ppm. Ethyl acetate is not a dermal sensitizer or an acute eye or skin irritant based on information currently available. Inhalation of 400 ppm (1.4 mg/l) ethyl acetate vapor by humans produces mild sensations of irritation in some individuals but 200 ppm (.7 mg/l) is without effect.

In a 13 week inhalation study, LOELs of 350 ppm (1.3 mg/l) (reduced food consumption and body weights and lower serum triglyceride levels) and 750 ppm (2.7 mg/l) (sedative effects) for systemic effects were observed in rats. Minimal to moderate degeneration of the nasal epithelium was observed in both male and female rats at all ethyl acetate exposure concentrations. Degeneration of the olfactory epithelium within the nose is a common lesion in rats exposed by inhalation to acetate esters of short-chain alcohols due to the liberation of acetic acid in these cells from the hydrolysis of the ester linkage. The significance of this lesion in human health is not clear. Ethyl acetate is

not mutagenic in *in vitro* systems. Conflicting results were obtained in the in vitro assays for clastogenicity with positive results being reported only at excessively high dose levels. However, negative results were obtained in the in vivo bone marrow assays for clastogenicity (micronucleus assay) using high dose levels (administered i.p.). In addition, the metabolites, ethanol and acetic acid do not have any significant mutagenic potential. Sufficient data is not available for ethyl acetate for the endpoints of reproductive or developmental toxicity as a result, data from ethanol will be used as a surrogate. In an inhalation study designed to observe repeat dose effects of ethyl acetate, minor reproductive parameters were observed in the male rat, sperm parameters (number or concentration of spermatids in the testes or epididymide; sperm motility; or morphology) were not affected at concentrations up to the highest dose tested 1500 ppm (5 mg/l). This data was further supported by a study with limited design (methodology) in male rats where it was determined that transient exposure to extremely high levels of ethyl acetate may be able to cause these effects, but subchronic exposures to doses as high as 6000 ppm (22 mg/l) did not effect sperm counts, motility or sperm concentration. In ethanol, oral exposure effect levels of 6400mg/kg by gavage and even higher by dietary exposure have been observed. In inhalation studies using ethanol, rats exposed up to 20,000 ppm (72 mg/l), equivalent to a blood alcohol concentration of 180 mg/100 ml, have not produced fertility or developmental effects. Inhalation exposures at concentrations greater than 2000 ppm (7 mg/l) were required to show any accumulation of ethanol in the blood and esterases are not saturated at levels as high as 10,000 ppm (36 mg/l). Rats exposed for 13 weeks to concentrations as high as 1500 ppm (5 mg/l) did not exhibit any evidence of cumulative neurotoxicity when motor activity, functional observational batteries, and scheduled controlled operant behavior were evaluated. Transient diminished response to delivery of an alerting stimuli was noted at the 750 ppm (3 mg/l) and 1500 ppm (5 mg/l) doses and was attributed to the acute sedative properties of ethyl acetate. Therefore, other than transient reversible sedation during exposure, ethyl acetate is not considered a neurotoxicant.

Environment

The available physicochemical data are adequate to describe the properties of ethyl acetate. The melting point for ethyl acetate is -83 ^{o}C, the boiling point is 77.1^{o}C and the log K_{ow} is 0.73. Ethyl acetate has a measured vapor pressure of 113hPa at 20 °C. Ethyl acetate has a specific gravity (density) of 0.90 and a flashpoint of –4^{0}C. Its aqueous solubility has been reported as about 83,000 mg/L at 20°C. Henry's Law constants for ethyl acetate were calculated or measured to be about 14 to 24 Pa m^3/mol at 25°C. Ethyl acetate is considered moderately volatile. Using a measured Henry's Law constant of 14 Pa m^3/mol, half-lives of volatilization from model rivers and lakes were calculated. Calculated half-lives of volatilization of ethyl acetate from a model river or lake were 5 hours and 5.6 days, respectively. Ethyl Acetate is stable to hydrolysis under neutral to acidic conditions (pH 4-7) but readily hydrolyses under alkaline conditions (pH 9). Ethyl acetate is not persistent in the environment and is not likely to bioaccumulate in food webs. Based on Level III fugacity-based multimedia modeling and assuming equal emissions to air, water, and soil, 17.2 % will be in air, 47.6 % in water, and 35.1 % in soil. Ethyl acetate in water and soil is expected to be easily biodegraded based on laboratory studies indicating that ethyl acetate is readily biodegradable. The amounts of ethyl acetate in other compartments (e.g., sediment and biota) are expected to be small. These predictions are supported by the limited data available on prevailing concentrations in indoor/outdoor air and concentrations in river/drinking water. Since the primary use of ethyl acetate is as a solvent, it is expected that ethyl acetate will initially volatilize to the atmosphere in many of these applications. The total tropospheric lifetime of ethyl acetate is estimated to be 6.28 days with degradation due to hydroxyl radical-mediated photo-oxidation. As a volatile organic compound in the atmosphere, ethyl acetate is a potential contributor to tropospheric ozone formation under certain conditions, however its photochemical ozone creation potential is considered to be low. The aquatic toxicity data in fish, invertebrates, and algae indicate a low order of toxicity with LC_{50}/EC_{50} concentrations generally greater than 100 mg/L. A 21 day chronic daphnia study had a no observed effect concentration (NOEC) of 2.4 mg/l. The rapid biodegradability of ethyl acetate in water and soil and photo-oxidation in air all suggest a low likelihood of adverse outcomes in aquatic species. Terrestrial data are not available, but based on negligible soil release and low potential for bioaccumulation, adverse terrestrial outcomes are considered unlikely.

Exposure

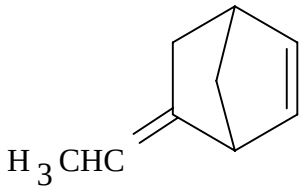
Worldwide ethyl acetate production was 1,011 Ktonnes in 1998. US production in 1997 was 118 Ktonnes (259 million pounds). Ethyl acetate is manufactured by a continuous, closed process and during normal operating procedures, releases are anticipated to be low. Ethyl acetate is used in liquid formulation products, typically

lacquers, solvent mixtures, inks, coatings, and adhesives. There is limited use in consumer products (coatings, adhesives) plus products such as nail polish remover. Application of these materials results in exposure via the dermal and inhalation routes and release of ethyl acetate into the environment through the volatile release of the material. There is reasonable quantity of published data on exposure of workers to ethyl acetate. This data shows that the vast majority of exposures are well below current occupational exposure limits (OELs). In general, exposures are greatest in the adhesives sector but available data still shows exposures below prevailing OELs. Ethyl acetate is a natural component of many foods including a variety of fruits and vegetables, beer and bourbon.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation. The chemical is currently of low priority for further work because of low toxicity to humans and the environment and low potential for exposure.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	16219-75-3
Chemical Name	5-Ethylidene-2-norbornene
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Ethylidene norbornene (ENB) has a relatively low degree of acute toxicity in several species via oral (LD_{50}: 2276-5071 mg/kg), dermal (LD_{50}: >7168 mg/kg), and inhalation (LC_{50}: 13.3-14.8 mg/L or 2717-3015 ppm) routes of administration. The substance is a mild irritant to skin and is a slight eye irritant to rabbits. There are no data available on skin sensitization. Repeated dose toxicity data include one 28-d oral (gavage) study and 3 subchronic inhalation studies up to 14-wk in duration. In the 28-d repeated oral dose study [TG 407], relative kidney weights were increased in rats of both sexes given 100 mg/kg/d. Histopathological examination revealed increased hyaline droplets in proximal tubular epithelium of the kidney, and hypertrophy of follicular epithelium, as well as a decrease in colloid or irregularly shaped follicles in the thyroids of males given 4 mg/kg/d or more ENB. Hypertrophy of thyroid follicular epithelium and a decrease in colloid were also observed in females given 100 mg/kg/d. The LOAEL of ENB in the 28-d repeated dose study was reported as 4 mg/kg/d for males, and the NOAEL was 20 mg/kg/d for females. Because the male rat kidney effects are consistent with alpha-2u-globulin nephropathy they are not relevant to humans. The mechanism producing thyroid effects in rats has little or no relevance to humans. Therefore, the oral NOAEL for systemic effects other than thyroid and kidney is 20 mg/kg/d, based on reduced body weight of females in the 100 mg/kg group. In inhalation exposure studies in rats, the major toxicity also appeared in the thyroid. For the most recent rat study, the NOAEL was reported to be 5 ppm based on thyroid effects. Other than the thyroid, no exposure related lesions were observed at concentrations up to 149 ppm. Because the increased relative liver weights were seen in both sexes at 149 ppm, the inhalation NOAEL based on effects other than thyroid is considered to be 25 ppm. ENB was not mutagenic with and without an exogenous metabolic activation system in bacteria and mammalian cells *in vitro* [OECD TG 471, 472, 473]. The chemical induced neither chromosomal aberrations nor sister chromatid exchanges in mammalian cells in culture. It also did not induce dominant lethal mutation in rats. There are two key studies that evaluated reproductive and developmental toxicity. One is an oral reproductive / developmental toxicity screening test [OECD TG 421], and the other is an inhalation development toxicity (teratogenicity) study. In the OECD TG 421study conducted in rats administered 0, 4, 20, and 100 mg/kg/day of ENB, a prolongation of the gestation period was noted in the 100 mg/kg/d group compared to controls but was within the normal historical range for the laboratory. The implantation and delivery indices were significantly lower in the 100 mg/kg/d group compared to controls. No other changes attributable to the compound were observed in any parameters including the mating index, the fertility index, the gestation index, number of corpora lutea, parturition state and lactation behavior. The total number of births and number of live offspring on

day 4 of lactation were decreased in the 100 mg/kg/d group. Among the pups, no other changes attributable to the compound were observed in parameters including the sex ratio, the live birth index, and the viability index on day 4, necropsy findings or external examination. Based on these findings, the oral NOAEL for reproductive/ developmental toxicity was 20 mg/kg/d. A teratogenicity study was conducted in rats exposed by inhalation to 0, 25, 100 and 354 ppm ENB (0, 123, 492, 1740 mg/m^3) during days 6-15 of pregnancy. There was no maternal mortality. Maternal body weights, body weight gain, and food consumption were reduced over the exposure period at 100 and 354 ppm, with partial or complete recovery post exposure. Increased relative liver weights were measured for the 100 and 354 ppm groups. There were no increases in the incidence of malformations or external and visceral variations. Three skeletal variants (bilobed 12th thoracic centrum, split 12th thoracic centrum, and poorly ossified second sternabra) were increased at 354 ppm, and one (bilobed 12th thoracic centrum) was increased at 100 ppm. Thus, fetotoxicity (skeletal variants) was seen in the 100 and 354 ppm group litters in the presence of maternal toxicity. For both maternal and developmental toxicity, 25 ppm (123 mg/m^3) was a NOAEL.

Environment

ENB has been tested for aquatic toxicity in three trophic levels including fish, daphnia and algae. For acute toxicity, a 72hEC_{50} of 2.61 mg/L and a 96hEC_{50} of 3.68 mg/L for algae (OECD TG 201, *Selenastrum capricornutum* biomass), 48hEC_{50} values of 3.34 and 7.3 mg/L for daphnid (OECD TG 202, *Daphnia magna*, immobilization), and for fish a 96hLC_{50} of 7.0 mg/L (OECD TG 203, *Oryzias latipes*) and of 7.6 mg/L (*Brachydanio rerio*) were available. In chronic studies, a 72-h NOEC of 0.852 mg/L in *Selenastrum* (OECD TG 201,biomass) and a 21-d NOEC of 1.51 mg/L in *Daphnia magna* (OECD TG 211, reproduction) were reported, respectively. The EC_{50} of multiple studies in different species of fish and in the daphnia and algae were consistent, however alga was the most sensitive among three trophic levels.

Exposure

The production volume of ENB is estimated to be ca. 20,000 tonnes/year in Japan, and ca. 54,000 tonnes/year worldwide; major producers are located in Japan, EU and the United States. ENB is a bicyclic diene compound used as a co-polymer in the production of ethylene-propylene diene monomer (EPDM) elastomers. ENB is produced in a closed system by a limited number of companies. At one company in Japan, ENB was not detected in the wastewater, rain sewer or in the air at the borderline of the Japanese manufacturing plant site. Data from one US manufacturer indicates 979 pounds (445 kg) per year are released as fugitive emissions to the atmosphere during production and storage of ENB. There are no discharges to soil or water (data reported to USEPA Toxic Release Inventory in 2000). The product use pattern can be described as "closed systems; non-dispersive use in the chemical industry as an intermediate." The major use of ENB is in EPDM rubber production, which occurs under controlled conditions. Data from a US and European EPDM plant have been obtained, and Mckay Level III fugacity calculations indicate "nanogram" quantities of ENB will be present in water that enters the waste water treatment plant where most will be released to atmosphere prior to discharge. Based on physical/chemical properties [log Pow (3.82), water solubility (80 mg/L), vapor pressure (5.6 hPa), and Henry's Law constant (>5 atm·m^3·mol^{-1})] ENB released in the environment is readily volatile and will rapidly partition to the air (Fugacity level I calculations). ENB is not readily biodegradable (OECD 301C) and is expected to be slightly to moderately mobile in soil based on calculated soil adsorption coefficients (log Koc) ranging from 2.96 to 3.01.Measured BCF of 61-160 in Carp confirm low potential for bioaccumulation (OECD 305C). If released into water, ENB is expected to volatilize to the atmosphere. The atmospheric half-life of ENB is estimated to be 52 minutes. Vapor phase ENB will be degraded in the atmosphere by reaction with photochemically produced hydroxy radicals and ozone molecules.

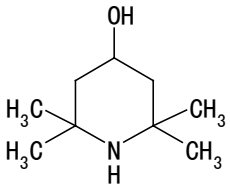
Occupational exposure to ENB may occur through inhalation and dermal contact with this substance at workplaces where ENB is produced and used. ACGIH and US/OSHA set a ceiling limit at 5 ppm (25 mg/m^3) for ENB to protect against eye and skin irritation. Since ENB is produced in a closed system the potential for exposure is primarily during maintenance operations and/or upset conditions. Workplace air monitoring in the EPDM production area has found full shift personnel exposures normally below 0.5 ppm with a range of <0.01 to 1.39 ppm. In the rubber production areas, potential for worker exposures exist in and around the distribution conveyors to the baling pits. Short-term area samples from open points in the system vary from 1 to 5 ppm. The exposure to the general population via the environment is theoretically possible through consumption of fish, which may accumulate this chemical to a limited degree. However, due to the anticipated short residence time of ENB in aquatic ecosystems,

chronic exposure of aquatic organisms is not expected. Another possible exposure route may be via migration of the chemical from food packaging polymers. However, estimation of worst case exposures revealed very low exposure levels which were considered insignificant.

NATURE OF FURTHER WORK RECOMMENDED

The chemical is currently of low priority for further work This conclusion is based on negligible human exposure and very low environmental releases.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2403-88-5
Chemical Name	2,2,6,6-Tetramethylpiperidin-4-ol
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics and metabolism of this substance. Oral LD_{50} of rats was 1482 mg/kg for males and 1564 mg/kg for females [OECD TG 401]. The major toxic signs were decreased locomotor activity, mydriasis and blepharoptosis, and tissue damages in the stomach and duodenum in both sexes. Dermal LD_{50} of rats was more than 2000 mg/kg. This substance is highly irritating to skin in rabbits [OECD TG 404], and it can be expected to cause serious damage to eyes but the study has not been performed. It has a moderate to strong grade of skin-sensitizing (contact allergenic) potential in guinea pigs [OECD TG 406].

In a (oral) combined repeat dose and reproductive/developmental study [OECD TG 422] rats received 0, 60, 200 or 600 mg/kg for at least 41-days. Animals died at 600 mg/kg (3/12 male, 1/12 female). Pathological changes were only observed in these animals; tissue damage to the gastro-intestinal tract, stomach and kidneys. The only effects seen at 60 and 200 mg/kg were drooping of the upper eyelid and dilation of the pupil in a dose related manner. A LOAEL of 60 mg/kg is identified for these clinical signs of toxicity. A NOAEL could not be identified.

In the above screening test [OECD TG 422], the substance was given from 14 days before mating to 20 days after mating in males, and to day 3 of lactation in females. In the 600 mg/kg group, the mean estrous cycle was prolonged with continuous diestrous in three females. With regard to the effects on neonates, viability and body weight on day 4 of lactation were decreased in the 600 mg/kg group. These effects are secondary non-specific consequence of systemic toxicity. The NOEL for reproductive /developmental toxicity was considered to be 200 mg/kg/day.

As for the genotoxicity, this substance was not mutagenic in bacteria [OECS TG 471 and 472]. An increase in chromosome aberrations in Chinese hamster lungs cells without S9 [OECD TG 473], were considered to be due to cytotoxicity and the study was considered to be "equivocal." A negative result was obtained in a rat bone marrow micronucleus assay [OECD TG 474]. Thus, on the basis of the available data, 2,2,6,6-tetramethylpiperidin-4-ol is not considered to be an *in vivo* genotoxicant, as the questionable genotoxicity observed *in vitro* is not expressed *in vivo*.

Environment

The generic fugacity model (Mackey level III) shows that if this substance is released into water, ca. 100% of this

substance is expected to stay in water due to the high solubility in water (> 100 g/L at 25°C, pKa 9.92 at 25°C). However as the substance is cationic form in the environment, it is likely that a certain portion of the substance is adsorbed in the sediment. This substance is not readily biodegradable (OECD TG 301C: 0 - 2% after 28 days) or hydrolyzed at pH 4, 7 and 9 at 50°C. But, it is expected to have low potential for bioaccumulation based on a low Log Pow (0.24) and a measured BCF of less than 5.7.

This substance has been tested in a limited number of aquatic species including fish, daphnia and algae. LC_{50} of the acute toxicity (96 h) for fishes (Medaka and Zebrafish) are 237 mg/L and > 1000 mg/L, respectively. A prolonged toxicity test using Medaka resulted in a LC_{50} (14 d) of 88.1 mg/L. The acute (immobility) and chronic data (reproduction) for daphnia were 100.1 mg/L for EC_{50} (48 h), and 46.2 mg/L for EC_{50} (21 d) and 3.7 mg/L for NOEC (21 d reproduction). The toxicity to *Selenastrum capricornutum* and *Scendedesmus subspicatus* of aquatic plants (algae) were 155 mg/L for EC_{50} (72 h) and 76 mg/L for NOEC (72 h), and 158 mg/L for EC_{50} (72 h) and 10 mg/L for NOEC (72 h), respectively. A predicted no-effect concentration (PNEC) of 0.037 mg/L for the aquatic organisms was calculated from the chronic NOEC for daphnia using an assessment factor of 100, because two chronic data (daphnia and algae) were available.

Exposure

This substance is used exclusively as an intermediate in synthesis of light stabilizer 'HALS' (Hindered Amine Light-Stabiliser) for plastics. The production volume in Japan was ca. 2,500 tons/year, while estimated global production was ca. 8,000 tons/year in 1999.

Workers may be exposed to this substance at production sites and user sites in industries. The production process is fully closed, but in packing and unpacking work, inhalation and dermal exposure is possible. Since this substance may cause irritation, corrosion and sensitization to the skin, a worker is allowed to work only after being equipped with appropriate protection implements at the workplace. Therefore, the amounts of exposure to a worker of this substance in the workplace would be practically low.

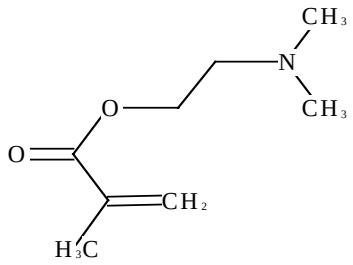
Consumer exposure is considered as follows. The amount of HALS in final consumer products, e.g. plastics is estimated to be less than 1.0%. The content of the substance itself in the consumer products should be far below that. Then exposure by the residues to a consumer through product surfaces would be very low.

During production and use in Japan, only the aquatic release of this substance from the production site seems to be possible. Although this substance is not readily biodegradable or hydrolysable, the bioaccumulation potential of this substance is low.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation based on the prerequisite of negligible human exposure and environmental release.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2867-47-2
Chemical Name	2-Dimethylaminoethyl methacrylate
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

2-Dimethylaminoethyl methacrylate is supposedly metabolized to methacrylic acid and N,N-dimethylaminoethanol. Then the methacrylic acid may form an acetyl-CoA derivative, which then enters the normal lipid metabolism. The oral LD_{50} in rats is greater than 2000 mg/kg. This chemical is considered to be severely irritating or corrosive to skin and eye. This chemical does not have a sensitizing potential.

The OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422] was conducted in rats at doses of 0, 40, 200 and 1000 mg/kg/day administered by gavage. For both sexes, a clear systemic toxicity was demonstrated only at 1000 mg/kg/day. Late onset of twitching, chronic convulsion and the suppression of body weight gain were observed. Three females out of 12 died. Histopathological examination revealed degeneration of nerve fibers in the brain and spinal cord, and hyperplasia of the mucosa, edema and inflammatory cell infiltration in the forestomach in both sexes. Increases in organ weights without histopathological changes were observed in the kidneys of both sexes, the livers of males, and the adrenals of females in this group. For the males in this group, BUN was slightly increased and anemic changes such as decreases in erythrocyte counts, hemoglobin concentration and hematocrit value, associated with a significant increase in reticulocyte ratio were observed. In males from the 200 mg/kg/day group, only slight anemic changes such as those observed at 1,000 mg/kg/day were seen, but the severity was considered toxicologically insignificant. The NOAEL for the repeat dose toxicity is considered to be 200 mg/kg/day.

A repeated inhalation study for 3 weeks revealed a NOEL of 100 ppm. Nose and eye irritation was observed at 250 ppm (LOEL).

Two independent gene mutation tests in bacteria [OECD TG 471 & 472] resulted in negative results except for a positive result in *S. typhimurium* TA 1537 at 2500 ug without metabolic activation in one study. A HPRT study on Chinese hamster cultured cells [OECD TG 476] was negative. A chromosomal aberration test *in vitro* [TG 473] and

a human lymphocyte test were positive with and without metabolic activation. However two *in vivo* studies [micronucleus assay, OECD TG 474] by i.p. or gavage respectively, gave negative results. Based on the weight of evidence, it is concluded that this chemical is not genotoxic *in vivo*.

In the above-described OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], there was no sign of reproductive toxicity up to 1000 mg/kg/day for males. Three females in the 1,000 mg/kg/day group, however, lost all of their pups in the lactation period. As to the developmental effect, the pups born from the females in the 1000 mg/kg/day group showed a lower body weight although no external abnormalities were observed. The NOAEL of the reproductive/developmental toxicity is considered to be 200 mg/kg/day for both parents and offspring.

Environment

Abiotically 2-dimethylaminoethyl methacrylate is hydrolyzed at pH7 and at pH 9 with a half-life of 4.54 days and 3.31 hours, respectively, whereas it is stable at pH 4. This chemical is readily biodegradable ([OECD TG 301E]; BOD: 95.3 % after 28 days), and has low bioaccumulation potential based on its log Kow of 1.13.

This chemical 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 41.6 mg/L (72 h-EC_{50}) and 18 mg/L (72 h-NOEC). The acute (immobility: [OECD TG 202]) and chronic (reproduction: [OECD TG 211]) toxicity results for daphnids are 33 mg/L (48h-EC_{50}), 16.6 mg/L (21d-LC_{50}), 7.86 mg/L (21d-EC_{50}), and 4.35 mg/L (21d-NOEC), respectively. The acute LC_{50} (96 hr: [OECD TG 203]) and prolonged LC_{50} (14 d: [OECD TG 204]) for fish (Medaka; *Oryzias latipes*) were 19.1 mg/L and 5.26 mg/L, respectively. Although 2-dimethylaminoethyl methacrylate can be hydrolyzed in these test conditions to methacrylic acid and dimethylaminoethanol, these results are, however, consistent with the aquatic toxicity of the metabolites reported in the respective SIARs issued in the past.

Exposure

The production volume of 2-dimethylaminoethyl methacrylate was estimated at approximately 8,000 t/year in Japan and 48,000 t/year world-wide in 2000. 2-Dimethylaminoethyl methacrylate is produced in a fully-closed system. Most of 2-dimethylaminoethyl methacrylate is industrially converted to the quaternary ammonium salt and polymerized for flocculant use in water treatment. This chemical is also used as a component monomer of copolymers in the polymer industry, and the products are used for paper agents, coatings and others. The workplace exposures during those application processes are controlled. Fugacity modeling (Mackay level III) predicts that 2-dimethylaminoethyl methacrylate released to water unlikely will migrate into other compartments. 2-Dimethylaminoethyl methacrylate is readily biodegradable and not persistent in the water phase. When this chemical is released to air, 72 % stays in air and 28 % is transported into water and soil.

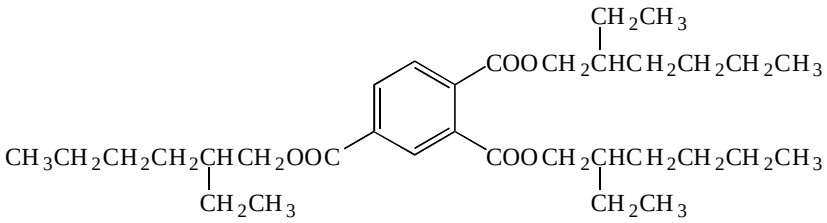
During production and use of this substance occupational exposure is possible by inhalation of vapor. Consumer exposure is controlled because it is limited to the non-dispersive use.

Migration of residual monomer from the polymer matrix is expected to be low. Nevertheless, the possibility of exposure cannot be excluded.

NATURE OF FURTHER WORK RECOMMENDED

The chemical is not a candidate for further work considering the low bioaccumulation potential, ready biodegradability and low aquatic toxicity.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3319-31-1
Chemical Name	Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In a single dose study of rats, 75 % of the orally administered chemical at 100 mg/kg bw was excreted in an unchanged form in the feces, 16 % as metabolites in the urine and 1.9 % was expired as CO_2.

The acute toxicity of the chemical is low because it showed no toxic signs at 2,000 mg/kg bw by oral route in rats [OECD TG 401] and at 2 mL/kg by dermal route in rabbits. During exposure by inhalation at 2600 mg/m^3, no death occurred in rats, but reddening patches in the lungs were observed after 14 days post exposure.. In an irritation-test for animals, the chemical was slightly irritating to the skin and the eyes. A sensitization test on guinea pigs showed no sensitization [OECD TG 406].

A feeding study with rats for 28 days showed a decrease of hemoglobin and an increases of leucocyte counts and serum cholesterol as well as an increased liver weight in the mid and high dose groups (0.67 and 2.0 %). Liver biochemistry revealed increases in palmitoyl CoA oxidation (increased in both sexes at 2.0% and males at all dose levels) and catalase activity (increased in males at 2.0%), suggesting the induction of peroxisome proliferation. Further analysis by an electron microscope indicated slight increased number of peroxisomes in hepatocytes at the high dose. It is generally accepted that the induction of peroxisome proliferation occurs specifically in rodents but much less in other species including humans. There were no dose-related histopathological changes in any treated groups. The NOAEL in this study was considered to be 0.2 % (184 mg/kg bw/day).

The OECD reproductive/developmental toxicity screening test [TG 421] for at least 46 days at doses of 100, 300 and 1,000 mg/kg/day demonstrated a decrease of spermatocytes and spermatids in testis in the 300 and 1000 mg/kg groups but not in the 100 mg/kg group.

Based on the testicular toxicity, the NOAEL for repeated dose toxicity is considered to be 100 mg/kg bw/day.

As for reproductive/developmental toxicity, the chemical showed no adverse effects on copulation, fertility, delivery and nursing of females nor on the viability, body weight and morphology of offspring in the above screening test [OECD TG 421]. However, the NOAEL for reproductive toxicity in males was considered to be 100 mg/kg bw/day

because of the testicular toxicity described above. Both NOAELs for reproductive toxicity in females and developmental toxicity of offspring were considered to be 1,000 mg/kg bw/day.

The genotoxicity of this chemical was evaluated in many *in vitro* assay systems. It was neither mutagenic in bacteria [OECD TG 471 & 472] nor clastogenic in mammalian cells [Guidelines for Screening Mutagenicity Testing of Chemicals (Japan)].

Environment

The Mackay level III fugacity Model was employed to estimate the environmental distribution of this chemical in air, water, soil and sediment. If released to air, this chemical will exist solely in the particulate phase in the ambient atmosphere. If released to soil, this chemical is not expected to be distributed to other compartments.

This chemical has to be considered as weakly toxic against aquatic organisms and is not biodegradable. This chemical has a high logPow value (5.94), the measured BCF is reported as less than 1 to 2.7 in carp for 6 weeks, but some uncertainty still remains regarding the bioaccumulation potential of this chemical. This result indicates that the bioavailability of this chemical is low. The toxicity results to aquatic plants (algae; *Selenastrum capricornutum*) were >100 mg/L for EC_{50} (72hr). The acute toxicity data in fish (medaka; *Oryzias latipes*) were >100 mg/L (96h, LC_{50}) and >75 mg/L (14d, LC_{50}). In *Daphnia magna*, the acute toxicity was >180mg/L (48hr: EC_{50}) and the chronic toxicity was >55.6 mg/L (21d, reproduction). All these data were obtained in supersaturated solution with the aid of solubilizer (HCO-40). The test solution was considered to be homogeneous. Another chronic toxicity data in *Daphnia magna* (NOEC >0.082mg/L) was reported (Procedure of ASTM and USEPA). Though this value is lower than the saturation point, the measured concentration data were less reliable.

Based on the description of the test results above, it can be concluded that Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate does not show any toxic effects at the limit of solubility towards those aquatic organisms, which were tested in the laboratory. Though it is difficult to determine a PNEC, this substance is not toxic at its water solubility (OECD TG105; 0.13 mg/L 25 C).

Exposure

This chemical is manufactured as a plasticizer for PVC.

The production volume in Japan is approximately 20,000 tonnes/year and there are 5 manufacturers in Japan. Estimated global production is 40,000-100,000 tonnes/year. This chemical is mainly used as a plasticizer for PVC electrical cable and wire.

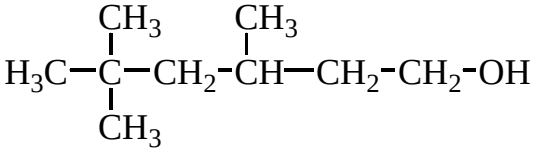
Occupational exposure may occur through dermal contact and inhalation of mist. This chemical is produced in closed system and workers wear protective gloves and goggles during the operation, so actual exposure in the work place is considered to be low.

Since this chemical is difficult to extract from the polymeric matrix, consumer and environmental exposure are considered to be low.

NATURE OF FURTHER WORK RECOMMENDED

There is no recommendation for further work. The hazards of this chemical towards the environment and human health are considered to be low. Both occupational and consumer exposure are considered to be low.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3452-97-9
Chemical Name	3,5,5-Trimethyl-1-hexanol
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics and metabolism of 3,5,5-trimethyl-1-hexanol. In an acute oral toxicity study [OECD TG 401] in rats, the LD_{50} for this substance was more than 2000 mg/kg. In both a semi-occlusive patch test and an OECD 405 eye irritation assay 3,5,5-trimethyl-1-hexanol was a moderate irritant to both skin and eye. There is no information on sensitization.

In the OECD combined repeated dose and reproductive/ developmental toxicity screening test [OECD TG 422], this substance was administered by gavage (male rat 46 days, female rat from 14 days before mating to day 3 of lactation) at the dose levels of 12, 60 and 300 mg/kg/day.

Histopathological examination revealed a slight to moderate degree of hyaline droplet and eosinophilic body in proximal tubular epithelium in kidneys in all dosed male rats, which were confirmed as an accumulation of alpha-2u-globulin complex by immuno-staining. A slight to moderate degree of renal tubular epithelial regeneration and formation of granular casts in kidneys in males of the 60 and 300 mg/kg groups, a slight degree of irregularity in the shape of follicles, columnar change of the follicular epithelium and a decrease of colloid in the thyroid in males of the 300 mg/kg group were observed. In female rats, a slight degree of renal epithelial fatty change in the 60 and 300 mg/kg groups, and atrophy of the thymus in the 300 mg/kg group were observed. On the basis of these findings, the NOAEL of 3,5,5-trimethyl-1-hexanol for repeat dose toxicity was considered to be 12 mg/kg/day for males and females.

In the above OECD combined repeated dose and reproductive/ developmental toxicity screening test [OECD TG 422], a decrease in implantation rate was observed in the 60 and 300 mg/kg group. Total litter loss in two dams of the 300 mg/kg group was observed, and the number of pups born alive decreased in the 60 and 300 mg/kg groups. Because of the limitation of the methodology employed, it is not possible to distinguish if the cause was due to maternal toxicity or due to a direct effect on the fetus. With regard to effects on neonates, viability on day 4 of lactation decreased in the 300 mg/kg group, and male and female pups of the 300 mg/kg group showed lower body weights on day 0 of lactation.

On the basis of these findings, the NOAELs for reproductive/developmental toxicity were considered to be 12 mg/kg/day for parents and 12 mg/kg/day for the F1 generation, respectively.

The chemical showed negative results in bacterial mutation tests [OECD TG 471 & 472] and a chromosomal aberration test *in vitro* [OECD TG 473] with and without metabolic activation.

Environment

3,5,5-Trimethyl-1-hexanol is slightly soluble in water (450 mg/L at 25 °C). Log Pow and vapor pressure of this substance are 3.42 (at 25 °C) and 0.0901 hPa (at 25 °C), respectively. The half life for degradation in air is estimated to be 36 hr. In water, this substance is stable at pH 4,7and 9 at 50°C.

If released into the aquatic environment from waste water, 3,5,5-trimethyl-1-hexanol would mostly remain in the water compartment. This substance is not readily biodegradable and has a low potential for bioaccumulation (BCF = 3.9-8.1).

This chemical has been tested in a limited number of aquatic species including algae, daphnids and fish. The 0-72 h-EC_{50} (growth rate: [OECD TG 201]) for algae (*Selenastrum capricornutum*) is 33.3 mg/L and the NOEC is 6.60 mg/L (the NOEC for biomass is 2.9 mg/L).

For daphnids, the acute 48h-EC50 (immobility: [OECD TG 202]) was 6.77 mg/L The chronic toxicity results (reproduction: [OECD TG 211]) were reported as: 21d-LC_{50} > 3.87 mg/L, 21d-EC_{50} = 2.09 mg/L (reproduction) and 21d-NOEC = 1.46 mg/L (reproduction). The LC50s for acute toxicity in fish (*Oryzias laptipes* and *Carasius auratus*) were reported to be 27.7 mg/L [OECD TG 203](96 h) and 16 mg/L (24 h), respectively. Furthermore in a prolonged toxicity test with fish [OECD TG 204], behavior change was observed, most frequently on the 3rd day of exposure, at each concentration higher than 3.2 mg/L. EC_{50} and NOEC values calculated based on the observation of the 3rd day were 3.20 and 1.28 mg/L, respectively.

Exposure

The production volume of this substance is approximately 1,300 t/y in Japan. This substance is produced in closed systems. The main use is an intermediate as a raw material for the synthesis of plasticizers (i.e. phthalate) and esters.

The fugacity model (Mackay level III) suggests that if released to air, water or soil, the majority of this substance would distribute into water and soil.

If released to water, this substance is not readily biodegraded (4% based on BOD during 28 day). The BCF of 3.9-8.1 suggests that the potential for bioaccumulation in aquatic organisms is low.

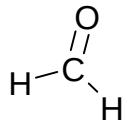
This substance is produced and used in closed system. Therefore, occupational exposure is limited to sampling and maintenance at the production facilities. Moreover, the exposure time is very short. A maximum exposure level is estimated in a production site of Japan. Workers are recommended to wear protective equipment (masks and gloves) during the work. Therefore occupational exposure through inhalation of its vapor or by dermal adsorption is assumed to be negligible.

The consumer would not be directly exposed to this chemical.

NATURE OF FURTHER WORK RECOMMENDED

This chemical is currently of low priority for further work, because this chemical is a closed system intermediate with a low exposure potential and workers are protected by proper equipment. It is not bioaccumulative in the environment, and no effect levels are greater than 1 mg/L.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	50-00-0
Chemical Name	Formaldehyde
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Formaldehyde had acute effects in mammals: LD_{50} (rat, oral) 600 – 800 mg/kg b.w., LC_{50} (rat, inhalation, 4 h) 578 mg/m^3 (480 ppm). Inhalation of high concentrations (> 120 mg/m^3) of formaldehyde caused hypersalivation, acute dyspnea, vomiting, muscular spasms, convulsions and finally deaths. Histopathology examination showed respiratory tract irritation, bronchioalveolar constriction and lung oedema. Formaldehyde was irritating to the eyes, and aqueous solutions of formaldehyde (0.1% to 20%) were irritating to the skin of rabbits. Formaldehyde was sensitising in the guinea pig maximisation test and the local lymph node assay with mice. On the other hand, specially designed studies (IgE tests, cytokine secretion profiles of lymph node cells) did not reveal evidence of respiratory sensitisation in mice.

In humans, transient and reversible sensory irritation of the eyes and respiratory tract has been observed in clinical studies and epidemiological surveys. Odour threshold for most people ranges between 0.5 and 1 ppm. In general, eye irritation, the most sensitive endpoint, is associated with airborne concentrations beginning in the range of 0.3 to 0.5 ppm. Eye irritation does not become significant until about 1 ppm, and rapidly subsides. Moderate to severe eye, nose and throat irritation occurs at 2 to 3 ppm. Sensory irritation has also been reported at lower exposure levels, but is then difficult to distinguish from background. Most studies show no effect on lung function in either asthmatics or non-asthmatics. Formaldehyde causes skin irritation and has corrosive properties when ingested. In some individuals, contact dermatitis may occur at challenge concentrations as low as 30 ppm.

Formaldehyde is a highly reactive gas that is absorbed quickly at the point of contact and is also produced by endogenous metabolism. It is rapidly metabolised, such that exposure to high concentrations (up to 15 ppm in rats) does not result in increased blood concentrations. Repeated formaldehyde exposure caused toxic effects only in the tissues of direct contact after inhalation, oral or dermal exposure characterised by local cytotoxic destruction and subsequent repair of the damage. The typical locations of lesions in experimental animals were the nose after inhalation, the stomach after oral administration and the skin after dermal application. The nature of the lesions depended on the inherent abilities of the tissues involved to respond to the noxious event and on the local concentration of the substance. Atrophy and necrosis as well as hyper- and metaplasia of epithelia may occur. The most sensitive No Observed Adverse Effect Levels (NOAELs) for morphological lesions were between 1 and 2 ppm for inhalation exposure and about 260 mg/l in drinking water.

Formaldehyde is weakly genotoxic and was able to induce gene mutations and chromosomal aberrations in

mammalian cells. DNA-protein crosslinks are a sensitive measure of DNA modification by formaldehyde. However, the genotoxic effects were limited to those cells, which are in direct contact with formaldehyde, and no effects could be observed in distant-site tissues. In conclusion, formaldehyde is a direct acting locally effective mutagen.

Chronic inhalation of concentrations of 10 ppm and higher led to clear increases in nasal tumour incidence in rats. Most of the nasal tumours were squamous cell carcinomas. Marked non-neoplastic pathological lesions of the nasal epithelium accompanied them. No increased incidence of tumours was found in other organs after inhalation, and administration routes other than inhalation did not result in local or systemic tumour formation. The damage of nasal tissue played a crucial role in the tumour induction process, since nasal cancer was only found at concentrations inducing epithelial degeneration and increased cell proliferation. Thus the stimulation of cell proliferation seems to be an important prerequisite for tumour development. Although formaldehyde exhibits some genotoxic activity, the correlation between cytotoxicity, cell proliferation and the induction of nasal cancer in rats provides a convincing scientific basis for aetiology of the carcinogenic response to be cytotoxicity driven. In contrast to that, no significant numbers of tumours were seen in mice and Syrian hamsters following chronic exposure to concentrations up to 14.3 or 30 ppm, respectively. These clear species differences appeared to be related, in part, to the local dosimetry and disposition of formaldehyde in nasal tissues. Species differences in nasal anatomy and respiratory physiology may have a profound effect on susceptibility to formaldehyde-induced nasal tumours.

In epidemiological studies in occupationally exposed human populations, there is limited evidence of a causal association between formaldehyde exposure and nasal tumours. Taking into account the extensive information on its mode of action, formaldehyde is not likely to be a potent carcinogen to humans under low exposure conditions.

There are no indications of a specific toxicity of formaldehyde to foetal development and no effects on reproductive organs were observed after chronic oral administration of formaldehyde to male and female rats. Amounts of formaldehyde which produce marked toxic effects at the portal of entry, do not lead to an appreciable systemic dose and thus do not produce systemic toxicity. This is consistent with formaldehyde's high reactivity with many cellular nucleophiles and its rapid metabolic degradation.

Environment

Formaldehyde is a colourless gas with pungent odour, soluble in water forming methylene glycol and low molecular mass poly(oxymethylene)glycols $HO(CH_2O)_nH$ (n = 1-8). It has a measured vapour pressure of 5185 hPa at 25°C.

The favourite target compartment for formaldehyde is water as indicated by Mackay Level I calculation (water: 99% equilibrium distribution). In air, formaldehyde is expected to be indirectly photodegraded, with a half life of 1.71 d. The substance is readily biodegradable. Hydrolysis is not expected under environmental conditions. However in water formaldehyde undergoes essentially complete hydration to yield the gem-diol, methylene glycol. The log P_{OW} was measured to 0.35 at 20 °C. Hence bioaccumulation is unlikely to occur.

The lowest valid effect value of 5.8 mg/l was found for *Daphnia pulex* (48h-EC_{50}). For fish the lowest effect value of 6.7 mg/l (96h-LC_{50}) was found for *Morone saxatilis* (marine). For freshwater fish the lowest effect value (96h-LC50 = 24.8 mg/l) was found for *Ictalorus melas*. For the green alga *Scenedesmus subspicatus* a 24h-EC50 of 14.7 mg/l and a 24h-EC10 of 3.6 mg/l is available for the endpoint oxygen production and consumption. Applying an assessment factor of 1000 according to EU Risk Assessment procedure to the lowest valid effect value, a $PNEC_{aqua}$ of 5.8 µg/l can be derived.

Exposure

Formaldehyde is ubiquitously present in the environment as a result of natural processes and from man-made sources. The major source of atmospheric formaldehyde is the photochemical oxidation and incomplete combustion of hydrocarbons. The global production of formaldehyde in 1999 is estimated to be 5 – 6 million tons. The substance is mainly used as an intermediate in the chemical industry for the production of condensed resins for the wood, paper and textile processing industries and in the synthesis of methylene dianiline (MDA), diphenylmethane diisocyanate (MDI), hexamethylenetetraamine (HTMA), trimethylol propane, neopentylglycol, pentaerythritol and acetylenic agents. Aqueous solutions of formaldehyde are employed as germicides, bactericides and fungicides. The use of

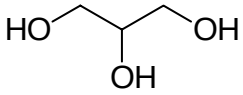
formaldehyde as biocide and in other applications is estimated to be 1.5 % of the total production, i.e. 75 000 to 90 000 t/a related to the worldwide production amount. Formaldehyde is used as a preservative in a large number of consumer products, such cosmetics and household cleaning agents. Tobacco smoke as well as urea-formaldehyde foam insulation and formaldehyde-containing disinfectants are all important sources of formaldehyde exposure. Releases into the environment are likely to occur during production and processing as intermediate as well as from use of products containing the substance. For almost all sites there is no information available about releases into the waste water from production and processing. In Canada, about 1424 t were released into the environment from industrial sites in 1997, from which about 20 t/a were releases to surface waters by 4 sites. The US TRI gives industrial releases of formaldehyde for 1999 with about 6,000 t/a to air and about 175 t/a to surface waters. From the direct use of the substance as e.g. biocide it can be assumed that a very high amount is released into the environment. With an amount of 75 000 to 90 000 t/a worldwide this is a significant pollution source. It can be estimated that formaldehyde contained in consumer products, like cleaning agents is released completely into the wastewater. In addition, reported use of formaldehyde in fish farming and in animal husbandry may lead to a significant environmental exposure.

NATURE OF FURTHER WORK RECOMMENDED

Environment: The substance is a candidate for further work. No information is available about releases into surface water from production and processing sites. In addition, it can be assumed that from the use of 1.5 % of the worldwide production volume (5 to 6 Mio t/a) as biocide and in other applications i.e. 75 000 – 90 000 t/a a high amount of formaldehyde is released into the environment (e.g. from fish and livestock farming). Product register information shows that fomaldehyde is contained in a large number of consumer products, like cleaning agents, detergents, soaps etc. For these applications it can be estimated that the whole amount is released into the waste water. Due to the low PNECaqua of 5.8 µg/l a risk to the aquatic environment cannot be excluded. Therefore, an exposure assessment is recommended.

Human Health: No recommendation for further work, because all SIDS endpoints are adequately covered and because exposure is controlled in occupational settings.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	56-81-5
Chemical Name	1,2,3-Propanetriol (Glycerol)
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

All SIDS health endpoints are fulfilled. It should be noted that much of the data on glycerol is historic and of rather low quality compared to current guideline requirements. Nevertheless, there is an overall consistency within the available data that allows conclusions to be drawn. Glycerol is absorbed following ingestion and metabolised by glycerokinase in the liver to carbon dioxide and water or incorporated in the standard metabolic pathways to form glucose and glycogen. The weight of evidence indicates that glycerol is of low toxicity when ingested, inhaled or in contact with the skin.

Glycerol is of a low order of acute oral and dermal toxicity with LD_{50} values in excess of 4000 mg/kg bw. At very high dose levels, the signs of toxicity include tremor and hyperaemia of the gastro-intestinal -tract. Skin and eye irritation studies indicate that glycerol has low potential to irritate the skin and the eye. The available human and animal data, together with the very widespread potential for exposure and the absence of case reports of sensitisation, indicate that glycerol is not a skin sensitiser.

Repeated oral exposure to glycerol does not induce adverse effects other than local irritation of the gastro-intestinal tract. The 2-year study of Hine (1953) was chosen to establish the overall NOEL after prolonged treatment with glycerol of 10,000 mg/kg bw/day (20% in diet), which is in agreement with the findings in other studies. At this dose level no systemic or local effects were observed. For inhalation exposure to aerosols, the NOAEC for local irritant effects to the upper respiratory tract is 165 mg/m3 and 662 mg/m3 for systemic effects.

Glycerol is free from structural alerts, which raise concern for mutagenicity. Glycerol does not induce gene mutations in bacterial strains, chromosomal effects in mammalian cells or primary DNA damage *in vitro*. Results of a limited gene mutation test in mammalian cells were of uncertain biological relevance. *In vivo*, glycerol produced no statistically significant effect in a chromosome aberrations and dominant lethal study. However, the limited details provided and the absence of a positive control, prevent any reliable conclusions to be drawn from the *in vivo* data. Overall, glycerol is not considered to possess genotoxic potential.

The experimental data from a limited 2 year dietary study in the rat does not provide any basis for concerns in relation to carcinogenicity. Data from non-guideline studies designed to investigate tumour promotion activity in male mice suggest that oral administration of glycerol up to 20 weeks had a weak promotion effect on the incidence of tumour formation.

No effects on fertility and reproductive performance were observed in a two generation study with glycerol administered by gavage (NOAEL 2000 mg/kg bw/day). No maternal toxicity or teratogenic effects were seen in the rat, mouse or rabbit at the highest dose levels tested in a guideline comparable teratogenicity study (NOEL 1180 mg/kg bw/day).

Environment

All SIDS environmental endpoints are fulfilled. It should be noted that much of the data on glycerol is historic and of rather low quality compared to current guideline requirements. However, the weight of evidence indicates that glycerol is of low toxicity to aquatic organisms and this conclusion is supported by QSAR predictions. The lowest LC50 for fish is a 24-h LC_{50} of >5000 mg/l for *Carassius auratus (*Goldfish*)* and for aquatic invertebrates, a 24h EC50 of >10000 mg/l for *Daphnia magna* is the lowest EC50. Several tests on algae are available, which suggest very low toxicity to a range of species, however their validity is uncertain. A QSAR prediction for the 96h EC50 to algae was 78000 mg/l. No toxicity towards the microorganism *Pseudomonas putida* was observed at 10000 mg/l after exposure for 16 hours. No long-term aquatic toxicity data is available. Screening studies are available on frog and carp embryos which indicate some effects on growth and hatching rates respectively at very high concentrations of glycerol, >7000 mg/l. However, their ecological relevance is not clear.

In view of the limited robustness of the studies present, it was decided to derive a tentative PNEC for aquatic organisms using QSAR predictions of acute toxicity. The tentative PNEC for aquatic organisms is calculated to be 780 mg/L, based on the lowest QSAR value (calculated for algae EC_{50} 77,712 mg/L) and applying an assessment factor of 100 in accordance with the OECD guidance. An assessment factor of 1000 for the aquatic PNEC compartment could also be considered to reflect the uncertainty in the use of QSAR-predicted values. There are no sediment or terrestrial effect data, but partitioning to both soil and sediment is expected to be very low, based on the very low log K_{ow} of glycerol. The equilibrium partitioning method was used to calculated tentative PNECs for soil and sediment based on the $PNEC_{aquatic}$ of 777 mg/l, $PNEC_{sediment}$ = 479 mg/kg wwt and $PNEC_{soil}$ = 92.1 mg/kg wwt.

Exposure

The worldwide market for glycerol for the year 2000 was 500,000 tonnes. Glycerol has widespread use and can be found in industrial, professional and consumer products. Glycerol is used as a constituent in numerous products and as an intermediate in industrial applications for the manufacture of products such as soaps/detergents and glycerol esters. It is found in consumer products such as pharmaceuticals, cosmetics, tobacco, food and drinks and is present in numerous other products such as paints, resins and paper.

There is a potential for occupational exposure through inhalation and skin contact. Consumers may be exposed to glycerol by the oral and dermal routes of exposure. Smoking may lead to an additional glycerol uptake by inhalation.

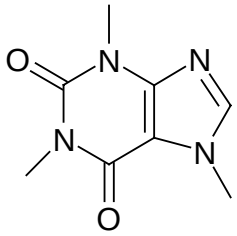
There is potential exposure to the aquatic compartment arising from the production and processing of this substance. Glycerol will enter the aqueous and terrestrial environment from end uses such as in consumer products and down hole lubricants for oil and gas fields.

Glycerol is a liquid with a calculated vapour pressure of 0.000106 hPa (at 25ºC), is fully miscible with water and has a Log K_{ow} of –1.76 (measured). It has a calculated half-life for photo-oxidation of ~7 hours and is not susceptible to hydrolysis. The experimental data indicate that glycerol is readily biodegradable under aerobic conditions. Fugacity modelling (Mackay Level III) predicts that glycerol will partition to the aquatic compartment (100%). Based on the low Log Kow, it has a low potential for sorption to soil and is not expected to bioaccumulate.

NATURE OF FURTHER WORK RECOMMENDED

No further work is indicated, because of the low hazard potential of this substance.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	58-08-2
Chemical Name	Caffeine
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Animal data

In animals studies caffeine showed acute toxicity LD50 rat oral 200-400 mg/kg bw, LD50 mouse oral 185 mg/kg bw, LC50 rat inhalative ca. 4.94 mg/l/4h; LD50 rat dermal > 2000 mg/kg bw). The undiluted substance was not irritating to the eyes of rabbits, the substance in a 50% aqueous dilution was not irritating to the skin of rabbits. In a 90-day-drinking water study in rats and mice a slight decrease of body weight gain was observed. No clinical signs of toxicity and significant gross lesion or microscopic findings were seen in either rats or mice. The NOAEL for rats was 1500 ppm (ca. 151-174 mg/kg bw/day) and for mice 1500 ppm (ca. 167-179 mg/kg bw/day). In all dose groups effects on salivary glands were observed, which were regarded as an adaptive and reversible response to the sympathomimetic effect of caffeine. There are numerous studies available concerning genetic toxicity *in vitro* and *in vivo*. In the majority of the studies caffeine produced negative results. Several positive responses were obtained only in studies which used extreme culture conditions, lethal doses or non-validated methods. There was no statistically significant increase in the tumor incidence in treated animals as compared to controls even at doses exceeding the maximum tolerated dose and given to rats over a major portion of their lifespan.

Caffeine resulted in reproductive effects occurring in the presence of general toxicity in parental rats and mice. A NOAEL in rats was not established. NOAEL: mouse 22 mg/kg bw/d (F0 parental, F1 offspring), 88 mg/kg bw/d (F1 parental, F2 offspring).

Gross malformations were observed in rats and mice only after bolus administration (i.p. or gavage) of very high maternal toxic doses. Fetotoxicity without maternal toxicity was observed in one drinking water study. NOAEL: 360 ppm (51 mg/kg bw/d) (maternal), 70 ppm (10 mg/kg bw/d) (fetotoxicity), 2000 ppm (205 mg/kg bw/d) (teratogenicity). However, in two other gavage studies with lower doses this finding was not confirmed. No NOAEL for maternal toxicity could be established; the NOAEL for developmental toxicity was 40 mg/kg bw/d; no teratogenic effects were observed.

Experience with human exposure

Absorption from gastrointestinal tract is rapid. Peak plasma levels are reached after 15 to 120 minutes after ingestion. The elimination half-life in adults is about 2.5 to 4.5 hours. A small percentage is excreted in bile, salvia, semen and breast milk. In both humans and rats, excretion mainly occurs via urine (about 90 % dose in rats; > 95 % in humans).

Caffeine metabolism is qualitatively similar in animals and humans. The main metabolic pathways are: demethylation and hydroxylation of the 8-position leading to the formation of the respective uracil and uric acid derivatives. There are, however, some quantitative differences in the metabolic profile.

Low doses (up to 2 µg/ml in blood) stimulate the central nervous system, while high blood concentrations (10-30 µg/ml) produce restlessness, excitement, tremor, tinnitus, headache, and insomnia. Caffeine can induce alterations in mood and sleep patterns, increase diuresis and gastric secretions. Acute toxicity is rare and is the result of an overdose. Lethal dose is estimated to be 5 g.

Caffeine and coffee consumption are highly correlated in most populations studied; thus it is difficult to separate the two exposures in epidemiologic investigations. No association between moderate consumption of coffee/caffeine and cardiovascular diseases was demonstrated in more recent studies. In short-term clinical trials an increase in blood pressure was seen, whereas in other surveys no relationship between caffeine consumption and elevation of blood pressure was observed. Caffeine consumed in moderate amounts did not cause persistent increase in blood pressure in normotensive subjects. Effect on cardiac rhythm is still in debate. Small increase in calcium excretion associated with coffee/caffeine intake was seen in subjects with dietary calcium deficiency. Caffeine has weak reinforced properties, but with little or no evidence for upward dose adjustment, possibly because of the adverse effects of higher doses. Withdrawal symptoms, although relatively limited with respect to severity, do occur, and may contribute to maintenance of caffeine consumption. Caffeine use is not associated with incapacitation. There is little evidence for an association of caffeine intake and benign breast disease. No association was found in a study with biopsy-confirmed controls.

A cohort study with short follow-up period showed no association between caffeine consumption and mortality from cancers at all sites. Case control studies of breast cancer showed no association with caffeine intake. Weak positive associations between caffeine intake and lung, bladder or pancreas cancer as well as a weak inverse association between caffeine intake and colon cancer may be due to bias or confounding. IARC evaluated that there is inadequate evidence of carcinogenicity in humans.

There are conflicting reports on the effect of caffeine on human reproduction. A teratogenic effect has not been proven. While caffeine intake up to 3-4 cups/day or 300 mg caffeine/day is unlikely to be causally related to spontaneous abortions or relevant reduction of birth weight, an association between higher daily caffeine intake and these endpoints can not be excluded. Conflicting results exist regarding a potential relationship between caffeine/coffee consumption and delayed conception or infertility.

Environment

Caffeine has a water solubility of 20 g/l, a vapor pressure of $4.7 * e^{-6}$ Pa and a log Kow of – 0.091.

Distribution modelling using Mackay, Level I, indicates that the main target compartment will be water with 99.99%.

Concerning biodegradation there is only a not valid study available for caffeine. However, from the structurally analogous compound theophylline it can be concluded that caffeine is readily biodegradable. The calculated hydrolysis rate is extremely slow. In the atmosphere caffeine will be indirectly photodegraded by reaction with hydroxyl radicals with a half-life of 19.8 hours (calculated).

Bio- and geoaccumulation are not expected according to the log K_{ow} (-0.091).

The acute aquatic toxicity has been determined for fish (*Leuciscus idus* LC50(96h) 87 mg/l), for aquatic invertebrates (*Daphnia magna* EC50(48h) 182 mg/l) and for algae (*Scenedesmus subspicatus* ErC50 (72h), ErC10 (72h) >100 mg/l). Results from prolonged or chronic studies are not available. Following the EU risk assessment procedure the PNEC aqua can be calculated to 0.087 mg/l by applying an assessment factor of 1000 on the most sensitive species (*Leuciscus idus* LC50(96h) 87 mg/l).

Exposure

Caffeine is produced with a volume of 10,000 to 15,000 tons per year, world-wide, including 3,000 to 4,000 tons of natural caffeine. It is mainly used in the food and pharma sectors.

Furthermore caffeine is a naturally occurring substance in various plant species (e.g. 0.9 to 2.6% in green coffee beans). It is a component in coffee, tea and cocoa. The use in food will be the predominant way of human exposure and of exposure of the environment.

Production sites for the technical product: EU (Germany) 1, NAFTA 2, Japan 1, India 4 and China 10. Production sites for natural caffeine are appr. 7 to 8 worldwide, thereof 4 in Europe.

Exposure to workers during production is adequately controlled by the use of engineering controlled methods in the industry of the sponsored country.

Workplace measurements during filter changes (Germany) : 0.1- ca. 1.2 mg/m^3 (8h).

At the German production site, process waters with relevant substance quantities are separated and combusted.

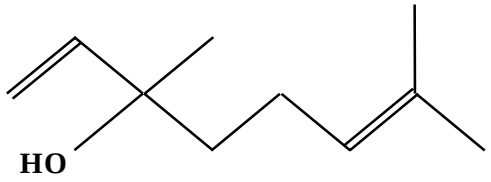
NATURE OF FURTHER WORK RECOMMENDED

Environment: No recommendation for further work, because the substance is readily biodegradable, has a low bioaccumulation potential and is only moderately toxic to aquatic organisms.

Human Health: No recommendation for further work for the following reasons:

The pharmacological properties of caffeine are well known. There are many studies relevant to reproductive toxicity; some suggest an adverse effect but the total data base is inconsistent. The case of caffeine is regulated by food and drug agencies of national governments.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-70-6
Chemical Name	Linalool
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Linalool has an acute oral mammalian LD_{50} close to 3,000 mg/kg bw; the acute dermal toxicity is ≥ 2,000 mg/kg bw. After inhalation exposure of mice and man, slight sedative effects were observed; however a dose response characteristic could not be determined. Linalool is irritating to the skin, based on animal studies, and is a mild irritant from human experience. It may be moderately irritant to the eyes at the same concentration where it produces nasal pungency. Linalool is considered not to be a sensitizer. The incidence of dermal reaction to Linalool is below 1% in naïve probands (not knowingly pre-sensitized) while in subjects pre-sensitised to fragrances it is up to 10%.

In a 28-day oral rat study (72.9% linalool) findings were increased liver and kidney weight, thickened liver lobes and pale areas on the kidneys and in females only hepatocellular cytoplasmic vacuolisation. Other findings were related to local irritation of the gastro-intestinal tract. Based on the effects on liver and kidney a NOAEL of 160 mg/kg bw/d (equivalent to 117 mg/kg bw/d linalool) was derived. In this study no effects on male and female gonads were found.

Linalool was not mutagenic in seven out of eight bacterial tests nor in two (one *in vitro* and one *in vivo*) mammalian tests; the one positive bacterial result is estimated to be a chance event.

Linalool (72.9%) was tested in a reproduction screening test (non-OECD). The NOAEL for maternal toxicity based on clinical signs and effects on body weight and food consumption was 500 mg/kg bw/d (equivalent to 365 mg/kg bw/d linalool). The NOAEL on reproduction toxicity and developmental toxicity is 500 mg/kg bw/d (equivalent to 365 mg/kg bw linalool), based on the decreased litter size at birth and pup morbidity/mortality thereafter.

Linalool seems not to be an immunotoxicant according to one animal study.

Environment

Linalool is a liquid with a vapour pressure of approx. 0.2 hPa (at 23.5 degree C), a water solubility of 1589 mg/l (at 25 degree C) and a Log Kow of 2.97 (at 23.5 degree C).

Most linalool, both natural and synthetic, is released to the atmosphere, where it is rapidly degraded abiotically with

a typical half-life below 30 minutes. In the aquatic compartment, linalool is readily biodegraded under both aerobic and anaerobic conditions, the same is predicted for soil and sediment. Linalool does not bioaccumulate to a major extent.

In acute aquatic ecotoxicity tests Linalool had a 96 hours LC_{50} value of 28 mg/l in fish, an 48 hours EC_{50} for daphnia of 20 mg/l and for algae an 96 hours EC_{50} of 88 mg/l. It had low toxicity to micro-organisms, from activated sludge to various species of bacteria and fungi, with most reported NOECs ≥ 100 mg/l. Based on the lowest acute EC_{50} for daphnia, an aquatic freshwater a PNEC of 200 µg/l is derived.

The NOEL of linalool on the germination and initial growth of terrestrial plants was 100 mg/l. A host of data show both contact and fumigant toxicity against insects; as an acetylcholinesterase inhibitor, it paralyses and ultimately kills insects at high concentrations. These effects are not easily quantifiable

Exposure

Worldwide, approximately 12,000 t linalool *per annum* are estimated by industry to be produced, while natural biosynthesis through plants, mostly herbs, spices, trees and citrus fruits, is higher by dimensions. More than 95% of synthetic linalool is used for its fragrance and odorant qualities in cosmetics, soaps, perfumes, household cleaners, waxes and care products, while only approximately 1% is added to food and beverages for aroma and flavouring. Only two measured environmental concentrations have been located, one for water from a relatively polluted European river, of up to 0.11 µg/l, and one for air from boreal forests in Finland, of up to 120 ppt during the summer peak of biogenic linalool release.

Chemical production workers are rarely exposed to linalool, due to *quasi*-closed synthesis; where direct contact is possible, standard occupational hygiene measures limit exposure. The public, in contrast, is widely exposed to linalool, both from natural and synthetic sources, as an ingredient of formulated food and beverages, cosmetics and household products, but also as a natural constituent of fruits and spices. Oral exposure to linalool from formulated food products was estimated at up to 72 µg/kg/d for Europe and the USA; adding linalool from natural sources may possibly double this, resulting in an estimated maximal daily intake of 140 µg/kg/d. This maximum corresponds to approximately one-quarter of the upper limit of the ADI. Inhalative exposure to linalool cannot be reasonably quantified, particularly for urban and indoors environments. Due to its odorant or fragrance function, short-term inhalative exposure will be above the olfactory threshold of approximately 1 ppm, but this is predicted to decline rapidly due to abiotic degradation.

NATURE OF FURTHER WORK RECOMMENDED

Currently not a candidate for further work.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-92-2
Chemical Name	Butan-2-ol or *sec*-Butanol (sBA)
Structural Formula	CH_3-CH(-OH)-CH_2-CH_3

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Analog Justification

Data are available for sec-Butanol (sBA) on the following endpoints: acute toxicity (oral, inhalation, dermal), irritation studies (skin, eye and respiratory tract), reproductive toxicity, developmental toxicity and genotoxicity assays. Data on methyl ethyl ketone (MEK; 2-butanone), a major metabolite of sBA and structurally similar to sBA, will be used to address the repeated dose toxicity and supplement the genotoxicity endpoints.

Toxicokinetics and Metabolism

SBA is absorbed, distributed and excreted rapidly in urine, mainly as MEK, following oral administration. A small percentage of sBA is also excreted via urine and exhalation. Orally administered sBA is metabolized via alcohol dehydrogenase to MEK. The maximum concentration of MEK in blood was seen six hours after dosing. Further oxidation of MEK appeared to proceed by hydroxylation of the ω-1 carbon to form 3-hydroxy-2-butanone, which is further reduced to 2,3-butanediol. 2,3-butanediol was also detected in human urine following inhalation exposure to MEK. The main portion of the inhaled MEK is converted to acetate or acetoacetate via 3-hydroxy-2-butanone intermediate metabolite.

Human Health

sBA has a low order of acute toxicity to mammals. Oral LD_{50} values for sBA in laboratory animals range from approximately 2.2 to 6.5 g/kg body weight. The inhalation LC_{50} for sBA is between 8,000 (24 mg/L) and 16,000 ppm (49 mg/L) for a 4-hr exposure. sBA, like many other organic solvents, produces reversible depression of central nervous system (CNS) activity at high exposures. Laboratory animals that were exposed to acutely toxic doses of sBA exhibited clinical signs of CNS depression that were reversible in survivors upon termination of exposure. The dermal LD_{50} value for sBA in rats is greater than 2 g/kg body weight. In animal studies, sBA liquid is not irritating or sensitizing to the skin however, it is irritating to the rabbit eye. Vapors are weakly irritating to the respiratory tract of mice.

Limited repeated-dose, reproductive and developmental toxicity studies on sBA indicate a low potential for toxicity. Primary effects appear to be typical CNS depression associated with many aliphatic alcohols, and effects on liver associated with enzyme induction. sBA is quantitatively metabolized to methyl ethyl ketone (MEK); over 97% of an oral dose of sBA is converted to MEK in rats. Although there is no definitive repeated-dose study of sBA, information on repeated-dose toxicity of sBA can be deduced from reproductive toxicity studies, and from studies with MEK. A comprehensive subchronic toxicity study with the sBA metabolite MEK was conducted in rats; none of the exposure concentrations (1,250, 2,500, or 5,000 ppm—4, 8, or 15 mg/L, respectively—MEK vapor for 6

hours per day, 5 days per week, for 90 days) were lethal or even significantly harmful. There were no adverse effects on the clinical health or growth of male or female rats except a depression of mean body weight in the 5,000 ppm group. The female rats exposed to 5,000 ppm for 90 days showed only slightly increased liver weight, slightly decreased brain and spleen weights, and slightly altered blood chemistry in comparison with controls. Male rats that received this exposure exhibited only a slightly increased liver weight. At the lower concentrations (1,250 and 2,500 ppm), there was only slightly increased liver weight for female rats and no significant differences for males. The pathological examination did not reveal any histopathological lesions that could be attributed to MEK exposure. The NOAEL was determined to be 5000 ppm.

In a two-generation drinking water reproductive toxicity study of sBA, which included hematological and histopathological evaluations, mild changes in the kidney (non-reactive tubular degeneration, tubular casts, foci of tubular regeneration and microcysts) were observed in animals treated with 2.0% sBA. These effects were considered non-specific due to increased renal workload, possibly from an increased urine volume and pressure at the high doses. As a result, the authors concluded these results to not be a result of direct toxicity nor indicate a clear pathological significance. The only reproductive effect reported was a slight but not significant depression in growth of weanling rats in the second generation; the no-effect level for systemic and reproductive effects was 1.0% (estimated to be 1500 mg/kg/day by the authors and 1771 mg/kg/day by EPA/IRIS).

sBA is not a primary developmental toxicant; rats were exposed by inhalation to 0, 3,500, 5,000 or 7,000 ppm sBA—11, 15, or 21 mg/L, respectively—7 hours/day on days 1-19 of gestation and at 7,000 ppm, narcosis was observed in all animals. At 5000 ppm, the dams were partially narcotized with locomotion activity impaired. Maternal weight gain and food consumption was significantly reduced in all dose groups. The number of live fetuses was significantly reduced and resorptions were increased in the high exposure group only. Fetal body weights were significantly reduced in the mid- and high dose groups. There was no evidence of teratogenic effects in this study, and there was also no evidence of selective developmental toxicity. The NOELs were < 3,500 ppm for maternal toxicity and 3,500 ppm for developmental toxicity. During the two-generation reproductive toxicity study (see above) a teratogenic phase was incorporated in which the parents (28-30/group) were rebred to produce a second litter. The females were subjected to Caesarean section on day 20 of gestation (Cox *et al.*, 1975; Gallo *et al.*, 1977). At 2.0%, sBA caused a significant depression in fetal weight, with evidence of delayed skeletal maturation, but no skeletal and visceral malformations. The authors concluded that these changes represented mild toxicity and were reminiscent of stress lesions. All findings at 0.3 and 1.0% were negative. The no-effect level for developmental toxicity was 1.0% (estimated to be 1500 mg/kg/day by the authors and 1771 mg/kg/day by EPA/IRIS].

sBA was inactive in *in vitro* tests for mutagenicity in both bacteria and yeast in either the presence or absence of metabolic activation. There was no structural damage to chromosomes in cultured mammalian cells (Chinese hamster ovary) treated with sBA. MEK *in vivo* genotoxicity data provide additional supporting information on the potential for *in vivo* genotoxicity of sBA. MEK did not cause an increase in micronucleated polychromatic erythrocytes in two *in vivo* assays. MEK was also negative in the mouse lymphoma test, the chromosome aberration assay, and liver hepatocyte unscheduled DNA synthesis assay.

Like many other organic solvents, sBA produces reversible depression of central nervous system activity in laboratory animals at high exposure doses. sBA was found to produce intoxication effects with a slower recovery to normal behaviour than ethanol.

In humans, excessive exposure by inhalation may result in headache, dizziness, drowsiness and narcosis. No adverse systemic effects have been reported due to exposure to sBA.

Environment

The physical chemical properties of sBA are as follows: melting point, -114 to –115°C; Boiling point, 99.5°C; vapor pressure, 16 hPA at 20°C; water solubility, 125 g/l at 20°C and the Log Kow of 0.61 at 20°C. In air, sBA is calculated to contribute minimally to the formation of tropospheric ozone and can be degraded by reaction with photochemically produced hydroxyl radicals (OH^-). sBA has a calculated degradation half-life of approximately 24 hours. Degradation proceeds through the formation of MEK, acetaldehyde, and other intermediate oxidation species.

If released to water, biodegradation of sBA is likely to be the primary removal process. The volatilization half-life is 3.5 days and 30 days at 20ºC and 0ºC, respectively. Hydrolysis will not contribute to the transformation of sBA in aquatic environments because it is not susceptible to this reaction. sBA has a low potential to bioaccumulate in aquatic species based on a calculated BCF of 1.7. sBA is not expected to absorb significantly to organic matter in soil and sediment and therefore has potential to migrate through the soil horizon. Although volatilization can contribute to the loss of sBA from terrestrial habitats, biodegradation is likely to be the primary route of removal, with an estimated half-life of 1 to 7 days.

sBA was shown to be readily biodegraded by aerobic and rapidly biodegraded by anaerobic processes. Results of standard biodegradation tests suggest that sBA can be largely degraded in a few days. The biodegradation data also suggest that sBA can be rapidly degraded in wastewater treatment plants, which can prevent it from entering surface waters.

Experimental and SAR data indicate that sBA has a very low order of acute aquatic toxicity. The fish 96-hr LC50 of 3670, and the daphnid 48-hr EC50 of 4227 mg/L were reported for sBA based on measured and nominal concentrations, respectively. The SAR data using ECOSAR are in agreement with these results. A calculated algal 96-hr EC50 value of 625 mg/L using ECOSAR and a measured 7-day EC3 value of 95 mg/L for growth inhibition are reported. Chronic effects from sBA exposures are not expected based on reported short lifetime due to degradative processes.

In the terrestrial environment, sBA is expected to exhibit a low order of toxicity based on calculated data for earthworms.

There are adequate experimental and calculated data to support characterizing sBA as a low order environmental hazard based on the available data for acute and chronic aquatic toxicity, terrestrial toxicity, and low potential to persist in the aquatic and soil dwelling environments.

Exposure

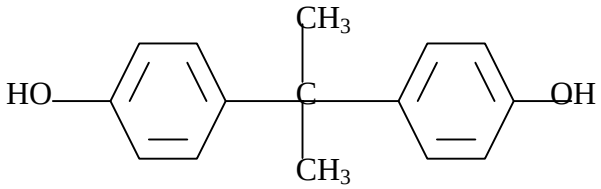
Worldwide capacity of sBA is approximately 1,000 kt, and production 900 kt. Production volume in the U.S. is estimated to be between 500 million – 1 billion pounds (2.3- 4.5 kt). It can enter the environment from its production as well as application in the manufacture of MEK. sBA can also be released from its use as a solvent, paint remover, and industrial cleaning agent. Based on limited information, sBA also appears to be released to the atmosphere in some combustion processes. sBA enters the environment from several natural sources and has been detected in several environmental compartments (e.g., ambient air, edible plants, and wastewater) at low and variable concentrations.

The occupational exposure limit values for sBA vapors in different country's range between 50 and 150 ppm (150 - 450 mg/m^3) for the TWA values. Occupational exposure monitoring indicates that sBA may be found in the occupational setting up to 6.5 ppm.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation for further work because of the low hazard profile of the chemical.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	80-05-7
Chemical Name	Bisphenol-A (2,2-bis(4-hydroxylphenyl)propane)
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Occupational exposure to bisphenol A will be in the form of inhalation/ingestion of dust and by skin contact with the flakes, prills or powder. In consumers, the main route of exposure is orally, via polycarbonate and epoxy resin food contact applications. Very low exposures by ingestion and inhalation may arise from releases to the environment from production of bisphenol A, and its use in the manufacture and processing of epoxy resins, PVC, and thermal paper containing bisphenol A.

Data in the rat demonstrates that following oral administration absorption is rapid and extensive, although it is not possible to reliably quantify the extent of absorption. An *in vitro* dermal absorption study using human skin suggests that there is limited absorption, in the region of about 10% of the applied dose. On the basis of organ weight changes in a repeat inhalation study, it would be prudent to assume that absorption via the inhalation route can occur, but the data do not allow a quantitative estimation of absorption to be made. Extensive first pass metabolism occurs following absorption from the gastrointestinal tract with glucuronide conjugation being the major metabolic pathway. Hence distribution of unconjugated bisphenol A in likely to be limited. There is also evidence of enterohepatic circulation occurring. Elimination is mainly in the faeces with the urinary route being of secondary importance.

The key toxicological endpoints are eye and respiratory irritation, skin sensitisation, local effects of repeated inhalation exposure on the respiratory tract and effects on the liver of repeated systemic exposure and reproductive toxicity. Since bisphenol A has the potential to cause eye and respiratory tract irritation, peak exposures need to be controlled. As bisphenol A is at least capable of inducing skin responses in hypersensitive individuals, skin exposure also need to be controlled. For the observed liver effect (multinucleated giant hepatocytes), of uncertain relevance to humans, only a LOAEL of 120 mg/kg has been identified for males and a NOAEL of 650 mg/kg for females in a 2-year dietary study in mice. For reproductive toxicity, data was available from a two generation and multi-generation in the rat and a continuous breeding study in the mouse. Effects on fertility (reduction in litter size) were observed in both species at doses of >=500 mg/kg/day. For the rat it is not clear whether or not the finding could be a secondary

consequence of parental toxicity or a direct effect of bisphenol-A. Comparing the rat and mouse data similar toxicological profiles were observed for effects on fertility at approximately the same dose level. Consequently, it is considered that the NOAEL of 50 mg/kg/day identified in a rat multi-generation study is also likely to produce no adverse effects in mice for which there is only a LOAEL available.

Regarding other toxicological endpoints bisphenol A is of low acute toxicity (rodent oral LD_{50} values from 4000 to 5200 mg/kg, a rabbit dermal LD_{50} value *2230* mg/kg and a rat 6 hour LC_{50} value >170 mg/m3). Few details exist of the toxic signs observed or of target organs. Bisphenol-A is not a skin irritant, however, it is severely irritating to the eyes. There are no data from which to evaluate the potential to be a respiratory sensitiser. The aneugenic potential of bisphenol A seems to be limited to *in vitro* test systems. The relevance of the finding that it can produce rat hepatic DNA adduct spots in a postlabelling assay is not entirely clear. However, given the absence of positive results for gene mutation and clastogenicity in cultured mammalian cells, as well as in a guideline micronucleus test for clastogenicity *in vivo*, it seems unlikely at present that these will be of concern for human health. Considering all of the available genotoxicity data, and the absence of toxicologically significant tumour findings in animal carcinogenicity studies, it does not appear that bisphenol A has mutagenic potential *in vivo*. In a dietary study in rats and mice, tumour findings are not considered to be toxicologically significant and taking into account all of the available animal data the evidence suggests that bisphenol A does not have carcinogenic potential. No evidence that it is a developmental toxicant was observed in standard development studies in rats and mice. However, conflicting results have been reported between studies using low doses (in the microgram/kg range). Some studies report an adverse effect on male reproductive tract development in rats and mice. Further studies from other laboratories have not been able to replicate these data. Furthermore, in a rat multi-generation study, a decrease in pup body weight gain and delays in development were seen in all generations (F_1-F_3) at 500 mg/kg/day, albeit in the presence of maternal toxicity. Further information gathering is being undertaken to resolve the uncertainties surrounding potential effects at 'low doses' seen in controversial studies (delete this issue), however, in the interim, a provisional NOAEL of 50 mg/kg has been identified.

Environment

The environmental effects database meets the requirements of the SIDS data package. Aquatic toxicity data are reported for freshwater and marine fish, daphnia and algae. The available data cover 'conventional' adverse endpoints with significance at a population level (such as reproduction and mortality) and non-conventional responses potentially mediated by an endocrine mechanism, such as mechanistic endocrine responses. The available data suggest that endocrine responses may occur at lower concentrations.

The lowest values from acute studies with freshwater species are: 96-hour LC_{50} of 4.6 mg/l for fish (fathead minnow *Pimephales promelas*) (results for saltwater species are similar); 48-hour EC_{50} of10.2 mg/l for *Daphnia magna* (based on measured concentrations – a lower value of 3.9 mg/l is reported based on nominal concentrations, and a 96-hour LC_{50} of 1.1 mg/l is reported for the saltwater mysid shrimp *Mysidopsis bahia*); 96-hour EC_{50} (based on cell count) of 2.73 mg/l for algae (*Pseudokirchneriella subcapitata*) (a 96-hour EC_{50} (based on cell count) of 1.1 mg/l is reported for marine algae (*Skeletonema costatum*)).

Chronic studies are also reported for fish, daphnia and algae. The lowest NOEC value for a 'conventional' endpoint from chronic studies is that for egg hatchability in *P. promelas* from a full life cycle test, at 16 µg/l. The lowest values from chronic studies for invertebrates and algae are a 21-day NOEC >3.146 mg/l for *D. magna* and a 96-hour $EC_{10}$of 0.40 mg/l for *S. costatum*. Based upon the lowest NOEC value for fish a PNEC of 1.6 µg/l is derived using an assessment factor of 10. Although other effects have been reported at lower concentrations in *P. promelas* (LOEC of 1 µg/l for effects on spermatogenesis) and in aquatic snails (effects on egg production), weaknesses in the data indicates a need for further investigation, which is underway. No effects on larval growth, development or sexual differentiation were reported for the African clawed frog (*Xenopus laevis*) at nominal concentrations up to 0.5 mg/l in a 90-day flow-through study.

Toxicity data for soil-dwelling organisms are not available, but a $PNEC_{soil}$ of 23 g/kg wet weight can be derived from the aquatic PNEC using the equilibrium partitioning method for screening risk assessment purposes.

Exposure

About 700,000 tonnes of bisphenol-A are manufactured in Europe each year (based on data for 1999). It is primarily used in the production of polycarbonate and epoxy resins, and there are a number of minor uses including in the thermal paper and PVC industries. Polycarbonates are used in a range of applications including optical media, glazing, food containers and as polycarbonate blends in the electronics industry. Epoxy resins are used as protective coatings, structural composites, electrical laminates, electrical applications and adhesives. The main route of environmental exposure is from its use in the thermal paper and PVC industries.

Bisphenol A is a solid of low vapour pressure (5.3×10^{-9} kPa at 25°C), with a water solubility of ~300 mg/l at 20°C and a log octanol-water partition coefficient (log K_{OW}) of 3.4. Hydrolysis and photolysis in water are negligible but it is considered readily biodegradable, possibly with a short period of adaptation. The log K_{OW} value implies a low to moderate bioaccumulation potential in aquatic species and moderate adsorption to soils and sediment. The substance chiefly partitions to water and it may be relatively mobile in the environment.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address hazard classification for all SIDS endpoints and for non-SIDS endpoints. However, the chemical is a candidate for further work as follows:

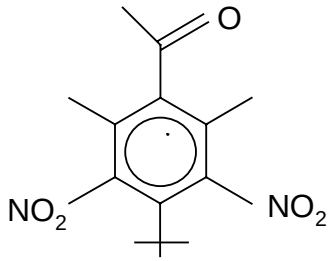
1. Further work needs to be done on the effects on aquatic snails and spermatogenesis in fish to clarify the levels at which effects may occur, and to consider the significance of these effects. This is a post-SIDS requirement.

2. No toxicity data are available for soil organisms. These data could be generated as a post-SIDS activity (a concern has been identified for the terrestrial compartment in the European risk assessment for a number of uses). At present, it is unclear which test(s) should be performed, although chronic tests based on reproduction parameters appear to be the more sensitive for aquatic organisms.

3. If indicated by national or regional Bisphenol A usage, information gathering on exposure may need to be considered for the water compartment and, if appropriate a risk assessment undertaken. Based on an existing regional risk assessment for Europe, using a PNEC of 1.6 microgram/l and worst-case estimated emissions, a need to limit environmental risks has been identified only for Bisphenol A use in PVC and for thermal paper recycling. If there is confirmation of effects at lower concentrations, this would lead to conclusions of risks for other uses.

4. The uncertainties surrounding potential effects at low doses (delete effects) of bisphenol A on mammalian reproductive development seen in some studies needs further consideration. A steering committee is set up to further develop details of the requirement of further research. This is a post-SIDS requirement.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	81-14-1
Chemical Name	3,5-dinitro-2,6-dimethyl-4-tert-butyl acetophenone (Musk ketone)
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work for the environment and human health.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The oral LD_{50} for rats and the dermal LD_{50} for rabbits are both greater than 2000 mg/kg bw. Data for acute inhalation toxicity are not available.

Musk ketone is not considered to be irritating for skin and eyes and is not a skin sensitiser. For respiratory tract irritation no data are available.

In a well performed dermal 90-day study with rats effects at the highest dose of 240 mg musk ketone kg/bw included a decreased body weight gain without a concomitant decrease in food consumption, decreases in red blood cell parameters and an increase in absolute and relative liver weight without a histopathological correlation. The decrease in body weight gain was also seen in females at the lower dose of 75 mg/kg bw. In the experiment no neuropathological effects, no effects on the reproductive organs, and no skin effects were seen. Therefore 24 mg/kg bw can be established as the NOAEL in this study. When administered as part of a fragrance mixture, inhalatory exposure to musk ketone up to a maximum tested dose of 170.5 $\mu g/m^3$ for 4 h per day, 5 days per week for 13 weeks did not result in any toxicity.

Musk ketone was negative in several *in vitro* tests (bacterial gene mutation tests, SOS chromosome aberration tests, a mammalian gene mutation test, a micronucleus test in mammalian cells *in vitro*, a SCEs in mammalian cells and an UDS test). A test for chromosome aberration in CHO cells provided an equivocal result, but as an *in vivo* mouse micronucleus test was negative, it can be concluded that musk ketone is a non-genotoxic substance.

With respect to carcinogenicity no data are available on musk ketone. Neither from the available repeated dose toxicity studies, nor from the genotoxicity data an indication is obtained that musk ketone might be a carcinogenic substance. In view of the similarities in structure with musk xylene the carcinogenic study with musk xylene can be considered for the evaluation of musk ketone as well. The conclusion for musk xylene is as follows:

Musk xylene is considered to be a carcinogen in mice acting by a non-genotoxic mode of action. The only tumours reported were liver carcinomas (malignant) in B6C3F1 mice, a mouse strain prone to develop this kind of tumours, and benign malformations in the Harderian gland. The latter type of tissue does not occur in humans and therefore these benign tumours are difficult to interpret with respect to their relevance to humans. It is concluded that there is limited evidence for carcinogenicity of musk xylene in animals as was also stated by IARC.

With respect to fertility no generation study was available for either route. In the 90-day dermal toxicity study with rats, musk ketone caused no effects on the reproductive organs.

In an oral peri/postnatal toxicity study (exposure of the F_1-generation to musk ketone was only *in utero* during the peri-natal phase or through any transfer in the milk of the lactating dams) slight toxicity (decreased body weight gain and food consumption) was seen at the highest dose level of 25 mg/kg bw in the dams. Pup toxicity at this dose included a lower weight and a later day of attainment for surface and air righting and fluxual maturation. The F_1 males in the mid dose of 7.5 mg/kg also had a marginal, but statistically significant lower body weight gain. Dosing up to 25 mg/kg bw did not result in behavioural changes or in reduced reproduction capacity. The lowest dose tested, 2.5 mg/kg bw/d, can be considered as the NOEL in this study. However, the effect at the next higher dose is very small, limited to males and is of uncertain biological significance. In a well performed oral developmental study with rats, maternal toxicity occurred in a dose related way at 45 and 150 mg/kg bw/day. This toxicity included reduced body weight gain, reduced food consumption and increased post implantation loss.

Developmental toxicity, including reduced fetal body weight, was only seen at 150 mg/kg bw/day. Therefore, the NOAEL for maternal toxicity can be established at 15 mg/kg bw, the lowest dose tested, and the NOAEL for developmental toxicity can be established at 45 mg/kg bw. No developmental toxicity studies are available for the dermal and inhalatory route.

The available data obtained from the peri/post natal study indicate that musk ketone can be secreted into the milk into sufficient quantities to elicit toxic responses in the offspring of the test animals.

In a 90-day dermal toxicity study with rats no indications for a neurotoxic potential was found for musk ketone.

Environment

EUSES (Simple Treat) estimates the following default distribution for musk ketone in an STP: air: 0%, water 68% and sludge: 32%. Based on the structure musk ketone is not expected to hydrolyse. Photodegradation has been demonstrated, but is expected to be minimal in the aquatic environment. Musk ketone is not readily biodegradable. The measured BCF in rainbow trout is 1380 L/kg, which is in agreement with the calculated BCF based on log Kow.

The lowest (L)EC50 values for musk ketone were 0.24 and > 0.46 mg/l for algae (growth rate)and Daphnia, respectively. NOEC values were derived for algae, daphnia (21-d) and fish (21-d): 0.088, 0.17 and 0.033 mg/l, respectively. For musk ketone two long-term terrestrial toxicity tests are available: for a shredder (4 weeks, springtail) and a detritivorous species (8 weeks, earthworm). The NOECs are 100 and 32 mg/kg soil, respectively. Musk ketone does not bind to the estrogen receptor in fish (*Oncorhynchus mykiss*) and clawed frog (*Xenopodus laevis*) *in vitro*. For the metabolites 2-amino musk ketone binding in both species was observed. The relevance of these *in vitro* tests for the environment is still unclear.

Exposure

Musk ketone is a solid powder, with a melting point of 135-137 ^{o}C. The Log Kow is 4.3. Using a vapour pressure of 0.00004 Pa at 20 ^{o}C and a water solubility of 0.46 mg/l a Henry's law constant of 0.026 Pa.m^3/mol is calculated.

The use volume of musk ketone in 1998 in Europe is approximately 40 tonnes, including export to non-EU countries. The use volumes are decreasing. There is no production of musk ketone in the EU. Industry sources estimate that 20-30% of their products is exported outside the EU as finished fragrance compounds or in consumer products. Musk ketone can enter the aqueous and terrestrial environment via formulation sites and private use. The calculated exposure concentration in air from formulation sites are minimal.

There is a potential for occupational and consumer exposure through inhalation and skin contact although exposures via inhalation are expected to be low due to the low vapour pressure. Consumer exposure to musk ketone will occur principally through its use in cosmetics. Indirect exposure via the environment is also possible.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address hazard classification for all SIDS endpoints and for other non-SIDS endpoints.

The chemical is a candidate for further work for the environment because:

- it is not readily biodegradable
- it has bioaccumulating potential (BCF > 1000 but < 2000) and
- its long-term toxicity (NOEC < 1 mg/l)

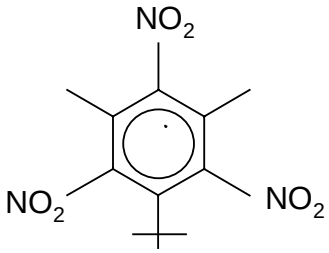
The chemical is a candidate for further work for human health because:

- exposure via breast milk can occur
- the effects on pups in the peri/post natal study cannot be disregarded.

In view of these hazards, national or regional exposure information gathering and risk assessment may be considered.

The EU risk assessment is close to completion.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	81-15-2
Chemical Name	1-tert-butyl-3,5-dimethyl-2,4,6-trinitrobenzene (Musk xylene)
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work for the environment and human health.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute oral LD_{50} in mice and rats was established at >2000 mg/kg bw. In a limited dermal study an application of 10000 or 15000 mg/kg bw caused no mortality in groups of three rabbits. The dermal test is not performed according to current standards. However, it is expected that the acute dermal toxicity is >2000 mg/kg bw. Data for acute inhalation toxicity were not available.

Musk xylene is not considered to be irritating for skin and eyes and is not a skin sensitiser. For respiratory tract irritation no data are available.

In a 90-dermal study with rat a NOAEL of 24 mg/kg bw was derived. Increased liver weight was observed at higher doses.

Musk xylene was negative in several *in vitro* tests (bacterial gene mutation tests, SOS-chromosome aberration test, mammalian gene mutation test, tests for chromosome aberrations and SCEs in mammalian cells, a micronucleus test in mammalian cells and an UDS test). In an *in vivo-in vitro* rat hepatocyte UDS test also negative results were obtained. Musk xylene is not-genotoxic.

Musk xylene is considered to be a carcinogen in mice acting by a non-genotoxic mode of action. The only tumours reported were liver carcinomas (malignant) in B6C3F1 mice, a mouse strain prone to develop this kind of tumours, and benign malformations in the Harderian gland. The latter type of tissue does not occur in humans and therefore these benign tumours are difficult to interpret with respect to their relevance to humans. It is concluded that there is limited evidence for carcinogenicity of musk xylene in animals as was also stated by IARC.

With respect to fertility no generation study was available for either route. However in a 90-day dermal toxicity study with rats and also in an oral carcinogenicity study with mice musk xylene caused no effects on the reproductive

organs. In a peri/post natal study no effects on sexual development and fertility were reported in pups which were exposed *in utero* and during lactation. A peri/postnatal study was performed, in which the F_1-generation was exposed to musk xylene *in utero* or through any transfer in the milk of the lactating dams. Slight pup toxicity, reflected in a reduced but statistically not significant body weight gain, was observed at the highest dose level. In this study 7.5 mg/kg bw/day could be considered as the NOEL for peri/postnatal effects.

In an oral developmental study with rats maternal toxicity, expressed as decreased body weight gain and food consumption, was seen in the mid and high dose level of 60 and 200 mg musk xylene/kg bw/day. Embryo toxicity (extra thoracic ribs and increased ossification) was seen at the highest dose level tested. The NOAEL for maternal toxicity in this study can be established at 20 mg/kg bw/day and the NOAEL for developmental toxicity at 60 mg/kg bw/day. There is no indication for teratogenicity.

The available data obtained from the peri/post natal study indicate that musk xylene can be secreted into the milk into sufficient quantities to elicit toxic responses in the offspring of the test animals.

In a 90-day dermal toxicity study with rats, no indications for a neurotoxic potential were found for musk xylene.

Environment

EUSES (Simple Treat) estimates the following default distribution for musk xylene in an STP: air: 0%, water 43% and sludge: 57%. Based on the structure musk xylene is not expected to hydrolyse. Photodegradation has been demonstrated but is expected to be minimal in the aquatic environment. Musk xylene is not readily biodegradable. The measured BCF in bluegill sunfish is 4400 l/kg, which is in agreement with the calculated BCF based on log Kow.

The t (L)EC50 values for musk xylene were > 0.15, > 0.15 and 1.2 mg/l for algae, Daphnia and fish, respectively. NOEC values were derived for algae, daphnia and fish: > 0.56, 0.056 and 0.01 mg/l, respectively. In a 14-day acute toxicity study on earthworms no effects on survival up to the highest concentration of 50 mg/kg soil was observed. Musk xylene does not bind to the estrogen receptor in fish (*Oncorhynchus mykiss*) and clawed frog (*Xenopodus laevis*) *in vitro*. For the metabolites 2-amino musk xylene and 4-amino musk xylene binding in both species was observed. The relevance of these *in vitro* tests for the environment is still unclear.

Exposure

Musk xylene is a solid powder, with a melting point of 112-114 ^{o}C. The Log Kow is 4.9. Using a vapour pressure of 0.00003 Pa at 20 ^{o}C and a water solubility of 0.15 mg/l a Henry's law constant of 0.0595 Pa.m3/mol is calculated.

The use volume of musk xylene in 1998 in Europe is approximately 86 tonnes, including export to non-EU countries. The use volumes are decreasing. There is no production of musk xylene in the EU. Industry sources estimate that 20-30% of their products is exported outside the EU as finished fragrance compounds or in consumer products. Musk xylene can enter the aqueous and terrestrial environment via formulation sites and private use. The calculated exposure concentrations in air from formulation sites are minimal.

There is a potential for occupational and consumer exposure through inhalation and skin contact although exposures via inhalation are expected to be low due to the low vapour pressure. Consumer exposure to musk xylene will occur principally through its use in cosmetics. Indirect exposure via the environment is also possible.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address hazard classification for all SIDS endpoints and for other non-SIDS endpoints.

The chemical is a candidate for further work for the environment because:

- it is not readily biodegradable
- it has bioaccumulating potential (BCF = 4400 l/kg) and
- its long-term toxicity (NOEC < 1 mg/l)

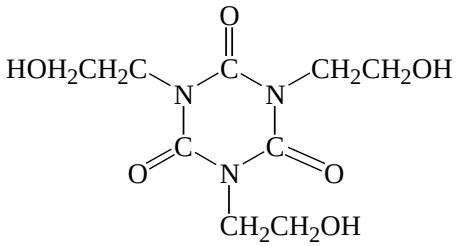
The chemical is a candidate for further work for human health because:

- exposure via breast milk can occur
- the effects on pups in the peri/post natal study cannot be disregarded.

In view of these hazards, national or regional exposure information gathering and risk assessment may be considered.

The EU risk assessment is close to completion.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	839-90-7
Chemical Name	1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris(2-hydroxyethyl)- (Synonym : Tris(2-hydroxyethyl) isocyanurate)
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Regarding acute toxicity, the oral LD_{50} of tris(2-hydroxyethyl) isocyanurate in rats is greater than 2,000 mg/kg bw [OECD TG 401]. The acute dust inhalation toxicity test for 8h in rat revealed no symptom and no mortality at 9.32 mg/L and 15 mg/L. Tris(2-hydroxyethyl)isocyanurate is not irritant to eye and skin. No data are available for sensitization.

In the combined repeated dose and reproductive/developmental toxicity test [OECD TG 422] in rats, which was performed at oral doses of 0, 30, 100, 300 and 1,000 mg/kg bw/day for at least 42 days, no deaths or abnormalities in all toxicological parameters were observed in any male and female animals. The NOAEL for repeated dose toxicity in rats is considered to be 1,000 mg/kg bw/day for both sexes.

In the above combined repeated dose and reproductive/developmental toxicity test in rats, the chemical showed no adverse effects on any reproductive/developmental parameters. No morphological abnormalities in external and visceral observation in pups were observed in any of the treated groups. The NOAEL values in reproductive/developmental toxicity for both parents and F_1 offspring are considered to be 1,000 mg/kg bw/day.

Bacterial mutation test [OECD TG 471] and all mammalian *in vitro* tests such as chromosome aberration tests [OECD TG 473 & NTP] and sister chromatid exchange assay [NTP] showed negative results. There is no data available from *in vivo* test.

Environment

As for the distribution of the chemical in the environmental, Fugacity model (level III) calculation shows that the chemical is likely to be distributed into water and soil if released into water, air or soil. Also, based on its high water solubility (820 g/L at 20°C), low LogPow value (-1.63 at 23°C) and low vapor pressure (0.0015 Pa at 50°C), the chemical is most likely distributed into the water phase. The half-life for photo-degradation is estimated to be 13.0

h. The chemical is highly stable in water (OECD TG 111) and is not biodegradable according to OECD test guidelines 301C (0%(BOD)), 301E and 302B (0%(DOC)), respectively. However, bioaccumulation potential of this substance is low based on the results of the bioaccumulation test using carp (*Cyprinus carpio*). In the test, the resulting BCF values were below 0.16 at 2.5 mg/L or 1.6 at 0.25 mg/L of test concentration, respectively.

The acute toxicity values to aquatic organisms were more than 1,000 mg/L for *Selenastrum capricornutum* (72h-NOEC, biomass and growth rate), greater than 1,000 mg/L for *Daphnia magna* (48h-EC_{50}, immobilization) and greater than 100 mg/L for *Oryzias latipes* (96h-LC_{50}, mortality) according to OECD TG 201, 202 and 203, respectively. In the chronic toxicity test to *Daphnia magna*, the 21d-NOEC (reproduction) was more than 100 mg/L (OECD TG 211). As no adverse effects were observed in any tests conducted using three different trophic level species, the chemical is considered to be non-toxic to aquatic organisms.

Exposure

The production volume of tris(2-hydroxyethyl) isocyanurate in 2000 was 6,000 tonnes in Japan and 5,000 tonnes in Germany. The production and the cleaning process of the facility are conducted in a closed continuous line under remote control system.

Mainly, the chemical is used as a monomer for the synthesis of polyesters and thus obtained polyesters are industrially used in thermosetting varnishes and thermosetting paints for metal. It is also used in polymer industry as a stabilizer. The content in polymers is approximately 0.5% or less. One of the uses of such polymers is as exterior building material.

The chemical would not be released into environment via wastewater from production or use (such as varnishes or paints industry) sites because organic solvent is used instead of water for the reaction media or cleaning process. Moreover, the solvent used is concentrated and then the residues are incinerated in a well-equipped facility. Releases from final polyester products are not expected. The chemical might be released from polymers which contain the chemical as a stabilizer. Although no data are available on the amount of the chemical used as a stabiliser, significant exposure is not expected.

The occupational exposure of the chemical might occur via the inhalation of dust or via the dermal route during packing/unpacking processes. However, the intake via dermal route is not expected due to the low value of the LogPow. Practically, workers are obliged to use personal protection equipment (mask, glasses and gloves) during the packing/unpacking process. Thus, the exposure to the chemical via dust inhalation is considered to be negligible.

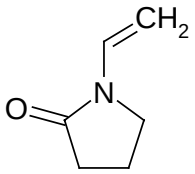
Polymers containing the chemical as a stabilizer are the only source of the chemical which might cause consumer exposure and indirect exposure in the general population.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

The chemical is not a candidate for further work because all SIDS endpoints are adequately addressed and the substance has a low toxicity profile.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-12-0
Chemical Name	1-Vinyl-2-pyrrolidone
Structural Formula	

RECOMMENDATIONS

The chemical is currently a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1-vinyl-2-pyrrolidone (NVP) is rapidly and extensively absorbed following inhalation and ingestion and its physicochemical properties suggest that it will readily cross the skin. Readily formed metabolites of NVP are eliminated within 24 hours after dosing, predominantly in the urine. There is no evidence that NVP is retained in any tissue and it has been shown that NVP and its metabolites do not bind to plasma proteins or DNA to any great extent.

Toxicity occurs in animals following a single exposure by inhalation, ingestion or in contact with the skin. The liver and kidneys have been identified as target organs by all three routes of exposure and following oral or inhalation exposure, irritation of the mucous membranes lining the gastrointestinal or respiratory tracts commonly occurs. A 4-hour LC_{50} of 3070 $mg.m^{-3}$ for aerosols of NVP has been identified in the rat. However, 6-8 hour exposures to saturated vapour (about 600 $mg.m^{-3}$) in a range of species produced some local irritation but no deaths. It is not clear why the signs of toxicity were less severe in the vapour experiments, although localised deposition of liquid NVP in the aerosol study may have increased the severity of reactions. No effects were observed in rats or mice inhaling 23 $mg.m^{-3}$ NVP vapour for 6 hours on 2 consecutive days, though slight liver toxicity was evident in rats immediately after 2 six-hour exposures to 69 $mg.m^{-3}$ NVP vapour. Oral LD_{50} values are around 1000 mg/kg for the rat and mouse. A dermal LD_{50} of 560 mg/kg has been reported for rabbits and deaths among rats administered around 1000 mg/kg on the skin indicate that the LD_{50} value may lie below 2000 mg/kg for this species.

NVP is not a skin irritant but in liquid form is a severe eye irritant. NVP has the potential to cause respiratory tract irritation based on observations of increased respiration rates and inflammation in nasal mucosa membranes in inhalation toxicity studies and the knowledge that NVP is severely irritating to the eye. NVP does not cause skin sensitisation and does not bind to proteins to any great extent. NVP would not be predicted to cause respiratory sensitisation, at least not by an immunological mechanism.

Repeated inhalation of NVP by rats and mice resulted in dysproteinaemia, haematological changes suggestive of anaemia and pathological changes in the liver, nasal cavity and larynx. In the liver, centrilobular hepatocyte necrobiosis and fatty infiltration accompanied by degenerative changes in the nucleus. In the nasal cavity, NVP caused inflammatory changes in the olfactory and respiratory epithelia and larynx. A NOAEL of 1 ppm (4.61

mg.m$^{-3)}$ has been identified in a 3 month study in the rat. In rats inhaling 5 ppm (23 mg.m^{-3}) NVP vapour for 3 months observations included clear evidence of nasal cavity irritation and slight dysproteinaemia. Although no histopathological changes were found in the livers of rats exposed to 5 ppm NVP for 3 months, liver toxicity became more marked when rats inhaled 5 ppm for longer durations. This suggests that NOAELs derived from 3-month studies might not apply to studies of longer duration and the lifetime exposure NOAEL might be below 1 ppm for rats and mice. Inhalation of concentrations of 15 ppm (69 mg.m^{-3}) NVP vapour or more resulted in liver toxicity and nasal cavity irritation within 1 week and mortality occurred at concentrations of 45 ppm (207 mg.m^{-3}) in mice and 120 ppm (553 mg.m^{-3}) in rats.

In contrast, when NVP is given by oral gavage to rats, the dose levels required to induce histopathological changes in the liver are considerably greater than those required by inhalation; the respiratory tract is not a target tissue with oral dosing. One explanation for the much lower systemic toxicity of NVP by the oral route is that the substance hydrolyses in the acidity of the stomach prior to absorption. A NOAEL of 3.6 mg/kg/day has been identified in a drinking water study. However, gavage doses of up to 60 mg/kg/day produced no clear pathological changes in the liver and only slight changes in a few biochemical and haematological parameters. There are no data relating to the effects of repeated dermal exposure to NVP.

NVP has yielded consistently negative results in genotoxicity tests in a wide variety of *in vitro* systems, and one well conducted *in vivo* test covering the endpoints of gene mutation, chromosomal aberration and DNA-binding. On this basis, it can be concluded that NVP is not a genotoxicant.

NVP vapour is clearly carcinogenic in rats, the only species tested. In a 2 year inhalation study, hepatocellular carcinoma, nasal cavity adenomas and adenocarcinomas, and squamous cell carcinomas in the larynx were observed. In another study, irreversible changes were produced in the liver of rats after only 3 months exposure, which resulted in liver tumour development at the end of a subsequent 21 month observation period in the absence of further exposure to NVP. This suggests that these tumours, and possibly also nasal and laryngeal tumours, arise by a process involving more than simply chronic tissue damage/inflammation. Overall, it is unclear what toxicological mechanism underlies the formation of NVP vapour-induced tumours and it is also unclear where a no-effect level lies. Given these uncertainties, and in the absence of evidence to the contrary, it is suspected that these tumours are of relevance for human health. The carcinogenicity of NVP by the oral and dermal routes has not been studied.

Fertility has not been specifically investigated. However, in repeated dosing studies NVP showed no adverse effects on the reproductive organs of rats and mice inhaling up to 45 ppm for 3 months, rats inhaling up to 20 ppm for 2 years and given up to 8.3 mg/kg NVP in drinking water for 3 months. On this basis it is considered that there is no evidence to suggest that NVP is likely to have an adverse effect on fertility. No further studies are required in the OECD SIDS programme.

In a developmental toxicity study in rats exposed by inhalation, foetotoxicity, consistent with delayed development, was seen at exposure concentrations producing significant maternal toxicity (20 ppm). No specific malformations or foetotoxicity was observed at concentrations that were not also maternally toxic. A NOAEL of 1 ppm (4.61 mg.m^{-3}) was indicated for maternal toxicity, with a NOAEL of 5 ppm (23 mg.m^{-3}) for effects on the foetus. In addition, there was some evidence that pregnant rats may be more susceptible to the toxicity of NVP than non-pregnant rats

Environment

The environmental effects database meets the requirements of the SIDS data package. The substance shows moderate to low toxicity to aquatic organisms in short-term tests. *Daphnia magna* was the most sensitive species tested, with a 48 hour EC_{50} of 45 mg/l. A predicted no effect concentration (PNEC) of 45 µg/l for surface water was derived from this value using an assessment factor of 1,000. A PNEC*microorganisms* for waste water treatment processes was estimated to be 19.95 mg/l based on an assessment factor of 100 on a threshold concentration of >1995 mg/l for effects on activated sludge respiration. PNECs for sediment and soil were estimated using the equilibrium partitioning method as PNEC*sediment* = 51.8 µg/kg wet wt. and PNEC*soil* = 18.7 µg/kg wet wt.

No data are available to allow a PNEC to be derived for the atmospheric compartment. However, the atmospheric concentrations of 1-vinyl-2-pyrrolidone are predicted to be very small and so adverse effects are unlikely.

Exposure

In 1999, there was understood to be only two producers of 1-Vinyl-2-pyrrolidone (NVP) worldwide in the EU and in the USA. The annual production volume in 1999 was 10-50 000 tonnes.

The majority of the NVP that is sold within the EU is used in the production of polyvinyl pyrrolidone or copolymers. According to manufacturers, the amount of residual monomer is less than 1000 ppm. Polyvinyl pyrrolidone has a range of uses, including in pharmaceuticals, cosmetics and food additives. Copolymers of NVP are used as viscosity improvers in oils and in water-borne paints and adhesives. 1-Vinyl-2-pyrrolidone is also used as a reactive thinner to produce copolymers in UV-cured inks and coatings. Radiation-curable inks contain up to 14% NVP and are used, for example, in advertising hoardings. Radiation-curable coatings and varnishes have a number of uses, including coating printed circuit boards, and on children's toys, and contain up to 9% of NVP. In all these cases there is only a very small amount of residual monomer (NVP) left in the finished product.

1-Vinyl-2-pyrrolidone is a liquid at room temperature with a melting point of 13-14^{o}C, a boiling point of 90-92^{o}C, a vapour pressure of 0.12 hPa at 20^{o}C. It is fully miscible with water and has a measured Log n-octanol water partition coefficient (log Kow) of 0.4.

Environmental releases can occur to the atmosphere and wastewater streams during production of NVP, polymer manufacture and processing, formulation of radiation-cured coatings and inks and via in-service losses of residual NVP-monomer during use of polymer products.

The substance is readily biodegradable and so is expected to biodegrade in water, soil and sediments under aerobic conditions. It is also expected to be rapidly degraded in the atmosphere by reaction with hydroxyl radicals and a half-life for this reaction of around 10.4 hours has been estimated. The rate constant for the reaction of NVP with hydroxyl radicals in aqueous solution has been measured and is 7.3 10^{9} l/mol·sec.

The substance has a low Henry's law constant (0.0056 Pa m^3 mol^{-1}) and so is not expected to volatilise rapidly from water. The low log Kow value indicates that the substance a low potential for adsorption onto soil, sediment or suspended matter, and a low potential for bioaccumulation. The organic carbon-water partition coefficient (Koc) has been estimated as 16.9. Based on the physicochemical properties, NVP would be expected to partition to water.

The manufacture and polymerisation of NVP is carried out in closed systems. Exposure by both the inhalation and dermal routes may occur during deliberate breaches of the system. The main sources of exposure from the manufacture of UV curing inks and lacquers are thought to arise during the charging of mixing vessels and during the filling of product containers and from incidental dermal contact with contaminated surfaces. The main source of exposure to NVP during the manufacture of contact lenses is during the preparation of the pre-polymer mix and when this mix is put into the moulds. In consumers, there is potential for inhalation exposure from the use of hairspray containing residual NVP monomer. There is very low potential for exposure from ingestion or contact with the skin to of residual NVP monomer in polyvinylpyrrolidone (PVP) used in consumer products. Individuals may also be exposed at a low level to NVP monomer indirectly via the environment from dietary sources such as drinking water, fish, leaf and root crops, meat and milk but NVP may also be inhaled.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address hazard classification for all SIDS endpoints and other non-SIDS endpoints. However, the chemical is a candidate for further work as follows:

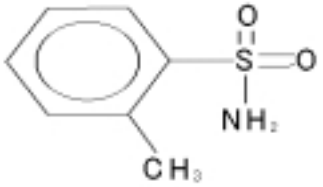
National or regional exposure gathering information, and if indicated risk assessment, may need to be considered.

A regional risk assessment has been carried out for Europe. As it was not possible to identify a NOAEL for carcinogenicity seen in rodents there were particular concerns for workers (with or without exposure to NVP from

the environment and/or consumer products) involved in the production of NVP and its use in the production of polymers, the use of NVP in the manufacture of UV curing inks/lacquers, the use of UV curing inks/lacquers containing NVP, and the use of NVP in the manufacture of contact lenses. In addition, there were concerns for single exposure toxicity and respiratory tract irritation in exposure situations where there is the potential for peak exposures to occur. Such peak exposures can occur during the production of NVP and its use in the production of polymers, the use of NVP in the manufacture of UV curing inks/lacquers, the use of UV curing inks containing NVP. It was recommended that steps should be taken to reduce exposures for these occupational uses. It was also recommended that steps should be taken to prevent eye contact with liquid NVP in any situation where this may occur. No concerns were identified for workers whose only form of exposure to NVP was as a residue in NVP based polymers owing to the very low level of NVP to which these workers would be exposed. For consumers and exposures from the environment there was no need for further information and/or testing or for risk reduction measures beyond those which are being applied already. As exposures were so low, there were no concerns for all environmental compartments for production, processing and use of NVP and release of NVP during use of polymers which contain residual NVP monomer.

A national risk assessment has been carried out in Australia. The occupational risk assessment concluded that a risk of acute eye effects is likely during formulation of NVP products and steps be taken to reduce exposure. There were concerns for workers involved in the formulation of NVP products and use of UV curing inks containing NVP. There were no concerns for the environmental compartments. The public health assessment concluded that it is prudent to limit the levels of NVP to below 200 ppm in PVP used in cosmetics as high consumer exposure is likely at levels greater than this level.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-19-7
Chemical Name	*o*-Toluenesulfonamide
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

o-Toluenesulfonamide orally administered was rapidly eliminated mostly to urine in rats. In human subjects it was excreted to urine more slowly than that in rats. The main metabolites were 2-sulfamoyl-benzyl alcohol and its sulphate and glucuronic acid conjugates in both rats and humans. Saccharin was also detected as a metabolite in urine especially in humans.

The oral LD_{50} value for rats was greater than 2,000 mg/kg b.w. in males and between 1,000 and 2,000 mg/kg b.w. in females [OECD TG 401]. Sedation, passivity and catalepsy appeared even at the lowest dose of 700 mg/kg b.w. It is reported that this chemical was moderately irritating to eyes in rabbits but the reliability of the study is uncertain. There is no available information on skin irritation and sensitization.

In accordance with an OECD combined repeated dose and reproductive/developmental toxicity screening test [TG 422], o-toluenesulfonamide was given to male and female SD rats by gavage at 0, 20, 100, 500 mg/kg b.w./day for at least 38 days. Three females died and two females were sacrificed in moribund condition during the pre-mating period at 500 mg/kg b.w. Decreased locomotor activity and appearance of prone position and salivation were observed in both sexes at 100 and 500 mg/kg b.w. In the same groups, low body weights were recorded in both sexes. In histopathological examinations, hypertrophy of the centrilobular hepatocytes with the cytoplasm having a ground glass appearance was observed in both sexes at 100 and 500 mg/kg b.w. in a dose-dependent manner. In addition, the incidence of fibrosis and cellular infiltration of the pericardium, and fibrosis and cellular infiltration of the capsule and atrophy of the thymus were significantly increased in females of at 500 mg/kg b.w.. In the kidneys, eosinophilic body was observed in males of all treated groups, maybe due to the complex accumulation of this chemical with the male rat specific protein, alpha-2u-globulin. Based on clinical signs and hepatic change, the NOAEL for repeated dose toxicity is considered to be 20 mg/kg b.w./day for both sexes.

Regarding genotoxicity, a bacterial test [OECD TG 471] and a chromosomal aberration test [OECD TG 473] *in vitro* were negative with and without metabolic activation. One mammalian spot test in mice demonstrated inconclusive results and two micronucleus tests *in vivo* in mice (gavage and i.p.) showed negative results. However the experimental condition of all these studies are not sufficiently reported. Therefore, the genotoxic potential of

this chemical *in vivo* is inconclusive.

In a two generation lifetime feeding study, male and female SD rats were given o-toluenesulfonamide in the diets at 0, 2.5, 25 and 250 mg/kg b.w./day. No increase in any tumour incidence was noted in all dose groups of both generations. Two 2-year oral rat studies also demonstrated no carcinogenicity of this chemical. Only one lifetime feeding study showed low incidence of urinary bladder tumors of rats but the reliability of this study is uncertain because of poor reporting. A cell transformation assay using mammalian cultured cells showed negative results. Based on a weight of evidence approach, the available data indicates that this chemical is not carcinogenic.

In an OECD combined repeated dose and reproductive/developmental toxicity screening test [TG 422], a significant reduction in body weights of pups was observed on days 0 and 4 in both sexes of rats at 500 mg/kg b.w. In a two generation lifetime feeding study, decrease of litter size and pup body weight was observed at 250 mg/kg b.w./day. Based on an overall evaluation of both results, the appropriate NOAEL for reproductive/developmental toxicity is considered to be 100 mg/kg b.w./day .

Environment

o-Toluenesulfonamide is soluble in water (1.6 g/L at 25 °C) and has a low vapor pressure (6.6×10^{-5} Pa at 25 °C) Its log Kow is 0.84. *o*-Toluenesulfonamide is not readily biodegradable (OECD TG301C: 0 % by BOD after 14 days), but its experimental BCF of less than 2.6 (OECD TG 305) suggests that this chemical does not bioaccumulate in aquatic organisms. Hydrolysis is not expected to occur. If released to the atmosphere, this chemical mainly exists in the particulate phase according to its low vapor pressure. Particulate phase of *o*-Toluenesulfonamide may be physically removed from the air by dry and wet deposition.

Acute toxicty of o-Toluenesulfonamide has been tested in three aquatic species of three trophic levels. For algae (*Selenastrum capricornutum*) a ErC50 of 170 mg/L (OECD TG 201, growth rate for 24-48hr and also 24-72 h) and a 72hEbC50 of 57 mg/L (OECD TG201, biomass) were determined. For daphnids (*Daphnia magna*) a 48 h EC50 of 210 mg/L (OECD TG 202 part 1), and for fish (*Oryzias latipes*) a 96 h LC50 of >100 mg/L (OECD TG 203) were reported.

Two chronic toxicity values, for alga (*Selenastrum capricornutum*) and daphnids (*Daphnia magna*) were available. For algae, a 72 h NOEC on growth inhibition of 7.7 mg/L(OECD TG 201, based on growth rate), and for daphnids, a 21 d NOEC of 49 mg/L(OECD TG 202, reproduction) were reported.

Exposure

o-Toluenesulfonamide was mainly produced as a chemical intermediate for the production of saccharin in the past, but now saccharin is normally manufactured without using this chemical although minor amounts are still used for this purpose. A mixture of *o*-Toluenesulfonamide with the *p*-isomer is used as a plasticizer for hot-melt adhesives, a chemical intermediate for fluorescent pigments and a chemical intermediate for plasticizer resins. The production volume of this chemical in Japan was about 50 tonnes in 2000.

NATURE OF FURTHER WORK RECOMMENDED

This chemical is not a candidate for further work because all SIDS endpoints are sufficient.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1333-82-0; 7775-11-3; 10588-01-9; 7789-09-5; 7778-50-9
Chemical Name	Chromium trioxide; sodium chromate; sodium dichromate; ammonium dichromate; potassium dichromate
Structural Formula	CrO_3; $NaCrO_4$; $Na_2Cr_2O_7$; $NH_4\ Cr_2O_7$; $K_2\ Cr_2O_7$

RECOMMENDATIONS

These chemicals are candidates for further work.

SUMMARY CONCLUSIONS OF THE SIAR

These five chromium (VI) substances have been assessed as a group, since after release to the environment the chromium species produced are the same from each substance, and so the fate and effects in the environment can be considered together. Similarly for human health, the species produced will behave similarly in biological tissues and so the effects can be treated as a group. (There is also an additional concern about the acidity of solutions of chromium trioxide.)

Human Health

The toxicological database for chromium (VI) (Cr(VI)) is generally extensive. Sodium chromate, dichromates of sodium, potassium and ammonium, and chromium (VI) trioxide, the substances covered in this review are all highly water-soluble hexavalent compounds.

Chromium (VI) trioxide in solution produces chromic acid, concentrated solutions that are highly acidic. Hence, of the five Cr(VI) compounds covered by the assessment, there are site-of-contact issues related to low pH that are a consideration for chromium (VI) trioxide but not for the other four.

Beyond this, the five Cr(VI) compounds will all readily dissolve in aqueous environments in the body, to release chromate (CrO_4^{2-}) or dichromate ($Cr_2O_7^{2-}$) ions. These two ions will co-exist, in equilibrium, regardless of the particular Cr(VI) compound involved. The chromate/dichromate ions produced from all five compounds will behave similarly in biological tissues and hence, other than the additional property of acidity and its potential influence on toxicity for chromium (VI) trioxide, the five can be treated as a common group. Furthermore, toxicological observations made with other chromium (VI) compounds that can similarly readily dissociate to produce chromate/dichromate ions in solution can be legitimately made use of in predicting the toxicity of these five compounds.

There is a reasonably good database available on the toxicokinetics of the chromium (VI) compounds under review, although there are relatively few human data. The available data indicate that generally the chromium (VI) compounds covered by this document are likely to behave in a similar manner in respect of toxicokinetics, and that the kinetic behaviour of these substances would be similar in those species studied, including humans.

Following inhalation exposure, animal studies have shown that 20-30% of the administered Cr(VI) is absorbed via the respiratory tract. Highly water-soluble Cr(VI) is poorly absorbed via the gastrointestinal tract (only 2-9% of the

dose was absorbed in human studies) due to reduction to the relatively poorly absorbed Cr(III). Only limited dermal absorption takes place through intact skin, with 1-4% Cr(VI) from an aqueous solution crossing the skin in guinea pig studies.

According to results of animal testing, chromium derived from these compounds can remain in the lungs for several weeks after inhalation exposure and also becomes bound to haemoglobin in erythrocytes for the lifespan of the cells. Cr(VI) becomes reduced to Cr(III) after entering the body due to the influence of reducing agents, for example glutathione. Distribution is widespread even after a single dose and includes transfer of absorbed Cr(VI) across the placenta. Excretion occurs in urine and faeces. Repeated exposure leads to accumulation of chromium in several tissues, particularly the spleen because of uptake of senescent erythrocytes.

Case reports show that inhalation by workers of aqueous solutions of Cr(VI) mists have resulted in irritation and inflammation of the respiratory tract, with symptoms and signs including dyspnoea and cyanosis; associated airborne levels were not reported. Accidental or deliberate oral ingestion has resulted in signs and symptoms some of which are indicative of corrosive damage and deaths have been reported in numerous cases in adults. Among the survivors, clinical manifestations of liver and kidney damage were present. There have also been cases of kidney damage and death following dermal exposure to Cr(VI). In most of these cases the skin was broken or damaged by the acidity or high temperature of the solution, facilitating Cr(VI) absorption across the skin.

The qualitative picture of acute toxicity seen in humans is supported by observations from studies in experimental animals.

Aerosols were toxic when inhaled by rats. LC_{50} values of 99 mg/m^3 (potassium dichromate) (35 mg Cr(VI)/m^3), 200 mg/m^3 (sodium and potassium dichromate) (70 mg Cr(VI)/m^3), 200 mg/m^3 (ammonium dichromate) (83 mg Cr(VI)/m^3) and 104 mg/m^3 (sodium chromate) (33 mg Cr(VI)/m^3) have been reported for male rats with a 4-hour exposure period. Similarly, an LC_{50} value of 217 mg/m^3 (113 mg Cr(VI)/m^3) for chromium (VI) trioxide has been reported for rats with a 4-hour exposure period. It is predicted that severe damage to tissues of the respiratory tract would occur at low concentrations due to the corrosive nature of this substance.

Available oral LD_{50} values for chromium (VI) trioxide were 52-113 mg/kg (27-59 mg Cr(VI)/kg) in rats and 135-175 mg/kg (70-91 mg Cr(VI)/kg) in mice. Aqueous chromium (VI) trioxide produced bleeding and ulceration of the stomach due to its corrosive properties. Oral LD_{50} values of 74 mg/kg (26 mg Cr(VI)/kg) (potassium dichromate), 59 mg/mg (23 mg Cr(VI)/kg) sodium dichromate), 55 mg/kg (23 mg Cr(VI)/kg) (ammonium dichromate) and 87 mg/kg (28 mg Cr(VI)/kg) (sodium chromate) have been reported for male rats. Female rats were more sensitive with LD_{50} values of 48 mg/kg (17 mg Cr(VI)/kg), 46 mg/kg (16 mg Cr(VI)/kg), 48 mg/kg (20 mg Cr(VI)/kg) and 40 mg/kg (13 mg Cr(VI)/kg) respectively. Toxic effects reported at necropsy included pulmonary congestion and corrosion of mucosa in the gastrointestinal tract.

Highly water-soluble Cr(VI) compounds were also toxic following skin application. In a standard dermal LD_{50} study in rabbit, the following values were determined: sodium dichromate 960 mg/kg (380 mg Cr(VI)/kg); potassium dichromate 1150 mg/kg (410 mg Cr(VI)/kg); ammonium dichromate 1860 mg/kg (770 mg Cr(VI)/kg) and sodium chromate 1330 mg/kg (430 mg Cr(VI)/kg). In another study, percutaneous doses of 207 mg/kg sodium chromate (66 mg Cr(VI)/kg) and 170 mg/kg sodium dichromate (66 mg Cr(VI)/kg) produced death in guinea pigs. A dermal LD_{50} value of 57 mg/kg (30 mg Cr(VI)/kg) has been reported for chromium (VI) trioxide.

In conclusion, highly water-soluble Cr(VI) compounds are very toxic by inhalation and toxic by ingestion. The respiratory tract and the kidney are damaged by these compounds following inhalation and oral exposure respectively. Although acutely harmful or toxic by the dermal route, more severe responses may be observed due to greater uptake via the skin if there is any prior or simultaneous damage to the skin. Depending upon the pH of the Cr(VI) solution, corrosive effects can occur on contact.

Single application of highly water-soluble chromium (VI) in solution to undamaged human skin resulted in only a mild irritant response around the hair follicles. Aqueous chromium (VI) trioxide is a corrosive substance due to its low pH. In addition, when high temperature solutions of Cr(VI) are splashed onto the skin, serious burns occur. Animal data are consistent with the observations made in humans. It is not possible to determine a clear

concentration-response relationship for human skin irritation from the single-exposure animal or occupational data available. Highly water-soluble chromium (VI) compounds can cause very severe skin effects under certain conditions. In workers repeatedly exposed to highly water-soluble chromium (VI), where there is some slight initial damage to the skin, ulcers can develop which constitute a serious and persistent effect. Again, animal data are consistent with the observations made in humans. It is not possible to determine a clear concentration-response relationship for repeated-exposure human skin effects from the occupational data available and quantitative data could be misleading given the potential for severe effects resulting from repeated contamination of slightly damaged skin. Overall, highly water-soluble chromium (VI) compounds should be regarded as corrosive.

Significant damage to the eye can occur upon accidental exposure to highly water-soluble chromium (VI) compounds. Severe and persistent effects occur when there is contact with the low pH aqueous chromium (VI) trioxide or Cr(VI) solutions at high temperature. Repeated, but not single administration of highly water-soluble chromium (VI) caused severe irritation in the rabbit eye. It is not possible to determine a clear concentration-response relationship from the data available.

Symptoms of sensory irritation of the respiratory tract are known to occur among chrome plating workers exposed to a mist of aqueous chromium (VI) trioxide. Since this is corrosive, such symptoms are to be expected. No quantitative data on such irritation are available from studies of workers. No studies reporting symptoms of sensory irritation are available for the other chromium (VI) compounds. Overall, it is not possible to determine a reliable concentration-response relationship for respiratory tract irritation using the available data.

Skin sensitisation resulting from contact with Cr(VI) is relatively common in humans working with the compounds. This has been demonstrated in patch testing of contact dermatitis patients and in investigations of various occupational groups. In addition, skin sensitisation potential has been clearly demonstrated in standard and modified guinea pig maximisation tests and in the mouse ear swelling test.

Current understanding of the mechanism involved in the sensitisation indicates that Cr(III) is the ultimate hapten. Skin contact with Cr(VI) leads to penetration of Cr(VI) into the skin where it is reduced to Cr(III). There is some evidence for cross-reactivity between Cr(III) and Cr(VI); Cr(VI)-sensitised subjects may also react to Cr(III). Overall, it is not possible to reliably determine a threshold for either induction or challenge in an exposed population using the available data.

The available case reports and evidence from well-conducted bronchial challenge tests, show that inhalation of chromium (VI) compounds can cause occupational asthma. As with skin, Cr(VI)-sensitised subjects may react to Cr(III). It is not possible to determine a no-effect level or exposure-response relationship for induction or elicitation of occupational asthma.

With respect to repeated exposure, a large number of studies are available relating to exposure of workers to highly water-soluble chromium (VI), specifically sodium or potassium chromate/dichromate and chromium (VI) trioxide. The main effects reported are irritant and corrosive responses in relation to inhalation and dermal exposure. These include inflammation in the lower respiratory tract, and nasal septum perforation in the upper respiratory tract. It is not possible to relate these effects to reliable measures of Cr(VI) exposure. Although in principle a threshold dose should be identifiable, in practice the location of such a threshold is not possible from the data available. Some evidence of kidney damage has also been found among chromate production and chromium plating workers. No exposure-response data or no-effect levels are available. However, it appears that the exposure levels at which kidney toxicity occurs overlap with the atmospheric concentrations at which respiratory tract effects have been reported.

Only limited animal repeated dose toxicity information is available. In general, the effects seen are consistent with those found in humans. Although in principle a threshold dose should be identifiable, in practice the location of such a threshold is not possible from the data available. Inhalation of sodium chromate dust for 8 months caused deaths in mice exposed to 0.3-3.7 mg/m^3 (0.1-1.2 mg Cr(VI)/m^3). Rats appeared to be less sensitive (no deaths occurring after 16 months). Concentrations down to 0.07 mg/m^3 (0.025 mg Cr(VI)/m^3) sodium dichromate (aerosol) produced increased alveolar macrophage and spleen lymphocyte activities following a 90-day exposure in the rat. Much of this enhancement was lost at 0.57 mg/m^3 sodium dichromate (0.2 mg Cr(VI)/m^3); this dose inhibited alveolar

macrophage phagocytosis. Repeated chromic acid mist (chromium (VI) trioxide) exposure produced irritant and corrosive effects in the respiratory tract at 3.5 mg/m^3 (1.8 mg Cr(VI)/m^3) and above in an 8-month study. Overall, little useful dose-response information is available.

In the rat, testicular degeneration was observed at a dose level (40 mg/kg/day (14 mg Cr(VI)/kg/day)) which caused a large decrease in body weight gain following gavage administration of sodium dichromate for 90 days. A NOAEL of 20 mg/kg/day (7 mg Cr(VI)/kg/day) was determined for effects on the testis, the only organ examined. Other studies found no significant toxicity following administration of potassium dichromate by the dietary route for 9 weeks. The highest dose levels in these studies were 24 mg/kg/day (8 mg Cr(VI)/kg/day) in the rat and 92 mg/kg/day (32 mg Cr(VI)/kg/day in the mouse.

No repeated dermal studies are available, although these substances are recognised as being corrosive on repeated dermal exposure.

Few studies of genotoxic potential in humans are available. No evidence of genotoxic activity has been found in adequately-conducted studies in circulating lymphocytes from chromium-exposed workers. In contrast, there is a vast array of genotoxicity data *in vitro* and less extensive testing in animals available. The evidence clearly indicates that highly water-soluble chromium (VI) compounds can produce significant mutagenic activity *in vitro* and *in vivo*. The chromium (VI) compounds under consideration are therefore regarded as *in vivo* somatic cell mutagens. In addition, toxicokinetic and dominant lethal data suggest that water-soluble chromium (VI) has the potential to be an *in vivo* germ cell mutagen.

Chrome plating workers exposed to chromium (VI) trioxide in aqueous solution have shown a clear excess in mortality from lung cancer. Therefore chromium (VI) trioxide should be regarded as a human carcinogen by the inhalation route. The excess in lung cancer mortality cannot be related to particular atmospheric Cr(VI) levels in any reliable manner. These chrome plating workers were exposed specifically to a mist of Cr(VI) in aqueous acidic solution, emanating from the surface of the plating bath. The acidic nature of the entity might be a significant contributory factor in the type and onset of lesions and uptake of Cr(VI), precluding direct extrapolation of the human carcinogenic activity of the trioxide to the ammonium, sodium or potassium chromates or dichromates.

With respect to the other chromium (VI) compounds under review, epidemiology data from chromate production, chromium pigment manufacture and other chromium-exposed groups showing clear increases in lung cancers cannot be specifically related to exposure to any of the chromium (VI) compounds under consideration here. However, it is highly probable that Cr(VI) ions in solution were the ultimate carcinogenic entity in these situations. Hence these epidemiological studies raise concerns for the carcinogenic potential of the other four chromium (VI) compounds covered in this review.

Animal carcinogenicity studies have been conducted on only two of the compounds covered in this review. In these studies, sodium dichromate was carcinogenic in rats, causing lung tumour production, when given by repeated long-term inhalation or intratracheal instillation. In rats and mice, inhalation or intrabronchial implantation studies using chromium (VI) trioxide produced 1-2 test group animals with lung tumours where such were mainly absent among corresponding controls. Thus, in animal studies there is some evidence of respiratory tract carcinogenic activity for sodium dichromate and chromium (VI) trioxide. Similar studies in rats using other chromium (VI) compounds (not covered by this review), able to produce Cr(VI) in solution, produced carcinogenicity in the lung. Hence there is good reason from animal studies to be concerned about the carcinogenic potential of all five Cr(VI) compounds covered by this review, in terms of the inhalation route and the respiratory tract as a site of action. Data for the oral and dermal routes and carcinogenicity studies on the other compounds under consideration are not available. Chromium (VI) compounds might be expected to have potential to cause cancer on repeated oral or dermal exposure. In the case of the oral route, any systemic carcinogenic potential could be limited by poor absorption from, and reduction to Cr(III) within the gastrointestinal tract although site of contact activity would remain an issue. Similar considerations apply to the skin.

Overall, therefore, all five chromium (VI) compounds covered by this review are considered to have proven or suspect carcinogenic potential by the inhalation route. From the available information, and taking into account the genotoxic potential of these substances, it is not possible to identify any dose-response relationship or thresholds for

this effect.

Human data relating to effects on reproduction are limited to poorly reported studies of female workers from which no conclusions can be drawn. There are two animal studies available which focus on fertility. Adverse effects were produced in mice receiving potassium dichromate for 12 weeks in drinking water at 333 mg/kg/day (120 mg Cr(VI)/kg/day) and 400 mg/kg/day (140 mg Cr(VI)/kg/day) and above in males and females respectively. A NOAEL of 166 mg/kg/day (60 mg Cr(VI)/kg/day) was identified in males but no NOAEL was found for females as 400 mg/kg/day was the lowest dose level tested. An increase in resorptions following treatment of males and a decrease in implantations in treated females were among the findings in this study. In another study, pregestational oral administration of potassium dichromate in drinking water to female mice produced adverse effects on fertility (reduced number of corpora lutea and increased pre-implantation loss) at 500 ppm (119 mg/kg/day (40 mg Cr(VI)/kg/day)) and above. NOAEL values of 119 mg/kg/day (40 mg Cr(VI)/kg/day) and 63 mg/kg/day (20 mg Cr(VI)/kg/day) can be identified from this study for maternal toxicity and fertility effects respectively. In a third study, also in the mouse, at 86 mg/kg/day (30 mg Cr(VI)/kg/day), the highest dose level tested, there were no effects of treatment on fertility parameters.

Fetotoxicity, including post-implantation losses, has been observed in the mouse following administration of potassium dichromate in drinking water during gestation (days 0-19). Significant developmental effects occurred at the lowest dose level tested, 60 mg/kg/day (20 mg Cr(VI)/kg/day) in the absence of maternal toxicity. Therefore no developmental NOAEL was determined. Qualitatively similar results were obtained in another study in which 350 mg/kg potassium dichromate (125 mg Cr(VI)/kg) was administered for a shorter period, on days 6-14 of gestation. In a pregestational study in female mice, fetotoxic effects were seen starting from the lowest dose level tested, 250 ppm (63 mg/kg/day (20 mg Cr(VI)/kg/day)) potassium dichromate. Significant levels of total chromium were found in treated animals at sacrifice. No NOAEL could be identified for the developmental effects which included post-implantation losses. These fetal effects may possibly be explained by the presence of chromium in the dams after the end of treatment. Overall, highly water-soluble chromium (VI) compounds should be considered to be developmental toxicants in the mouse. These findings can be regarded as relevant to humans.

It is noted that some of the adverse effects on reproduction observed in animal studies may be related to the germ cell mutagenicity of these chromium (VI) compounds (see Mutagenicity section). No reproductive toxicity studies are available using the inhalation or dermal routes of exposure.

Environment

The database on the effects of chromium (VI) ion compounds to aquatic organisms is extensive. Acute toxicity tests are available for algae (range of EC_{50} values 0.13 to 4.6 mg/l), invertebrates ($L(E)C_{50}$ values 0.03 to 35 mg/l), fish (LC_{50}values 18 to 213 mg/l) and amphibians (LC_{50} values 43 to 100 mg/l), all expressed as concentrations of chromium (VI). The acute toxicity of chromium (VI) depends on a number of factors, including pH, water hardness, salinity and temperature. In general the toxicity increases with decreasing pH, water hardness or salinity and with increasing temperature, although there are also studies which appear to show little change in toxicity with changing water properties. Invertebrates appear to be generally more sensitive in acute tests.

There are also a large number of long term studies on aquatic organisms, though far less than the number of acute studies. These show less variation of toxicity with water properties, although the smaller number limits the comparisons that can be made. Valid long-term NOEC values have been identified for 28 species (some derived by combining the results of multiple determinations). The species include representatives of algae, macrophytes, crustaceans, coelenterates, insects, molluscs, fish and amphibians, and the range of NOEC values is 0.0047 mg Cr(VI)/l (for reproduction in the cladoceran *Ceriodaphnia dubia*) to 3.5 mg Cr(VI)/l (for fish). A PNEC of 0.47 µg Cr(VI)/l can be derived using an assessment factor of 10. However, due to the large amount of data, a statistical approach has also been used in the EU. The data were assumed to come from a log normal distribution and the lower 5% value from the distribution at the 50% confidence level (HC_5) was determined as 10.2 µg Cr(VI)/l. To take account of limitations in the database (only one representative of molluscs and insects, and no corroborating mesocosm or field studies) an assessment factor of 3 was applied, giving a PNEC of 3.4 µg Cr(VI)/l for the surface water compartment.

Using the equilibrium partitioning method and different partition coefficients for acidic and neutral-alkaline environments gives sediment PNECs of 1.5 mg Cr(VI)/l for 'acidic' conditions and 0.15 mg Cr(VI)/l for 'alkaline'.

For the terrestrial compartment, long-term toxicity data are available for three trophic levels (plants, earthworms and soil processes/micro-organisms), with plants generally being the most sensitive species group (although a clear NOEC has not been determined for earthworms, the EC_{50} values are generally higher than those found in the plant experiments). The lowest NOEC from a plant growth test is 0.35 mg Cr(VI)/kg dry weight. Applying an assessment factor of 10 to this gives a PNEC in soil of 35 μg Cr(VI)/kg dry weight (31 μg/kg on a wet weight basis).

Soil studies tend to show a rapid reduction of chromium (VI) to chromium (III), and so toxicity data for chromium (III) may be more relevant for effects in the terrestrial environment. For earthworms, a NOEC of 32 mg Cr(III)/kg dry weight has been determined, while for plants the NOEC is around 100 mg Cr(III)/kg dry weight. For soil processes, a large number of values (30) has been used in a statistical extrapolation to give a HC_5 value of 5.9 mg Cr(III)/kg. A PNEC of 3.2 mg Cr(III)/kg dry weight (2.8 mg/kg wet weight) was derived from the earthworm NOEC using an assessment factor of 10. It should be noted that the soil tests were carried out with a highly soluble (and hence bioavailable) form of chromium (III). In the environment, chromium (VI) is likely to be reduced to forms of chromium (III) of limited solubility and bioavailability, and it is unlikely that the concentration of "dissolved" and hence available chromium (III) will reach the levels where effects might be expected. Similarly, there are many natural soils where the levels of total chromium (present as poorly bioavailable chromium (III) complexes) are above the PNECs derived here. The PNECs are therefore not appropriate for such situations.

Exposure

The first manufacturing step involves the production of sodium chromate from chromite ore. The production of sodium chromate in the EU was 103,000 tonnes in 1997. The vast majority of this sodium chromate is converted into sodium dichromate (110,000 tonnes in 1997), and the other three substances are made from sodium dichromate.

The major uses for the chromium (VI) compounds are in the manufacture of other chromium-containing chemicals (e.g. pigments and dyes, chromium sulphate for leather tanning), in metal treatment (mainly chrome plating, but also conversion coatings and brightening) and in wood preservation.

All five substances are solids (coloured crystals). Water solubilities are in the range 115-1670 g/l. Vapour pressures and octanol-water partition coefficients are not relevant for this type of substance.

Emissions to air and to water are possible from production of the five substances. Releases from their use are expected to be to water. Chromium (VI) ions are recognised as toxic to aquatic organisms, and so methods are available to remove them from water before release; however, it is not clear how widely these methods are applied.

The main route of occupational exposure is inhalation from the use of Cr (VI) compounds. Manufacture is largely in enclosed systems although there is potential for exposure during breeches in the system and bagging of product. Although dermal exposure may occur, due to the corrosive nature of Cr (VI) compounds, it is considered that measures taken to prevent substantial skin contact, mean that under intended exposure conditions there would be no prospect of systemic effects arising through dermal exposure. Significant oral exposure is not anticipated in the workplace. The potential for consumer exposure due to the presence of residual chromium VI compounds in copper chromium arsenate (CCA) wood preservative treated timber is very low - the exposure may be higher if CCA treated wood is still wet after impregnation. In the EU it is reported that there is no consumer exposure to Cr(VI) compounds from leather goods, pigments, dyestuffs, stainless steel goods, products derived from vitamin K or montan waxes. Potential exposure by contact, inhalation or ingestion of Cr(VI) from environmental sources (air, water, food) is very low.

Once in the environment, the major dissolved species are $HCrO_4^-$ and CrO_4^{2-} - dichromate species are only important at high concentrations (> 0.4 g Cr/l). Chromium (VI) is a strong oxidising agent, and reacts with a range of reducing agents in the environment to give chromium (III) species. The reverse reaction is possible but requires a

strong oxidising agent and is unlikely under general environmental conditions. It is expected that the majority of the chromium released to the environment will be converted to chromium (III), although this may not be rapid for all releases.

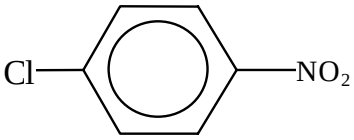
Chromium (VI) species are more mobile in soils and sediments than chromium (III) species. The sorption of chromium (VI) species decreases with increasing pH, while the sorption of chromium (III) species increases with increasing pH. Chromium (VI) does not appear to bioconcentrate significantly in aquatic organisms, but reduction to chromium (III) once in the organism can lead to higher levels of total chromium in organisms.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address the hazard classification for all SIDS endpoints, and for a number of other non-SIDS endpoints. However the substances are candidates for further work as follows:

- National or regional exposure information gathering, and if indicated, a risk assessment may need to be considered for the water and soil compartments (based on an existing regional risk assessment for Europe, where a need to limit risks has been identified for a number of uses).
- No toxicity data are available for sediment organisms. These data could be generated as a post-SIDS activity (as the European risk assessment has already identified a risk to surface water, this will not be pursued in the EU).
- A need to limit the risks for all occupational exposure scenarios and from exposures via the environment in view of the mutagenic and carcinogenic properties. For workers, there is also a need to limit the risks for acute toxicity as a result of short-term exposure, skin and eye irritation, respiratory tract sensory irritation, skin sensitisation, occupational asthma and reproductive toxicity (fertility and development).
- No risk assessment for consumer exposure to wood wet from CCA impregnation was performed by the sponsor (UK) as there are controls to prevent the sale of wood which has not been fully dried. If specific controls are not available, then there may be need for exposure data gathering, and if indicated, risk assessment for this exposure scenario.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-00-5
Chemical Name	1-Chloro-4-nitrobenzene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1-Chloro-4-nitrobenzene is rapidly absorbed via skin, gastrointestinal tract or respiratory tract and distributed in the tissue predominantly in fat, blood cells, skeletal muscles, liver and kidney. Most of the substance was excreted with the urine followed by excretion with feces. 1-Chloro-4-nitrobenzene undergoes three major types of transformation *in vivo* in mammals: nitro-group reduction, displacement of the chloride in glutathione conjugation, and ring-hydroxylation. From accidental exposure of workers to 1-chloro-4-nitrophenol, large amounts of 2-chloro-5-nitrophenol, N-acetyl-S-(4-nitrophenyl)-L-cysteine, 4-chloroaniline and 4-chloroformanilide were identified.

The oral LD50 for 1-chloro-4-nitrobenzene in male rats is 294 or 694 mg/kg bw and in female rats 565 or 664 mg/kg bw. Cyanotic appearance was the predominant symptom. The 7-hour-inhalation of a highly saturated vapor-air mixture (concentration up to 77 mg/m^3) represented no acute hazard to male and female rats. In addition, the LC50 level could not be reached up to 16100 mg/m³ during a 4-hrs exposure against vapor and microcrystalline particles. The LD50 (dermal) for male rats is 750 mg/kg bw and for female rats 1722 mg/kg bw; the LD50 for male rabbits is 3550 mg/kg bw and for female rabbits 2510 mg/kg bw after acute dermal application. Cyanotic appearance was the predominant symptom. For the evaluation of acute toxicity it has to be taken into account that 1-chloro-4-nitrobenzene is a methaemoglobin forming chemical.

Experience with human exposure: all available reports relate to mixed exposure, frequently in combination with 1-chloro-2-nitrobenzene and/or nitrobenzene. A critical aspect in this context is that 1-chloro-4-nitrobenzene is rapidly absorbed via skin and the respiratory tract. The signs of acute intoxication include methaemoglobinaemia, vomiting, headache and in severe cases collapse.

The available study-reports on skin irritation have deficiencies with regard to the description of the results, nevertheless, 1-chloro-4-nitrobenzene is judged to be slightly irritating to the skin (intact or scarificed) of rabbits using a paste of the test substance and occlusive dressing and not irritating to the skin using undissolved, solid test substance and occlusive dressing.

In two available studies 1-chloro-4-nitrobenzene caused slight irritational effects to the eyes of rabbits which were reversible within 4 hours (first study: slight conjunctival injections, observed only in washed eye) resp. 8 days (second study: transient slight corneal cloudiness).

Due to the limited and poor quality information available regarding skin sensitization it cannot be concluded whether or not the chemical has a sensitizing activity.

The repeated dose toxicity via inhalation has been examined in rats for a period of 4 weeks and 13 weeks. In both studies, NOAECs were not achieved, the LOAECs were 5 mg/m³ (4 week-study) and 1.5 ppm (9.81 mg/m^3, 13 week-study), respectively, based on methemoglobinemia (3 % and 4 %, respectively) as the most sensitive effect. The maximum methemoglobin value was 42 % in females of the 24 ppm group in the 13-weeks study. The repeated dose toxicity via inhalation for a period of 13 weeks in mice revealed a NOAEC for histopathologic injury of 6 ppm (39.24 mg/m³). As target organs liver, kidney (rat only), spleen and blood were identified in both species.

Similarly, repeated dose toxicity by oral administration in rats [OECD TG 408 and 453] revealed changes predominantly consistent with methaemoglobinaemia. In the long term test a clear NOAEL could not be identified because histopathological examinations of most of the organs of the low- and mid-dose groups was performed only when macroscopic lesions were observed. The adverse effect level was 0.7 mg/kg bw/day. In the subchronic study the LOAEL was 3 mg/kg bw/day due to methaemoglobin formation and a NOAEL could not be derived. In both studies methaemoglobin formation and oxidative damage to red blood cells, leading to a regenerative anemia and a recognized spectrum of tissue damage and changes secondary to erythrocyte injury, were the main adverse effects.

1-Chloro-4-nitrobenzene induced reverse mutations in bacteria. It was not mutagenic in mammalian cells *in vitro* (HPRT test) and in insects *in vivo*. A mouse lymphoma assay was positive. *In vitro* it induced chromosomal aberrations and sister chromatid exchanges at high doses; no UDS in rat hepatocytes was reported.

The chemical induced micronuclei in mouse bone marrow *in vivo* at a toxic dose. In rat bone marrow it did not induce chromosomal aberrations *in vivo*. An *in vivo* SCE test was weakly positive in bone marrow cells of Chinese hamsters. DNA strand breaks were observed in liver, kidney and brain of mice. 1-Chloro-4-nitrobenzene is consequently capable of expressing mutgenic activity *in vivo* with low potency.

A combined chronic toxicity/carcinogenicity study (OECD Guideline 453) with 1-chloro-4-nitrobenzene in rats produced an increased incidence in interstitial cell tumours of the testes which were within the range of the historical control data and evaluated as not compound related. These tumours were described in literature as common tumours in male Sprague-Dawley rats. In another rat study which doesn't meet the criteria of today and is reported in brief, no tumours were found. In the available study with mice which doesn't meet the criteria of today and is only reported in brief, vascular tumors (localization not specified) were found. This tumor type is not uncommon in the substance class of substituted amino- or nitrobenzenes. Overall, taking into consideration the results of the genotoxicity tests and the limitations in the available long term studies, a carcinogenic potential cannot be ruled out.

Toxicity to reproduction of 1-chloro-4-nitrobenzene has been examined in rats and mice by oral administration. In a two generation study with rats [OECD guideline 416] no impairment of fertility was observed up to 5 mg/kg bw (high dose group), nevertheless, at this dose histopathological effects in testes were observed. But the evaluation of the effect on the male reproductive tract is limited because the testes in the low and mid dose group were not examined histopathologically. Therefore a NOAEL (male reproductive organ toxicity) was not established. The NOAEL for general toxicity of adults was not achieved. A LOAEL (adults) of 0.1 mg/kg bw/day based on histopathological effects in the spleen of F1 adults is indicated. The NOAEL for general toxicity of offspring is 0.1 mg/kg bw/day. In mice a study was performed using the NTP continuous breeding protocol. The NOAEL (fertility) is 125 mg/kg bw/day, the LOAEL (offspring general toxicity) is 62.5 mg/kg bw/day. The NOAEL (adult general toxicity) is 125 mg/kg bw/day, but full evaluation is not possible because evaluation of the animals of the two lower groups were very limited. Two subchronic inhalation studies with rats and mice with histopathologic evaluations on reproductive organs are available. There was evidence of decreased spermatogenesis (24 ppm) and decrease in average estrous cycle length in rats exposed to 1-chloro-4-nitrobenzene (6 ppm and above). In female mice an increase in estrous cycle length was noted at the highest exposure group (24 ppm).

Developmental toxicity of 1-chloro-4-nitrobenzene has been examined in rats and rabbits by oral administration [OECD TG 414]. In rats, a NOAEL for maternal toxicity was not achieved, the LOAEL(maternal toxicity) is 5 mg/kg bw/day; the NOAEL (developmental toxicity) is 15 mg/kg bw/day. The study with rabbits suffered from methodology deficiencies. Due to high mortality rate at the highest dose level, only two doses could be evaluated: the LOAEL (maternal toxicity) is 5 mg/kg bw/day and the LOAEL (developmental toxicity) is 5 mg/kg bw/day. Thus, in both species developmental toxicity occurred in the presence of maternal toxicity.

There are indications of immunotoxic potency following single and repeated applications of 1-chloro-4-nitrobenzene.

Environment

1-Chloro-4-nitrobenzene has a melting point of 83 °C, a solubility in water of 243 mg/l at 20 °C, and a vapour pressure of 8.5 Pa at 20°C. The measured log Kow is 2.39. The flash point is ca. 127 °C.

According to Mackay fugacity model level I the main target compartments for 1-chloro-4-nitrobenzene are air (65%) followed by water (33%). A measured Henry constant of 0.5 $Pa \cdot m^3 \cdot mol^{-1}$ indicates a moderate potential for volatilization of 1-chloro-4-nitrobenzene from aqueous solution. It is expected that in the atmosphere a degradation of 1-chloro-4-nitrobenzene occurs due to indirect photolysis ($t_{1/2air}$: ca. 62 days) and direct photolysis. 1-Chloro-4-nitrobenzene is not readily biodegradable. Various tests showed adapted cultures to degrade 1-chloro-4-nitrobenzene. However, the degradation was inhibited at concentrations ≥ 8 mg/l. For *Pseudomonas putida* a O_2 consumption test resulted in a EC10 (30 min) of 59 mg/l. Bioconcentration factors determined for fish were in the range of 5.8– 20.9 and thus indicate no significant bioaccumulation potential of 1-chloro-4-nitrobenzene. A calculated Koc (Koc=309) suggests the substance to have a medium geoaccumulation potential.

Concerning the toxicity of 1-chloro-4-nitrobenzene towards aquatic species reliable experimental results of tests with fish, daphnia, and algae are available. The acute toxicity determined for fish (*Brachydanio rerio*) was of 14.36 mg/l (96 h LC50) and 2 mg/l (48 h) for *Leuciscus idus* and for daphnia (*Daphnia magna*) of 2.7 mg/l (48 h-EC50). In the growth rate tests with algae (*Scenedesmus subspicatus)* the values 4.9 mg/l (48 h-ErC10) and 16 mg/l (48 h-ErC50) were achieved while for *Chlorella pyrenoidosa* an effect value of 4.9 mg/l (96h-EC50) was found.

The prolonged toxicity to fish (*Brachydanio rerio)* for the endpoint sub-lethal effects (feeding, malposition) was evaluated through a 14 days test and a NOEC value of 1.53 mg/l was determined.

Two chronic tests with Daphnia (*Daphnia magna*) are available that were performed with analytical monitoring of the test substance concentration. In one test a 21 d-EC_{10} of 0.103 mg/l (effective concentration) was observed for the endpoint reproduction rate. The second test resulted in a 21d-NOEC of 0.19 mg/l (effective concentration) for the same endpoint. Calculating the geometric mean of these two values gives a NOEC of 0.14 mg/l. A PNECaqua = 2.8 µg/l is derived from this value, using an assessment factor of 50.

Exposure

About 220,900 tons 1-chloro-4-nitrobenzene were produced by about 30 producers worldwide in 1995 (excluding Eastern Europe). All 1-chloro-4-nitrobenzene is a basic chemical for the synthesis of intermediates which are further processed to pharmaceuticals, plant protection agents, auxiliaries in the rubber and plastics industry, dyestuffs/pigments, and others within the chemical industry. A direct use is not known.

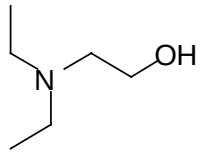
RECOMMENDATION

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 the Sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-37-8
Chemical Name	2-Diethylaminoethanol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

2-Diethylaminoethanol was rapidly absorbed via the oral route. It is presumably absorbed by dermal and inhalation routes of administration. In the rat it was widely distributed to many tissues. It was primarily excreted unchanged via the urine in rats. Excretion via the feces was also observed in rats, but to a lesser extent. Urinary excretion was also reported in humans. The major metabolites in rats were reported to be diethylaminoacetic acid and diethyl-(2-hydroxyethyl)-amino-oxide.

The LD_{50} for the rat after oral administration was 1320 mg/kg bw. The main clinical signs described were apathy and dyspnea. After inhalation of vapors of 2-diethylaminoethanol an LC_{50} of ca. 4600 mg/m^3/4 hour was estimated in rats using Haber's rule. Severe signs of irritation were observed, e.g. mucous membrane irritation and dyspnea. A dermal LD_{50} in guinea pigs was reported to be ca. 885 mg/kg bw.

2-Diethylaminoethanol was corrosive to the skin of rabbits; since the pH was measured to be 11.5 (100 g/l) at 20°C, the corrosive effects are not surprising. The potential for severe damage to the eyes can be expected based on the animal studies available and on the pH. 2-Diethylaminoethanol was not sensitizing to the skin in studies with guinea pigs.

Repeated exposure of rats to 2-diethylaminoethanol vapors (up to 365 mg/m^3) for 14 weeks caused local toxicity (irritation) at the site of contact, namely, the upper respiratory tract and the eyes; however, systemic toxicity was not observed (NOAEC, systemic toxicity, 365 mg/m^3 or 76 ppm). After inhalation exposure, the main symptom described was respiratory irritation which led to noises called rales and irritation of the eyes. The LOAEC for local toxicity (irritation) to the respiratory tract was 120 mg/m^3 (25 ppm) and the NOAEC for local toxicity was 53 mg/m^3 (10 ppm) based on histopathological effects in the nasal cavity. However, since an effect (rales) was seen at the lowest concentration a NOEC was not reached.

2-Diethylaminoethanol gave no evidence of *in vitro* mutagenic activity nor *in vivo* clastogenic potential.

Repeated exposure of rats to 2-diethylaminoethanol vapors (365 mg/m^3) for 14 weeks did not cause any adverse effects on the reproductive organs when administered by inhalation. In pregnant rats even the highest concentration tested of 486 mg/m^3, which already produced maternally toxic effects, did not lead to adverse developmental effects.

In a limited study, 2-diethylaminoethanol was not carcinogenic to rats when given by feed (tested up to ca. 50-400 mg/kg/d).

An odor threshold of 0.011 ppm (approx. 0.053 mg/mg^3) has been reported. In a laboratory worker short-time

exposure to approx. 100 ppm (480 mg/m^3) 2-diethylaminoethanol caused nausea and vomiting. Subjects exposed to 2-diethylaminoethanol vapor by humidified air in office buildings complained about eye, nose and throat irritation, dizziness, nausea and vomiting. Also several cases of asthma were observed. However, these symptoms were more consistent with reactive airway dysfunction syndrome than with an allergic respiratory reaction. In one case detectable amounts of 2-diethylaminoethanol were 0.05 and 0.04 mg/m^3.

Environment

2-diethylaminoethanol is a colourless – light yellowish organic liquid. The hygroscopic substance is miscible with water in all proportions, has a vapor pressure of about 1.8 hPa at 20 °C. The density is 0.885 g/cm³. Melting point and boiling point are – 68 °C and 162-163 °C (at 1013 hPa) respectively.

The distribution of the substance between the compartments of air, biota, sediment, soil and water was calculated according to Mackay Level I. The non-charged molecule distributes mainly to the water (99.1 %).

A soil adsorption coefficient (K_{OC}) of 5.98 was estimated for 2-diethylaminoethanol (DEAE). This Koc value suggests that this compound would be mobile in soil and adsorption to suspended solids would not be important. From the pKa-value of 9.87 it can be assumed that under environmental conditions the substance is available as acation. 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 calculated Henry's law constant ($3.16*10^{-4}$ Pa m³ mol^{-1} at 25 °C) and complete water solubility of 2-diethylaminoethanol suggest that volatilization from water would not be an important fate process. The substance has no considerable potential for bioaccumulation (log Kow = 0.21, measured). The compound is readily biodegradable (OECD 301 A, 95% after 22 days 10d-window fulfilled). The EC_{20} (30 min) for activated sludge was determined to be >1000 mg/l. The photodegradation rate in the atmosphere is fast under environmental conditions (50% after 3.9 hours).

The following aquatic effect concentrations are available:

Leuciscus idus LC_{50} (96 h) = 147 mg/l (nominal concentration). The toxic effect may be (partly) due to the high pH of the non-neutralized test solutions, since the pH adjusted 1000 mg/l dose group tolerated the substance for 96 h without mortality.
Pimephales promelas LC_{50} (96 h) = 1780 mg/l (measured concentration, adjustment of pH)
Daphnia magna: EC_{50} (48 h) = 83.6 mg/l (nominal concentration) (toxicity due to pH effects cannot be excluded)
Daphnia magna EC_{50} (48 h) = 165 mg/l (nominal concentration, adjustment of pH)
Scenedesmus subspicatus: E_rC_{50} = 44 mg/l, with a NOEC of 5 mg/l (corresponding values for biomass are 30 and 5 mg/l respectively; nominal concentration).

Using the aquatic toxic effect on the most sensitive species, *Scenedesmus subspicatus*, of 44 mg/l for the endpoint growth rate (30 mg/l endpoint biomass) a $PNEC_{aqua}$ of 44 µg/l is derived by applying an assessment factor of 1000. This factor is justified, because only short-term toxicity values were available.

The following terrestrial effect concentration was reported:

Chrysanthemum morifolium cultivar "Indianapolis white" EC_{50} (22 d) = 0.12 mg/l (in the nutrient solution; endpoint: chlorosis; nominal concentration). However, no PNECsoil can be derived from this result as no soil concentration is given.

Exposure

The production volume of this chemical at BASF, Germany, was more than 1000 tons in 2000. No information about the worldwide production volume is available.

The organic compound is used for the synthesis of pharmaceuticals and as a catalyst in the synthesis of polymers in the chemical industry. It is also used as a pH stabilizer. According to Swiss, Danish and Swedish Products Registers

and the Hazardous Substances Data Bank, 2-diethylaminoethanol is contained in a large number of products. Some of them may be available to consumers.

Releases into the environment are likely to occur during the production and processing of 2-diethylaminoethanol as an intermediate, as well as from the use of the substance itself and use of products containing the substance.

Assuming worst case conditions, less than 9.5 kg of 2-diethylaminoethanol per day were released into the Rhine from an industrial site. During production and internal processing, less than 25 kg/a were emitted into the air from the same production site. From the reported use in consumer products, it can be concluded that most of the 2-diethylaminoethanol is released into wastewater, but part of it may also be released into the atmosphere.

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. Due to the corrosive potential, exposure to humans at the workplace and from consumer products has been regulated in the sponsor country. However, if this is not the case in other countries, further exposure assessment and, if necessary, risk assessment are recommended.

Environment: In addition to its use as chemical intermediate, European product registers indicate a wide dispersive use of 2-diethylaminoethanol. No information is available about the total production volume and about total environmental releases. However, the low aquatic toxicity, the low bioaccumulation potential and the ready biodegradability lead to the recommendation, that the chemical is currently of low priority for further work

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	10043-52-4
Chemical Name	Calcium chloride
Structural Formula	$CaCl_2$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Calcium chloride is easily dissociated into calcium and chloride ions in water. The absorption, the distribution and the excretion of the ions in animals are regulated separately. Both ions are essential constituents of the body of all animals. Calcium is essential for the formation of skeletons, neural transmission, muscle contraction, coagulation of the blood, and so on. Chloride is required for regulating intracellular osmotic pressure and buffering.

The acute oral toxicity is low: LD_{50} in mice is 1940-2045 mg/kg bw, 3798-4179 mg/kg bw in rats, and 500-1000 mg/kg bw in rabbits. The acute oral toxicity is attributed to the severe irritating property of the original substance or its high-concentration solutions to the gastrointestinal tract. In humans, however, acute oral toxicity is rare because large single doses induce nausea and vomiting. The dermal acute toxicity is negligible: LD_{50} in rabbits >5000 mg/kg bw. No significant change was found by gross necropsy examination except skin lesions at or near the site of administration. Hypercalcemia may occur only when there exists other factors that alter calcium homeostasis, such as renal inefficiency and primary hyperthyroidism.

Irritation/corrosiveness studies conducted under OECD test guidelines indicate that calcium chloride is not/slightly irritating to skin but severely irritating to eyes of rabbits. Prolonged exposure and application of moistened material or concentrated solutions resulted in considerable skin irritation, however. Irritating effect of the substance was observed in human skin injuries caused by incidental contact with the substance or its high-concentration solutions.

A limited oral repeated dose toxicity study shows no adverse effect of calcium chloride on rats fed on 1000-2000 mg/kg bw/day for 12 months. Calcium and chloride are both essential nutrients for humans and a daily intake of more than 1000 mg each of the ions is recommended. The establishment of the ADI for calcium chloride has not been deemed necessary by JECFA (Joint FAO/WHO Expert Committee on Food Additives). Considering further the well-established metabolism and mechanisms of action of calcium and chloride ions in the human body, no further study is considered necessary for this endpoint.

Genetic toxicity of calcium chloride was negative in the bacterial mutation tests and the mammalian chromosome aberration test.

No reproductive toxicity study has been reported. A developmental toxicity study equivalent to an OECD Guideline study, on the other hand, reveals no toxic effects on dams or fetuses at doses up to 189 mg/kg bw/day (mice), 176 mg/kg bw/day (rats) and 169 mg/kg bw/day (rabbits). In view of the nutritional aspects, the metabolism, and the mechanisms of action of calcium and chloride ions, no further study is considered necessary for these endpoints.

Environment

Calcium chloride's vapour pressure is negligible and its water solubility is 745 g/L at 20°C. Calcium chloride is readily dissociated into calcium and chloride ions in water. These physico-chemical properties indicate that calcium chloride released into the environment is distributed into the water compartment in the form of calcium and chloride ions.

Acute toxicity studies (lowest effect values) reveal a 72-hour EC_{50} of 2900 mg/L for algae (*Selenastrum capricornutum*), a 48-hour EC_{50} of 1062 mg/L for daphnids (*Daphnia magna*) and a 96-hour LC_{50} of 4630 mg/L for fish (*Pimephales promelas*).

The chronic toxicity study with *Daphnia magna* shows that a 16% impairment of reproduction (EC_{16}) is caused at the concentration of 320 mg/L. The 72-hour EC_{20} for *Selenastrum capricornutum* determined by the OECD TG 201 study is 1000 mg/L. All the data compiled on the acute and chronic toxicity are greater than 100 mg/L.

Calcium is known as an essential nutrient for higher plants and one of the basic inorganic elements of algae. Calcium plays crucial roles in strengthening cell walls and plant tissues, reducing the toxicity of soluble organic acids, elongating roots, and so on. Chloride is also an essential micronutrient for plants and has important roles in the photosynthesis and osmoregulation.

Deicing agents used as road salts are usually chloride salts, mainly sodium chloride or calcium chloride with minor amounts of magnesium chloride and potassium chloride. The primary cause of the damage to roadside plants is considered to be the accumulation of chloride in plant tissues to a toxic level by excess loading of inorganic chloride salts.

Calcium chloride constituted 2% of the total composition (approx. 5 million tonnes) of deicing agents used in Canada in the 1997-1998 winter season, while sodium chloride constituted 95% of the total. In addition, there is a report that shows the uptake of chloride by plants is considerably inhibited in the presence of calcium chloride. The impact of calcium chloride on plants is expected to be minimal compared to other chloride-containing agents, given the factors discussed above as well as the difference of usage of calcium chloride as compared to sodium chloride.

Exposure

The production capacity of calcium chloride in North America was reported in 2002 to be approximately 1,687,000 tonnes per year. The estimated production volume in Japan was approximately 245,000 tonnes in 2000. The total amount used in Western Europe including Scandinavia is around 300,000 tonnes per year.

Calcium chloride is produced in the closed system by refining of natural brine, by ammonia soda process as a by-product or by neutralization reaction of limestone with hydrochloric acid. Commercial products are supplied as flakes, pebbles, pellets, powders and solutions with varying concentrations. Calcium chloride is used for deicing, road stabilization, dust control, accelerator in concrete, industrial processing, oil and gas well fluids, and for others such as food additives and medication.

Almost half of the volume of calcium chloride is consumed as deicing agents and road stabilizers, and directly released into the environment, where the substance is dissociated into calcium and chloride ions. In the 1997-1998 winter season, 5 million tonnes of road salts including sodium chloride (95%), calcium chloride (2%), magnesium chloride, potassium chloride and ferrocyanide salts were used in Canada. Based on the global water quality monitoring conducted by UNEP, the mean, 10th-percentile and 90th-percentile of calcium concentrations in 76 rivers were 37.4, 5.1 and 86.5 mg/L, respectively. In addition, the mean, 10th-percentile and 90th-percentile of chloride concentrations in 77 rivers were 41.1, 1.1 and 64.8 mg/L, respectively. It should be noted that both the concentrations of calcium and chloride ions are tightly related to various factors, such as geological parameters, weathering and human activities.

As for human exposure, oral intake is expected via foods that contain calcium chloride in the dissociated form as food additives or as residues of food processing agents. There is potential for exposure to workers and consumers via skin contact and dust inhalation at working places or elsewhere by versatile uses such as road stabilizers.

RECOMMENDATION

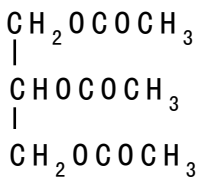
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

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

Because of the effects of calcium chloride on soil dwelling organisms and plants and the exposure associated with the use of calcium chloride as a deicing agent in some countries, these countries may decide to assess the environmental risk related to this exposure scenario.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	102-76-1
Chemical Name	Triacetin
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Triacetin is readily hydrolyzed to free glycerol and acetic acid, when incubated with rat intestine *in vitro*. The chemical infused in dogs undergoes intravascular hydrolysis and the majority of the resulting acetate is oxidized nearly quantitatively.

The acute oral and dermal toxicity of triacetin are very low: in an oral acute toxicity study in rats [OECD TG 401], a limit dose of 2,000 mg/kg bw caused no mortality and no signs of systemic toxicity during the 14-day observation period. The LD_{50} in rats by gavage is determined to be >2,000 mg/kg bw for both sexes, and dermal LD_{50} in rabbits and guinea pigs were >2,000 mg/kg bw. Acute inhalation toxicity is considered to be very low, since the LC_{50} in an acute inhalation toxicity study in rats was >1,721 mg/m^3 for both sexes [OECD 403] and repeated daily exposure of rats to 73,700 mg/m^3 produced no sign of toxicity after 5 days.

In an oral study in rats by the OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], animals received gavage doses of 0 - 1,000 mg/kg bw/day of triacetin for 44 days from 2 weeks prior to mating for males and for 41 - 48 days from 14 days before mating to day 3 postpartum for females. Triacetin had no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. There were no abnormalities in haematological or blood chemical parameters in males. The NOAEL for repeated dose oral toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes.

An inhalation study was conducted in rats given triacetin for 90 days at a dose of 249 ppm (2,220 mg/m^3) under non-GLP condition. No toxic signs were noted during the exposure. The NOAEL is considered to be 249 ppm (2,220 mg/m^3) for 90 days. Although the inhalation study is considered to be useful, it does not fully comply with the current testing protocol.

The combined repeated dose and reproductive/developmental toxicity study in rats at doses of 0 - 1,000 mg/kg bw/day [OECD TG 422] showed no statistically significant adverse effects on reproductive parameters including the mating index, fertility index, gestation length, numbers of corpora lutea and implantations, implantation index, gestation index, delivery index, parturition and maternal behavior at delivery and lactation. In addition, there were no significant differences in numbers of offspring or live offspring, the sex ratio, the live birth index, the viability index or body weight. Developmental toxicity, clinical signs of toxicity, and change in necropsy findings were not found in offspring. Therefore, the NOAEL is considered to be 1,000 mg/kg bw/day for parental animals and offspring.

Triacetin did not induce gene mutation in bacteria at concentrations up to 5,000 ug /plate (OECD TG 471 and 472).

Induction of chromosome aberrations, however, was observed in the Chinese hamster cultured cells only at the highest concentration (2.2 mg/mL, 10 mM) in the presence of an exogenous metabolic activation system (OECD TG 473). Because of high toxicity (75 %) that might be caused by low pH (4.9) at the end of the treatment, the chromosomal aberration observed might not be biological relevant. Under un-physiological culture condition, such as low pH, it was reported that the frequency of chromosomal aberrations could be increased. Polyploidy was not induced under any of the conditions tested. Taking all data into consideration, triacetin could be considered to be non-genotoxic.

Triacetin is not irritating to skin [OECD TG 404] and to eyes [OECD TG 405] in rabbits. There is no skin sensitisation in guinea pigs by triacetin. In the tests using human volunteers, triacetin induced no skin irritation or skin sensitization. However, one case concerning allergic contact eczema caused by triacetin has so far been reported in a cigarette factory.

Based on the available data and anticipated daily intake (7.8 mg/day/adult), triacetin and a group of related triglyceride did not represent a hazard to human health (JECFA, 1975, Commission, 1992 and SCF, 1995). Triacetin was given GRAS status by FEMA (1965) and is approved by the FDA for human food use.

Environment

Triacetin is a liquid with a boiling point of 258 °C and vapour pressure of 0.003306 hPa at 25°C. It is soluble in water (70 g/L at 25°C) and miscible with alcohols, aromatic hydrocarbons and diethyl ether.

The generic fugacity model (Mackay Level III Fugacity Model) shows that triacetin will be distributed mainly to water if it is released into water, whereas approximately one third and two third of the chemical will stay in water and soil, respectively when released at equal amounts to water, soil and sediment (1:1:1). An estimated Henry's law constant of 1.23×10^{-8} atm m^3/mol indicates that the compound is essentially non-volatile from water.

The rate constant for the vapour-phase reaction with photochemically produced hydroxyl radicals has been estimated to be 7.81×10^{-12} cm^3/molecule sec at 25°C, which corresponds to an atmospheric half-life of about 48 hours at an atmospheric concentration of 5×10^5 hydroxy radicals/cm^3.

Triacetin is readily biodegradable (OECD TG 301C: 77 % after 14 days based on BOD, OECD TG 301B: 93 % after 28 days based on $ThCO_2$, OECD TG 301D: 79 % after 30 days based on BOD). The chemical is expected to have a low potential for bioaccumulation based on a low Log Pow (0.21).

The half-lives in water at pH 7 and 9 are estimated to be 60.4 days and 16.5 hours at 25 °C, respectively, whereas no hydrolysis at pH 4 occurs at 50 °C in 5 days. Triacetin is expected to have high soil mobility and may leach readily in soil based on Koc value of 10.5 from a regression-derived equation. Therefore, aqueous hydrolysis may be a major degradation process for triacetin in moist alkaline soils.

The 72-h toxicity of triacetin to alga (growth inhibition, *Selenastrum capricornutum*) is > 1,000 mg/L for EC_{50} and 556 mg/L for NOEC [OECD TG 201]. In *Daphnia magna*, EC_{50} values (48 h) for acute toxicity [OECD TG 202] are 768 mg/L, 810.9 mg/L and 380 mg/L, while the NOEC (21-d reproduction) for chronic toxicity [OECD TG 211] is 100 mg/L. The acute toxicity to fish is > 100 mg/L (Medaka; *Oryzias latipes*) and 165.3 mg/L (Fathead minnow; *Pimephales promelas*) for 96 h LC_{50} [OECD TG 203]. The prolonged toxicity to fish (Medaka; *Oryzias latipes*) is 100 mg/L for 14 d LC_0 [OECD TG 204].

Exposure

Triacetin is manufactured in a closed reaction system. The production volume in Japan is approximately 5,000 tonnes/year, while the estimated global production is 10,000-50,000 tonnes/year. Commercially available triacetin contains less than 0.1 % of diacetin and 0.01 % of monoacetin. Since triacetin produced in Japan is used industrially in a variety of applications including a solvent for basic dyes, fixative in perfumery, food additive, pharmaceuticals, CO_2 remover from natural gas and in manufacture of cigarette filters, celluloid, photographic films etc., in consumer products as well as at industrial sites, both workplace and consumer exposure has to be assumed according to the

following three scenarios.

(1) Occupational exposure: inhalation and dermal route during operations such as cleaning of strainers, sampling, analysis and drum filling.
(2) Consumer exposure: intake and dermal/inhalation route in food additive and topical antifungal or perfume fixative and cigarette filter.
(3) Environmental exposure: emission to aquatic compartment from waste water and evaporative emissions associated with its use in the perfume and cosmetic industries and its use as a solvent and CO_2 remover from natural gas, and disposal of consumer products containing triacetin.

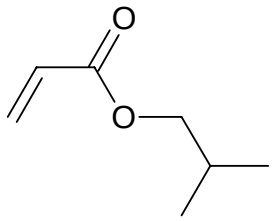
RECOMMENDATION

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 because of its low hazard potential.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-63-8
Chemical Name	Isobutyl acrylate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

n-Butyl acrylate (CAS No. 141-32-2) will be used as an analog for iso-butyl acrylate based on structural similarities. A comparison of the experimental data on both chemicals for toxicokinetics, acute toxicity, corrosiveness and irritation, and genetic toxicity (*in vitro* and *in vivo*) further supports the analogy. Data on n-butyl acrylate will be used to address the repeated-dose, reproduction, and developmental toxicity endpoints. In addition, it will be used to supplement existing acute aquatic toxicity data.

Human Health

Results from an *in vitro* study indicate that iso-butyl acrylate is rapidly hydrolyzed to acrylic acid and alcohol by porcine hepatic esterases in phosphate buffer. The rate of this reaction is comparable to the hydrolysis of n-butyl acrylate.

Acute toxicity data on rats and rabbits are available for iso-butyl acrylate. In the three oral studies in rats, the LD50 were 4895 mg/kg bw (narcosis, staggering, apathy, lateral position), 6292 mg/kg bw (heavy breathing at 17800 mg/kg bw), and 6639 mg/kg bw (no clinical symptoms). In two acute rat inhalation (vapor) studies, the 4-hour LC50 values were 10.6 mg/L and 15 mg/L. Two acute dermal toxicity studies in rabbits indicate LD50 of 800 mg/kg bw (occlusive) and 4000 mg/kg bw (semi-occlusive).

Undiluted iso-butyl acrylate is irritating to rabbit skin and slightly irritating to rabbits eyes. Vapors of the material are irritating to the skin, eyes, and the respiratory tract. Though there is no evidence for a sensitizing effect from a study with a limited number of patients, iso-butyl acrylate should be considered as a potential sensitizing agent based on its structural similarity to n-butyl acrylate, a known sensitizer in animals and humans.

Iso-butyl acrylate has not been tested in repeated dose studies. In an n-butyl acrylate oral (drinking water) 90-day study in rats, using a satellite group (gavage) at 150 mg/kg/day, the only effects reported were a slight reduction in water consumption in all dose groups and a decrease in body weight gain in the highest dose group. The NOAEL (males) = 84 mg/kg bw/day and NOAEL (females) = 111 mg/kg bw/day. The NOAEL (gavage) (males and females) = 150 mg/kg bw/day. In a 90-day inhalation study rats were exposed to n-butyl acrylate, at 0, 21, 108, 211, and 546 ppm (0, 0.11, 0.57, 1.12, 2.90 mg/L). The primary effects at 211 ppm (1.12 mg/L) were irritation of eyes and nasal mucosa, reduced body weights (13.3 percent in males and 3.76 percent in females compared with controls), decreased potassium values (females) and an increase in alkaline phosphatase activity (females). At the highest dose of 546 ppm (2.90 mg/L), 31 of 40 animals died. The primary cause of death was due to the severe irritation of the

respiratory tract. The NOAEL = 108 ppm (0.57 mg/L/day) and the LOAEL = 211 ppm (1.12 mg/L/day). In a two–year inhalation study on n-butyl acrylate, rats (male/female) received whole body exposures of 0, 15, 45, or 135 ppm (0, 0.086, 0.258, 0.773 mg/L). There was a slight decrease in food consumption and slightly lower relative heart, kidney, liver and thyroid weights at the highest dose. A NOAEL was determined to be 45 ppm (0.258 mg/L/day) based upon localized and diffuse stippling of the corneal epithelium, cloudiness of the cornea, and various degrees of vascularization. The severity of nasal mucosa effects increased with dose and occurred at all doses in males and females. Effects ranged from slight atrophy of the neurogenic part of the olfactory epithelium at 15 ppm (0.086 mg/L) to partial loss of the columnar cell layer and stratified reserve-cell hyperplasia at 45 and 135 ppm (0.258 and 0.778 mg/L, respectively).

Iso-butyl acrylate was not mutagenic in the Ames assay, both with and without metabolic activation, when tested up to cytotoxic concentrations. *In vivo*, iso-butyl acrylate did not induce chromosome aberrations in a mouse bone marrow micronucleus test.

No carcinogenicity studies are available for iso-butyl acrylate. However, n-butyl acrylate was not carcinogenic to rats via inhalation up to 135 ppm (0.773 mg/L/day).

No reproductive or developmental toxicity studies are available for iso-butyl acrylate. However, repeated-dose studies (noted above) using n-butyl acrylate showed no effects in the reproductive organs. In developmental toxicity studies with rats via inhalation, n-butyl acrylate caused fetotoxic effects (resorptions and reduced number of live fetuses at $\geq$135 ppm) at maternally toxic concentrations. Following exposures of 25, 135 and 250 ppm, the NOAEL (maternal) = 25 ppm, based on reduced body weights and irritation to the eyes and nose; the NOAEL (developmental) = 25 ppm, based on post-implantation loss; and the NOAEL (teratogenicity) = 250 ppm. In a separate study, pregnant female rats were exposed to 100, 200 and 300 ppm n-butyl acrylate during gestation. A NOAEL for maternal toxicity could not be determined based on a reduction of absolute body weight gain at all doses. At 200 and 300 ppm there was a reduction in fetal body weights. Sporadic malformations occurred at 300 ppm and in the control group. The developmental NOAEL was 100 ppm and the NOAEL for teratogenicity was 300 ppm, the highest dose tested.

Environment

Iso-butyl acrylate is soluble in water at 2 g/L (25 °C), has a specific gravity of 0.89 g/cm^3 at 25 °C, and a log K_{ow} of 2.22. The vapor pressure is 9.34 hPa at 25 °C, and the melting point and boiling point are – 61°C and 139°C, respectively. Iso-butyl acrylate is indirectly photodegraded by reaction with hydroxyl radicals in the atmosphere with an estimated half-life of approx. 28 hours (calculated). Distribution modeling using Mackay Level I, indicates that iso-butyl acrylate is likely to partition mainly into the air (95.3 %) with smaller amounts partitioning into water (4.6 %) and negligible amounts distributing into other environmental compartments (0.05 % in soil and sediment, each.) The Level III fugacity model was run using TRI release data available for n-butyl acrylate. Results were comparable with Level I results. Level III modeling results are as follows: air 90.1 %, water 7.85 %, soil 2 % and sediment 0.0856 %. In a biodegradation test (according to ISO 14593), iso-butyl acrylate was degraded 71 % after 7 days and 89% after 14 days, showing that it is readily biodegradable. Based on a log K_{ow} of 2.22 and a calculated BCF of 10.22, the potential for bioaccumulation is expected to be low. HYDROWIN modeling gives a hydrolysis half-life of 16.5 years at 25°C and pH=7.

Acute aquatic toxicity studies are available for iso-butyl acrylate in fish, daphnia and algae. The most sensitive species was the freshwater fish *Pimephales promelas* (fathead minnow) with a 96-hour LC50 of 2.09 mg/L (measured). The 48-hour EC50 for *Daphnia magna* is 9.7 mg/L (nominal), and for algae (*Desmodesmus subspicatus)* the 72-hour EC50s were 3.18 mg/L (measured) for biomass and 5.28 mg/L (measured) for growth rate. Results from prolonged or chronic studies are not available. No information is available on terrestrial effects. In addition, supporting data from n-butyl acrylate indicate toxicity values with in the same ranges. In acute aquatic toxicity studies, n-butyl acrylate was determined to have toxic effects in the concentration range of 2.1 to 8.2 mg/L. A measured fish 96-hr LC50 of 2.1 mg/L was determined in a flow-through test in *Cyprinodon variegates.* A measured aquatic invertebrate 48-hr EC50 of 8.2 mg/L was determined in a flow-through test in *Daphnia magna.* Finally, in algae (*Selenastrum capricornutum*) a growth-rate study using nominal concentrations resulted in a 96-hr EC50 of 5.2 mg/L.

Exposure

Iso-butyl acrylate is used as a co-monomer in the manufacture of polymers. Polymers made with iso-butyl acrylate are primarily used in surface coatings, in films and pressure sensitive adhesives, in dispersions, and construction materials. The worldwide annual production is in the range of 1000 to 10000 tonnes per year. Exposure may occur during manufacture, transportation and industrial use. Worker exposure is adequately controlled at the production plants in the US. As a result of polymerization, end-use products contain only trace levels of iso-butyl acrylate.

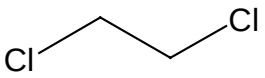
RECOMMENDATION

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 a low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-06-2
Chemical Name	1,2-Dichloroethane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,2-Dichloroethane has to be considered as harmful after inhalation and oral application and as uncritical after dermal exposure, based on the GHS system. LD_{50} values ranging from about 400 – 1000 mg/kg bw (oral), > 4000 mg/kg bw (dermal) and from approx. 4000 mg/m^3 (7 h) to >49,000 mg/m^3 (0.5 h). A respiratory 4-h NOAEL is approximately 1400 mg/m^3 in rats. However, a steep concentration-response relationship associated with sudden, often unexpected mortality is characteristic of 1,2-dichloroethane. Death is thought to occur through CNS (Central Nervous System) and cardiovascular depression.

Studies on primary irritation of the substance demonstrated a low irritation potential both to the skin and eyes. In contrast to other species tested, specifically dogs experienced corneal turbidity and oedema after single and repeated atmospheric exposure to systemically toxic concentrations (about 4000 mg/m^3), but not when exposed to lower ones.

No studies on contact allergy were located.

Several repeated dose toxicity studies following oral and inhalation exposure in rats and mice showed mild histopathological effects after inhalation in lung, liver and in the kidneys of rats and mice at high doses or, after gavage dosing, minimal local lesions of the kidney and the forestomach. A subchronic drinking-water study does not allow to derive a NOAEL because of the highly reduced water consumption by the test animals. The lowest NOAEL for subchronic oral exposure by gavage is assumed to be 120 and 150 mg/kg bw/d for male and female rats, respectively, based on treatment-related effects in the forestomach and clinical symptoms, while the chronic oral NOAEL of about 25 mg/kg bw is equivalent to the highest dose administered to rats for two years in the diet. For inhalation, studies are conducted on a broad spectrum of species. A two-year-study shows a NOAEL of 50 ppm in rats. At subchronic to chronic exposure to 200 ppm variable responses from unremarkable to toxic and lethal were observed even within the same species. Based on the GHS-system, 1,2-dichloroethane should be regarded as harmful following repeated inhalation exposure.

1,2-Dichloroethane is mutagenic and genotoxic in bacterial and mammalian *in vitro* test systems, but gave no evidence of *in vivo* mutagenic activity (mouse micronucleus and DL assay), while some *in vivo* genotoxic potential was demonstrated in mice. However, evidence of DNA damaging *in vivo* activity/genotoxicity is presented by positive results in SCE assay and single DNA strand-break analysis. The cytochrome-P450 and glutathione-dependent pathways are assumed to be responsible for the generation of intermediates capable of binding to and damaging DNA.

1,2-Dichloroethane was shown to produce carcinogenic effects at multiple sites in rats and mice of both sexes after oral gavage administration for 78 weeks (up to 195 and 300 mg/kg/d, respectively), but not after inhalation in both species exposed to a reasonably high concentration of 150 ppm (about 600 mg/m^3) for the same period of time. Based on the GHS-system, 1,2-dichloroethane has to be regarded as suspected human carcinogen. The route of application-specific expression of tumorigenesis may be explained by the difference in pharmacokinetics and

dominance of metabolic pathways under either dosing mode: Systemically toxic inhalation concentrations result in significantly lower blood and organ levels than toxic gavage doses and, therefore, are expected to be (hypothetically) less likely to form oncogenic intermediates.

There was no evidence of 1,2-dichloroethane-induced impairment of reproductive performance in rats and mice including fertility of either sex and fetal viability parameters after repeated oral doses of 50 mg/kg bw/d (feed and drinking water) and after inhalation exposure to up to 150 ppm in several one-and two-generation studies. Furthermore, no histopathological adverse effects on the gonads were reported in two oral long-term studies in rats and mice.

In Several investigations on developmental toxicity, no significant toxicity was noted in the offspring of rats receiving up to maternally toxic oral (gavage) and inhalation doses during pregnancy. The NOAELs for developmental effects were the highest doses employed, 240 mg/kg bw/d and 300 ppm, respectively.

In humans, incidental ingestion has been reported as cause of death; occupational dermal and inhalation exposure have produced marked systemic intoxication: primarily unspecific neurotoxic symptoms developed such as nausea, vomiting, headache, stupor, dysequilibrium, and - in fatal cases – coma followed by respiratory arrest. Severe cases also involved lesions of liver, kidney, and adrenal glands. High dermal and respiratory exposures caused skin and eye irritation. There have been no human case reports on skin sensitisation in the literature. In workers exposed to a mixture of vinyl chloride monomer (VCM) and 1,2-dichloroethane a statistically significant increase in SCE frequency of about 24 % in the higher exposed subgroup (20 individuals) was found. This increase was also obvious in non-smoking workers, and it was additionally shown that the SCE frequency was positively correlated with smoking but not with drinking habits and VCM exposure.

Environment

1,2-Dichloroethane has a water solubility of 8490 – 9000 mg/l, a vapor pressure of 81 hPa at 20°C and a log Kow of 1.45. According to a Mackay I model the atmosphere is the target compartment for the substance (~95 %), followed by water (~5 %). A Henry's law constant of 95.7 – 149 Pa $*$ m^3/mol was determined. Due to its chemical structure the substance will not undergo both hydrolysis in water and photodegradation by direct sun-light. A half-life of 42 to 73 days was calculated for indirect photodegradation by hydroxyl radicals in the atmosphere. Field measurements confirmed, that the photodegradation in the atmosphere prevents the global distribution and the atmospheric enrichment of emissions, released by industry mainly in the northern hemisphere.

1,2-Dichloroethane is not biodegradable under non-adapted test conditions but it could be demonstrated that appropriately adapted bacteria or enrichment with degradation promoting factors lead to acceptable and fast biodegradation rates. However, under environmental conditions biodegradation is not likely to occur. No potential for bioaccumulation (measured BCF = 2) or geoaccumulation (measured Koc = 33) could be identified. In acute and long-term ecotoxicity tests with aquatic organisms the following results were found:

LC_{50} (96 h)	= 66 mg/l (*Micropterus salmoides*)
LC_{50} (96 h)	= 115 mg/l (*Limanda limanda*)
EC_{50} (24 h)	= 36 mg/l (*Artemia salina*)
EC_{50} (24 h)	= 150 mg/l (*Daphnia magna*)
EC_{50} (72 h)	= 189 mg/l (*Scenedesmus subspicatus*)
NOEC (32 d)	= 29 mg/l (*Pimephales promelas*)
NOEC (28 d)	= 11 mg/l (*Daphnia magna*, Reproduction)

All effect values are based on measured concentrations or were performed in closed systems.

Taking into account the results of the different chronic toxicity studies conducted in aquatic organisms and considering the lowest valid NOEC of 11 mg/l obtained in a chronic aquatic toxicity reproduction test conducted in *Daphnia magna* a PNEC of 1100 µg/l is being derived applying a safety factor of 10.

Exposure

The worldwide production volume of 1,2-dichloroethane exceeds 1,000,000 tonnes/year. The main uses are as chemical intermediate in the vinylchloride monomer (VCM) manufacture with a contribution of about 95%. The remaining 5% of produced 1,2-dichloroethane enter applications such as raw materials for ethyleneamines, tri- and tetrachloroethylene, extraction and cleaning solvent as well as lead scavengers for gasoline. Due to the increasing use of unleaded fuel the latter application is assumed to subside gradually. 1,2-Dichloroethane emissions to the aquatic environment and to the atmosphere come nearly exclusively from manufacturing industrial locations and only to a minor extent from its use as extraction and cleaning solvent and as lead scavenger, respectively. It is not clear, however, whether 1,2-dichloroethane is still being used in aircraft gasoline.

Production and handling of 1,2-dichloroethane takes place in closed systems and it is directly transported via pipelines during filling processes, e.g. loading of tanker ships. In all countries with production plants occupational exposure limit values are established, during maintenance operations personal protection is mandatory.

In 1993 it was reported that 150 tonnes were emitted to the atmosphere during production and processing in Germany by 9 production and/or processing sites. Releases into the hydrosphere were estimated to be about 4.46 t for 7 producers/processors.

European Product Registers have several entries of paints and lacquers, adhesives and fertilizers containing 1,2-dichloroethane. But according to national laws these products are only available for professional use.

RECOMMENDATION

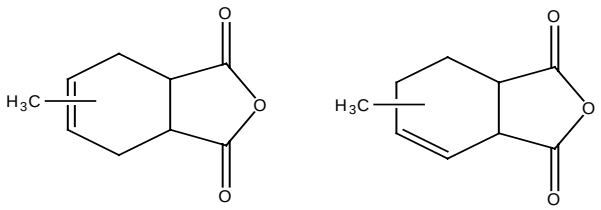
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The substance is currently of low priority for further work. Although hazardous properties have been identified for this substance (possible genotoxic and carcinogenic effects), the overall exposure in humans is low, as it is mostly used as a chemical intermediate. In some countries, where products for professional use containing 1,2-dichloroethane may still be available, further exposure assessment and if necessary risk assessment is recommended.

Environment: The substance is currently of low priority for further work. This can be concluded from the main use as chemical intermediate, the very low bioaccumulation potential and the low toxicity to aquatic organisms.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	11070-44-3
Chemical Name	Tetrahydromethyl-1,3-isobenzofuranedione
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

This chemical is a mixture of several chemical species as defined by the above described structure.

Human Health

There is no available information on metabolism or toxicokinetics of this substance in animals. This chemical is, nevertheless, known to metabolized to di-carboxylic acid and excreted in urine in human, when inhaled. $T_{1/2}$ for the excretion is estimated as ca. 3-6 hr.

In acute oral toxicity studies [OECD TG 401] in rats, the LD_{50} of tetrahydromethyl-1,3-isobenzofuranedione ranged from 1900 mg/kg to more than 2000 mg/kg. The major toxicity was inflammation of the forestomach, such as thickening of the forestomach mucosa, squamous hyperplasia and granulomatous inflammation.

In a primary irritation study [Federal Regulations, Title 16, Section 1500.41] with rabbits, this chemical was considered to be a moderate irritant to rabbit skin. In an eye irritation study with rabbits, this chemical is an irritant to eyes. There is no available information on sensitization in animals. Human epidemiological studies are available, showing that this chemical has sensitizing potential.

In the OECD combined repeat dose and reproductive/developmental toxicity screening test [OECD TG 422], this chemical was administered by gavage (male rats for 49 days, female rats from 14 days before mating to day 3 of lactation) at the dose levels of 30, 100 and 300 mg/kg/day. Salivation was transiently observed in males of the 300 mg/kg group after day 36 of treatment. Increased adrenal weights were observed in males of the 300 mg/kg group. Mucosal thickening of the forestomach was found in both sexes of the 300 mg/kg group. Squamous hyperplasia of the forestomach and submucosal granulomatous inflammation of the forestomach was observed in both sexes of the 300 mg/kg group. On the basis of these findings, the NOAEL of tetrahydromethyl-1,3-isobenzofuranedione was considered to be 100 mg/kg for both sexes.

In the above mentioned OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], no adverse effects were found in reproduction and development. The NOAEL for reproduction and development is considered to be 300 mg/kg/day.

Bacterial genotoxicity studies showed negative results in *S. typhimurium* and *E. coli* with and without metabolic activation. In a chromosomal aberration test conducted in cultured Chinese hamster lung (CHL/IU) cells [OECD TG 473], structural chromosomal aberrations were not induced up to 0.30 mg/ml. Polyploidy (1.13 %) was induced at 0.30 mg/ml with a 48 hr continuous treatment without metabolic activation, and, polyploidy (1.25-1.88 %) was

induced at 0.11-0.43 mg/ml in short-term treatment with an exogenous metabolic activation system. The limited evidence available indicates that this substance is not genotoxic.

Environment

The vapor pressure of tetrahydromethyl-1,3-isobenzofuranedione is estimated to be 0.0044 hPa at 25°C. When this chemical is released into water or other environment compartment it is rapidly and thoroughly hydrolyzed to the corresponding di-carboxylic acids. It is very water soluble (>10 g/L). The acidity of the hydrolysate results in pH=4.3 at 270 mg/L. The calculated log Kow for the original anhydride form is 2.4-2.6 and for a representative hydrolysates is 0.7-1.4. These hydrolysates are not readily biodegraded. The potential of bio-accumulation of these hydrolysates estimated to be low, because experimental BCF values of related substances are low and the calculated BCF for a hydrolysate is consistently low (BCF=21.2).

The effects of tetrahydromethyl-1,3-isobenzofuranedione in aquatic organisms were studied using the hydrolysate and the values obtained were expressed as anhydride. The chemical is hydrolysed to the corresponding dibasic acids at a rate determined by the mode of mixing with water.

In acute toxicity studies to aquatic species, the toxicity to daphnids [OECD TG 202] was 130 mg/l for EC_{50} (immobility in *Daphnia magna*, 48 hr). The toxicity to fish (Medaka) [OECD TG 203] was more than 100 mg/l for LC_{50} (96 hr). The prolonged toxicity to fish (Medaka)[OECD TG 204] was more than 100 mg/l for LC_{50} (14 d).

The toxicities of tetrahydromethyl-1,3-isobenzofuranedione to algae [OECD TG 201, *Selenastrum capricornutum*] were 55 mg/l for ErC_{50} (growth rate 24-48 h) and 64 mg/l for EbC_{50} (biomass, 72 hr), 27.5 mg/l for NOEC (growth rate 24-72 h) and 27.5 mg/l for NOEC (biomass, 72 h).

The chronic toxicity to daphnids [OECD TG 202 part 2] was 9.2 mg/l for EC_{50} (reproduction, 21 d) and 0.94 mg/l for NOEC (reproduction, 21 d).

Exposure

The production volume of tetrahydromethyl-1,3-isobenzofuranedione is estimated to be 8000 t/y in Japan and 20000 t/y world-wide in 2001. The producing countries are Japan, Italy, United States of America and People's Republic of China. In Japan, this chemical is produced in closed systems. The main use is as a hardener for epoxy resins. This substance is not usually released to the environment from the production and use site, except during sampling and maintenance. This chemical is hydrolyzed to several dicarboxylic acids in water. So, the potential environmental distribution was estimated for 4-methyl-4-cyclohexene-1,2-dicarboxylic acid, one of the hydrolysation products of tetrahydromethyl-1,3-isobenzofuranedione. The fugacity model (Mackey level III) suggests that if released to air, water and soil the majority of this hydrolyzed chemical would distribute into water and soil.

Occupational exposure at production sites and processing sites may occur by the inhalation and dermal route. This substance is classified as a "sensitizing substance" in Germany (List of MAK and BAT values 2000). The Japan society for occupational health recommended 50 ug/m^3 as a limit for this substance exposure during an 8 hr work shift.

Consumer exposure of this chemical is considered to be negligible.

RECOMMENDATION

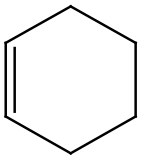
The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The sensitizing properties indicate a hazard for human health. No further work is recommended, if sufficient control measures in place to avoid significant human exposure, including prevention of accidental exposure. In situations where this is not the case, risk assessment and, if necessary, risk reduction measures are recommended.

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 for the environment. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-83-8
Chemical Name	Cyclohexene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

An oxidation of cyclohexene at the allylic position has been shown by *in vitro* studies but there is no detailed information *in vivo* regarding absorption, metabolism and excretion.

The oral acute toxicity of cyclohexene is low: the LD_{50} in rats is 1,000-2,000 mg/kg [OECD TG 401]. Some clinical signs including hypoactivity were observed. Dermal acute toxicity is negligible: the LD_{50} in guinea pigs is >16,220 mg/kg. Acute inhalation toxicity is very low: exposure of rats to 21,388 mg/m^3 produced no deaths. There is no reliable information on eye and skin irritation and sensitization.

According to a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], SD rats received gavage doses of 0, 50, 150 and 500 mg/kg b.w./day for 48 days in males and for 42-53 days from 14 days before mating to day 4 of lactation throughout the mating and pregnancy period in females. Salivation was observed for about 5 minutes after dosing in 3 of 12 males and 2 of 12 females at 150 mg/kg b.w./day and up to 6 hours after dosing all of 12 males and 12 females at 500 mg/kg b.w./day. Blood chemical examination showed a decrease in triglyceride in males at 150 and 500 mg/kg b.w./day, and increases in total bilirubin in males at 500 mg/kg b.w./day and in total bile acid in both sexes at 150 mg/kg b.w./day and more. In males of the 500 mg/kg b.w./day group, there was an increase in relative kidney weight. On histopathological examinations, no dose-related changes were observed. Therefore, the NOAEL for repeated dose toxicity was considered to be 50 mg/kg b.w./day for both sexes.

In a reverse gene mutation assay [OECD TG 471], this chemical was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *urv*A with and without exogenous metabolic activation. In a chromosomal aberration test [OECD TG 473], structural chromosomal aberrations and polyploidy were not induced with and without exogenous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells.

There is no data available on carcinogenicity.

Regarding the effects on the reproductive/developmental parameters, in the above-mentioned combined study [OECD TG 422], no effects of this chemical were observed on mating, pregnancy, delivery, lactation of parent animals and viability, body weight, general appearance and the autopsy finding of offspring. The NOAEL for reproductive/developmental toxicity was considered to be 500 mg/kg b.w./day.

Environment

Cyclohexene has a vapour pressure of 119 hPa (25degree C), a water solubility of 250 mg/L, a LogPow of 2.99. Its Henry's law constant is 4.55E-2 atm.m3/mol.

Cyclohexene is not readily biodegradable and its BCF is less than 45. In the air, this chemical is expected to be photodegraded ($T_{1/2}$= 1.4 hours) by ozone. Hydrolysis is not expected to occur.

In acute toxicity to aquatic organisms, for daphnid a 48hEC50 of 2.1 mg/L (*Daphnia magna*, OECD TG202, closed system) and for fish a 96hLC50 of 5.8 mg/L (*Oryzias latipes*, OECD TG 203 semistatic) and a 96hLC 50 of 12.4 mg/L (*Poecilia reticulata*,semistatic) have been reported.

Three chronic toxicity values from two trophic level species were available: a NOErC of 0.67 mg/L and a 72hNOEbC of 1.8 mg/L in algae (*Selenastrum capricornutum*, OECD TG 201, closed system) and a 21dNOEC of 0.53 mg/L in the daphnid (*Daphnia magna*, OECD TG 211, semistatic) on reproduction.

Exposure

Cyclohexene is used as an intermediate for the production of cyclohexanol and cyclohexeneoxide and as a solvent. The fugacity model (Mackay level III) suggests that if cyclohexene is released to one of the compartments of air, water and soil, it has a tendency to remain in the original compartment.

Occupational exposure to cyclohexene through inhalation and dermal routes is possible.

No information is available on consumer exposure.

RECOMMENDATION

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

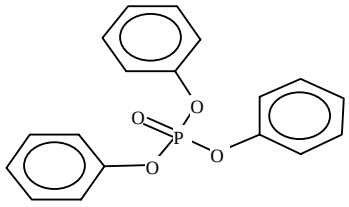
Environment: The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

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

Environment: There is no information available on the production volume or use as a solvent, and since the substance shows chronic toxicity to aquatic organisms, an environmental exposure assessment is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	115-86-6
Chemical Name	Triphenyl phosphate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Triphenyl-phosphate (TPP) is degraded by hydrolysis in rat liver homogenate to diphenyl-phosphate as the major metabolite. Acute toxicity after oral and dermal administration is very low: acute oral administration in rats, mice, rabbits and guinea pigs produced LD50 values in a range of 3000 to above 20 000 mg/kg bw. Only one study in mice with limited documentation gave a value of 1320 mg/kg bw. After dermal application an LD50 of above 7900 mg/kg bw was established in rabbits. No valid studies are available regarding the inhalation of triphenyl phosphate. Triphenyl phosphate is not irritant to the skin. The irritation potential of triphenyl phosphate on the mucous membrane of the eye is very low. No animal data regarding skin sensitisation are available. There are few human case reports showing evidence of skin sensitisation. The incidence of skin sensitisation is very low.

Based on the available data the toxicity after repeated oral treatment of rats with triphenyl phosphate was low. A 35 day study using doses of up to 350 mg/kg bw/day produced a slight depression of body weight gain and an increase of liver weights at the highest dose. An estimated dose of ~ 70 mg/kg bw/day was without any effect. Three studies for 4 month with doses of up to 1% in the diet (~ 700 mg/kg bw/day) confirmed the effect on growth. Whereas in two studies body weight gain was depressed only at the highest dose of 1 %, in another study a decrease was observed even at 0.5 %. The general well being as well as neurotoxic or immunotoxic parameters were not affected in all dose groups. Therefore the overall NOEL for these studies is 161 mg/kg bw/day due to reduced body weight gain. The low toxicity was confirmed also after dermal exposure of 100 and 1000 mg/kg bw/day in rabbits for 15 days without any sign of toxicity besides a depression of acetylcholinesterase as the only dose related effect. The toxicological relevance of this effect is hard to evaluate since quantitative data as well as the purity of the test material are not available.

Neurotoxicity is a potential adverse effect of many organophosphates. In available studies in hens and cats pure triphenyl phosphate did not induce immediate nor delayed neuropathy. The findings of a decreased activity of choline esterase and paralysis predominantly in cats in older studies indicating a neurotoxic potential were not reproduced in later studies and may be due to contamination of the tested samples by other organophosphorus esters. At the high doses of triphenyl phosphate used even small concentrations of impurities might have sufficient activity.

Tests for gene mutations in bacterial as well as yeast and mammalian cells did not reveal any sign of mutagenicity. An UDS-test in syrian hamster fibroblast cells showed no genotoxic effect. There is no test concerning chromosomal aberration.

There are no findings indicating any adverse effects on fertility or the development of the fetus up to the highest tested dose level of 1% in the diet (~ 700 mg/kg bw/day) in the rat treated for 4 months during gametogenesis prior to mating and throughout mating and gestation.

The mouse lung adenoma assay gave no indication of a carcinogenic potential.

Environment

Triphenyl phosphate has a solubility in water between 0.2 mg/l (river water) and 1.9 mg/l (distilled water) at 20 °C, a vapour pressure of 0.000835 Pa at 25 °C and a log Kow of 4.6. According to a Mackay Level I model calculation, triphenyl phosphate is mainly distributed to soil (43.9 %) and sediment (41.0 %), and to a lesser extent to water (14.3 %) and air (0.7 %). Triphenyl phosphate is hardly volatile from aqueous solution (calculated Henry constant: 0.018 - 0.036 Pa · m³/mol). The substance is strongly adsorbed to soil and sediment (measured Koc-values in the range of 2514 – 3561). In the atmosphere rapid degradation of triphenyl phosphate via indirect photolysis occurs ($t_{1/2air}$: ca. 12 h). While triphenyl phosphate is relatively stable under neutral and acidic conditions ($t_{½}$ = 19 d at pH 7; $t_{½}$ > 28 d at pH 5), it undergoes hydrolysis under alkaline conditions ($t_{1/2}$ = 7.5 d at pH 8.2; $t_{1/2}$ = 1.3 d at pH 9.5). In soil DT_{50} for primary degradation is 37 and 21 days under aerobic and anaerobic test conditions, respectively. Triphenyl phosphate is readily biodegradable (83 - 94% degradation after 28 d). Under anaerobic conditions with river sediment ca. 90 % triphenyl phosphate were primary degraded after 40 days of incubation. Mineralisation was about 22 % after 40 days. Measured bioconcentration factors in fish were in the range of 110 - 144, indicating a moderate bioaccumulation potential. As the BCF values are related to the parent compound, there is no information on possible accumulation of stable metabolites. BCFs for *Lemna minor* and *Typha sp*. are stated to be < 50. As the substance was found in dolphins collected in the Gulf of Mexico, accumulation via the food chain may occur.

The acute toxicity has been determined for fish (*Oncorhynchus mykiss*: 96 h-LC_{50} = 0.4 mg/l) and invertebrates (*Mysidopsis bahia:* 96 h-EC_{50} > 0.18 - 0.32 mg/l, *Daphnia magn*a: 48 h-EC_{50} = 1.0 mg/l). In tests with algae (*Selenastrum capricornutum, Scenedesmus subspicatus, Chlorella vulgaris*) NOEC values in the range of 0.25 - 2.5 mg/l were obtained after exposure periods of 96 h. In long term tests with fish (*Oncorhynchus mykissi*) a 30 d - EC10 of 0.037 mg/l was found. A PNECaqua = 0.74 µg/l is derived from the aforementioned long term NOEC using an assessment factor of 50.

Exposure

The world wide (excluding East Europe) production of triphenyl phosphate is estimated to about 20 000 to 30 000 tonnes by approx. 15 producers in the year 2000. Major application areas for triphenyl phosphate are the use as a flame retardant in PVC (about 50 %) where it has also plasticizing properties, but also as a flame retardant in other polymers (about 22 %) and printed circuit boards (about 11 %), and in photographic films (about 7 %). Minor areas (about 10 %) are covered by the use of triphenyl phosphate in hydraulic liquids (main area), and adhesives, inks, and coatings (minor area).

RECOMMENDATION

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

Environment: The chemical is a candidate for further work.

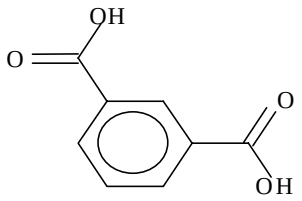
RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

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

Environment: Triphenyl phosphate has a wide dispersive use as flame retardant. Environmental releases are likely to occur during production, during the use as flame retardant e.g. in polymer applications as well as during the service life and the disposal of products containing the substance. Also accidental spill and leakage of hydraulic liquids in different application areas can be a source of environmental release. However, no exposure information is available,

except for the production at the sponsor company. Triphenyl phosphate is highly toxic to aquatic organisms (LC50 < 1 mg/l for fish, PNECaqua = 0.74 µg/l) and has a potential to accumulate in biota. Therefore, an exposure assessment and, if then indicated, an environmental risk assessment is recommended. Environmental exposure during production at the Sponsor company is adequately controlled.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	121-91-5
Chemical Name	Isophthalic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

For most SIDS endpoints, adequate data are available for isophthalic acid (IPA) to provide a characterization of its toxicity. Due to not having sufficient data for the endpoints of reproductive toxicity and *in vivo* genotoxicity with IPA, information on terephthalic acid (or TPA, CAS No. 100-21-0), an isomer of IPA was used as a surrogate. IPA and TPA are structural isomers, with carboxylic acid groups on the benzene ring at 1,3- and 1,4-carbons, respectively. Both IPA and TPA have similar physicochemical properties and show similar metabolic pathways and toxicological properties.

Human Health

In rats, both IPA and TPA are eliminated from the body unchanged primarily via urinary excretion. A steady state in blood is achieved fairly rapidly after inhalation exposure (on the first day) to IPA. One week after cessation of exposure, IPA was no longer detectable in the blood. Based on the Log Kow (-2.34), IPA is not expected to accumulate appreciably in tissues and is likely to be readily excreted from the body.

IPA exhibits low acute toxicity by the oral, dermal, and inhalation routes. The oral LD50 has been reported from >5000 mg/kg (no deaths) to 13,000 mg/kg in rats. No mortality was observed in rats following acute inhalation exposures to 11,400 mg/m^3 or acute dermal doses in rabbits of 23,000 mg/kg. IPA is not a skin sensitizer as skin reactions were only seen in 10% of the animals. IPA has negligible skin irritation potential and was considered slightly irritating to the eyes.

In repeated dose studies, the target organ is the kidney. A NOAEL of 250 mg/kg-day for IPA for kidney effects (crystalluria, mild hydronephrosis, pelvic calcification) has been reported for rats following repeated oral exposures. No systemic effects were observed in rats following repeated inhalation exposures to 10 mg/m^3 of IPA. Evidence regarding the genotoxicity of IPA is mixed. While negative results have been consistently reported for IPA in studies that use mammalian cell systems, both positive and negative results have been reported in *S. typhimurium* at very high concentrations (5,000-10,000 µg/plate). No data is currently available for IPA in *in vivo* toxicity tests. As a result, data from TPA, indicates that IPA is not likely to be an *in vivo* genotoxicant. In TPA, results from an *in vivo* genotoxicity study (micronuclei formation in mice with doses of 200-800 mg/kg/day) were negative. In a two year bioassay, rats that were fed TPA (greater than 2%) 1000 mg/kg b.w./day developed bladder calculi, bladder hyperplasia and bladder tumors. Fetotoxicity was observed in an oral reproductive toxicity study for TPA (NOAEL (parental and F1 generation) = 240-307 mg/kg/day) with no effects on reproductive performance (NOAEL >2480 mg/kg/day). However, no signs of fetotoxicity or developmental effects were noted following inhalation exposures to IPA (NOAEL = 10 mg/m^3).

Environment

In its ionised form, IPA is a crystalline powder that has a melting point of 347 ^{0}C, sublimes, a vapor pressure of 3.5 x 10^{-6} Pa at 25 ^{0}C, a measured log K_{ow} of –2.34 and a water solubility of 5400 mg/L at 25 ^{0}C. In IPA's non-ionized form the log Kow is 1.76 and has a water solubility of 130 mg/L at 25 ^{0}C. IPA is not persistent in the environment and is not expected to bioaccumulate in food webs. The half-life of IPA in air is estimated to be 8 to 12 days due to direct reactions with photochemically generated hydroxyl radicals. IPA is readily biodegraded under aerobic and anaerobic conditions. Limited environmental monitoring data suggest that ambient levels of IPA in air are low with levels ranging from 1.3 – 3.4 ng/m^3 in California and Japan (background levels were estimated to be 0.03 ng/m^3). Based on IPA's physical chemical properties, IPA will partition primarily to the water compartment, whether in its ionised or non-ionised form. Acute toxicity testing in fish, invertebrates, and algae indicate low toxicity with no effect concentrations of >895, >876 and >969 mg/l (the highest concentration tested for all test species), respectively.

Exposure

IPA is mainly used in the synthesis of resins, and in packaging fibers and plastics. In 1998, U.S. production was approximately 100,000 metric tonnes. Approximately 70% of the IPA produced is used in coatings and resins, while the remaining 30% is used in packaging fibers and fabrics. Exposures to workers may occur via inhalation and dermal contact. Because IPA present in consumer products is bound in a polymer matrix, the potential for exposures to consumers is low. Additionally, because IPA is not persistent in the environment, the potential for environmental exposures is low.

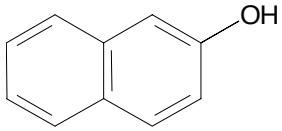
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	135-19-3
Chemical Name	2-Naphthol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

2-Naphthol can be absorbed through the skin. Rapid conjugation with glucuronide and sulphate in the liver and renal excretion of the unchanged and conjugated forms seems to be the principal mechanism of elimination. The acute oral LD_{50} in rats was determined as 1320 mg/kg bw in a study following OECD TG 401. Clinical signs included reduced activity, accelerated breathing, closure of eyes, nasal discharge and diarrhoea, and at exposure levels near to or exceeding the LD_{50} also tumbling, reduced reflexes and seizures.

The inhalation 4-hour-LC_{50} in rats was determined as 2200 mg/m^3 (aerosol; OECD TG 403). Clinical signs included irregular breathing, reduced activity, impaired motility and reflexes, nasal discharge, corneal opacity and diarrhea.

2-Naphthol was not irritating to the skin of rabbits in a test performed according to OECD TG 404, but caused serious damage to the eyes of rabbits in a study in accordance with OECD TG 405 (corneal vascularization/opacity). 2-Naphthol is a skin sensitiser, based on results from a guinea pig maximization test [OECD TG 406]. An increased incidence of contact dermatitis in exposed workers is reported in an old and poorly documented study.

After repeated administration to rats by the oral route for 28 days, there were indications of a possible effect on the adrenals in both sexes at dose levels of 50 mg/kg bw/day and above (increased relative and absolute adrenal weights). At 150 mg/kg bw/day, an increase in serum creatinine and changes in serum electrolytes were found in males, indicating an effect on the kidneys.

Poorly documented studies in dogs and rats involving repeated administration by the subcutaneous and inhalation route showed effects on the liver and kidneys. Concentration dependent disturbances in blood clotting and functional impairment of the liver and kidney with accompanying histopathological effects occurred at 10.1 and 1.35 mg/m^3.

2-Naphthol was not mutagenic in several Ames tests both in the absence and in the presence of metabolic activation, even at cytotoxic concentrations. Inconsistent results have been observed in bacterial DNA repair tests, but it did not induce unscheduled DNA synthesis in rat hepatocytes in a test performed according to current standards. 2-Naphthol was not tested for its potential to induce chromosomal aberrations *in vitro*. In an *in vivo* micronucleus assay with 2-naphthol, no evidence of genotoxicity was found. These data show that 2-naphthol is not mutagenic *in vivo*.

There are no adequate data available for the evaluation of the carcinogenic potential of 2-naphthol.

2-Naphthol 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 generation. No teratogenic effects were observed (NOEL for male reproductive toxicity: 160 mg/kg bw/day (highest tested dose); NOELs for female reproductive toxicity and for toxicity to the offspring: 40 mg/kg bw/day each). (160 mg/kg

bw/day may suppress nursing; reduced body weights and reduced viability was seen in the offspring at 160 mg/kg bw/day). The LOEL for systemic toxicity in males was 10 mg/kg bw/day (salivation), the NOEL for systemic toxicity in females was 10 mg/kg bw/day (nasal discharge, reduced food consumption, decreased locomotor activity and salivation at 40 mg/kg bw/day).

In workers exposed to 2-naphthol an increased incidence of dermatitis, conjunctivitis, and rhinitis have been reported in poorly documented studies. In addition, changes in kidney function, and an increased incidence in chronic hepatitis and impairment of the nervous system were reported from workers who were also exposed to a variety of other chemicals.

Environment

2-Naphthol has a water solubility of 0.6 - 0.8 g/l, a vapor pressure of 1.4 Pa and a measured log Kow in the range of 2.01 – 2.84. 2-Naphthol is readily biodegradable as shown in a MITI test according to OECD 301C with non-adapted inoculum. A biodegradation of 68 % after 14 days was found. There is no information on the degradation kinetic. The measured log Kow in the range of 2.01 to 2.84 does not indicate a significant potential for bio- or geoaccumulation. With a fugacity model (Mackay I) the following distribution can be predicted: hydrosphere: 83 %, atmosphere: 8 %, soil: 4.5 % and sediment: 4.5 %. The hydrosphere is therefore the target compartment for this substance. In water solution, photodegradation has been observed, but the half-life under environmental conditions was not estimated. The calculated half-life due to photochemical-oxidative degradation in the atmosphere by OH-radicals is about 2 hours.

For 2-naphthol there are short-term tests with fish, invertebrates and algae available. The lowest effects values from the short-term tests are:

Pimephales promelas: 96h-LC_{50} = 3.46 mg/l,
Gammarus minus: 48h-EC_{50} = 0.85 mg/l, and
Nitzschia palea: 4h- EC_{50} = 6.3 mg/l.

As there is no standard algae study available, the ECOSAR model was employed to predict the toxicity of 2-naphthol to green algae, resulting in a 96h-EC_{50} of 12.9 mg/l. This supports that algae are not likely to be the most sensitive species in short-term tests. With an assessment factor of 1000 a PNECaqua of 0.85 µg/l was derived from the 48h-EC_{50} for the most sensitive species, *Gammarus minus*.

Exposure

The worldwide production capacity of 2-naphthol is approximately 100,000 metric tonnes per year. The substance is used as an intermediate for the production of dye-stuffs, pharmaceuticals, fungicides, insecticides and odor agents. The substance is also used as an antioxidant for rubber and plastic, grease and lubricants.

Releases into the environment may occur during production and processing of 2-naphthol and from its direct use as e.g. antioxidant. Further sources are:

- the waste water from the conversion of coal to liquid and gaseous fuel products. A "typical concentration" of 50 mg/l is cited.
- the waste water of the petroleum industry.
- the groundwater near waste sites from wood-treatment processes.

An exposure of the terrestrial compartment is to be expected, as 2-naphthol is a metabolite of the herbicide naproanilide. As no further exposure data are available, the relevance of the exposure of the terrestrial compartment cannot be assessed.

2-Naphthol is a product from the atmospheric reaction of naphthalene (CAS No. 91-20-3) with hydroxyl radicals.

Occupational exposure may occur during production and processing of 2-naphthol. In Germany, the production was stopped in 1992; no workplace exposure information is available with regard to processing sites. From a European production plant workplace peak exposures between 0.0005 and 1.632 mg/m^3 are reported.

Consumers may be exposed to 2-naphthol through cigarette smoke. The use of 2-naphthol in cosmetics is not allowed in the European Union and marketing of medicines containing 2-naphthol is prohibited in Germany.

RECOMMENDATION

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

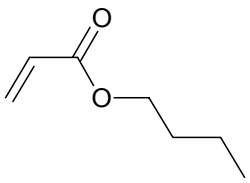
Environment: The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work based on its low hazard potential. It is noted that the chemical can cause serious eye damage and is a skin sensitiser.

Environment: Little information is available about releases into the environment from production and processing sites and from the direct use of the substance. However, this information indicates that significant releases into the environment may occur. In addition, the relevance of releases into the terrestrial compartment from the metabolisation of the herbicide naproanilide should be clarified. Therefore, an exposure assessment is recommended. This recommendation is based on the high toxicity of 2-naphthol to aquatic organisms. A PNECaqua of 0.85 µg/l was derived from the available short-term data. Dependent on the exposure situation further tests with aquatic and/or terrestrial organisms may be required.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	141-32-2
Chemical Name	n-Butyl Acrylate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

In some circumstances, available data on iso-butyl acrylate (CAS No. 106-63-8) may be presented to assist in the weight of evidence approach for n-butyl acrylate, based on structural similarities. Since sufficient data exists for n-butyl acrylate for the majority of SIDS endpoints, data on iso-butyl acrylate is presented only for those endpoints in which further supporting data may assist in adding to the characterization of a particular endpoint. This was done primarily for the aquatic toxicity endpoints.

Human Health

After oral administration, n-butyl acrylate is rapidly absorbed and metabolized in male rats (75% was eliminated as CO_2, approximately 10% via urine and 2% via feces). The major portion of n-butyl acrylate was hydrolyzed by carboxyesterase to acrylic acid and butanol.

Following acute exposure, n-butyl acrylate exhibits low toxicity. n-Butyl acrylate has oral LD_{50}s of 3143 mg/kg bw (rats) and 9050 mg/kg bw (male rats), an inhalation LC_{50} (4-hour, rat) of 10.3 mg/L and a dermal LD_{50} (rabbit) of 2000 to 3024 mg/kg. n-Butyl acrylate is irritating to skin and eyes and showed a skin sensitizing potential in animals. In humans, skin sensitization to butyl acrylate was reported.

In an oral (drinking water) 90-day study in rats, using a satellite group (gavage) at 150 mg/kg bw/day, the only effects reported were a slight reduction in water consumption in all dose groups and a decrease in weight gain in the highest dose group. The NOAEL (males) = 84 mg/kg/bw/day and NOAEL (females) = 111 mg/kg/bw/day. The NOAEL (gavage) (males and females) = 150 mg/kg/bw/day. In a 90-day inhalation study, rats were exposed to 0, 21, 108, 211, and 546 ppm (0, 0.11, 0.57, 1.12, 2.90 mg/L) n-butyl acrylate. The primary effects at 211 ppm (1.12 mg/L) were irritation of eyes and nasal mucosa, reduced body weights (13.3 percent in males and 3.76 percent in females compared with controls), decreased potassium values (females) and an increase in alkaline phosphatase activity (females.) At the highest dose of 546 ppm (2.90 mg/L) 31 of 40 animals died. The primary cause of death was due to the strong irritation of the substance on the respiratory tract. The NOAEC = 108 ppm (0.57 mg/L/day) and the LOAEL = 211 ppm (1.12 mg/L/day). In a two-year inhalation study, rats (male/female) received whole body exposures of 0, 15, 45, or 135 ppm (0, 0.086, 0.258, 0.773 mg/L). There was a slight decrease in food consumption and slightly lower relative heart, kidney, liver and thyroid weights at the highest dose. A NOAEC could not determined for this study. A LOAEC was determined to be 45 ppm (0.258 mg/L/day) based upon localized and diffuse stippling of the corneal epithelium, cloudiness of the cornea, and various degrees of vascularization. The severity of nasal mucosa effects increased with dose and occurred at all doses in males and females. Effects ranged from slight atrophy of the neurogenic part of the olfactory epithelium at 15 ppm (0.086 mg/L) to partial loss of the columnar cell layer and stratified reserve-cell hyperplasia at 45 (0.258 mg/L) and 135 ppm (0.773 mg/L).

n-Butyl acrylate was negative in the Ames test with *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 with and without metabolic activation tested up to 10,000 µg/plate. In a cytogenetic assay with Chinese Hamster

ovary cells, n-butyl acrylate showed no clastogenic potential in concentrations where no cytotoxicity occurred. Without metabolic activation, an increase of aberrant cells was observed at cytotoxic concentrations. No genotoxic effects were found in an *in vitro* micronucleus test and an UDS-test with Syrian hamster fibroblasts. In an *in vivo* cytogenetic assay, n-butyl acrylate showed no clastogenic effect in rats and hamsters after inhalation exposure.

n-Butyl acrylate was not carcinogenic to rats via inhalation up to 135 ppm (0.773 mg/L/day), the highest dose tested.

No reproductive toxicity studies were available. However, in repeated-dose studies (noted above), no effects were seen in the reproductive organs. In developmental toxicity studies with rats via inhalation, n-butyl acrylate caused fetotoxic effects (resorptions and reduced number of live fetuses at $\geq$135 ppm) at maternally toxic concentrations. At exposures of 25, 135 and 250 ppm (0.13, 0.72 and 1.33 mg/L/day), the NOAEC for maternal toxicity = 25 ppm (0.13 mg/L/day), based on reduced body weights and irritation to the eyes and nose. The NOAEC for developmental toxicity = 25 ppm (0.13 mg/L/day), based on post-implantation loss and the NOAEC for teratogenicity = 250 ppm. In a separate study, female rats were given 100, 200 and 300 ppm. A maternal NOAEC could not be determined based on a reduction of absolute body weight gain at all doses; the maternal LOAEC was set at 100 ppm. At 200 and 300 ppm there was a reduction in fetal body weights. The NOAEC for developmental toxicity was 100 ppm and the NOAEC for teratogenicity was 300 ppm (highest dose tested).

Environment

The water solubility of n-butyl acrylate is 2 g/L (25 °C) and specific gravity is 0.898 g/cm^3 at 20 °C. The measured log Kow is 2.38 (25 °C). The vapor pressure (based on a regression analysis of measured values from several data sources) is 7.27 hPa at 25 °C. The melting point is - 64°C and the boiling point is 148 °C. The chemical is highly flammable and its flashpoint is approximately 36 ^{0}C. n-Butyl acrylate is photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 1.2 days (calculated). The hydrolysis rate of n-butyl acrylate is extremely low. At pH 7, the approximate half-life is calculated to be 1100 days. The Henry's law constant is 4.7 x 10^{-4} atm/m^3/mol, indicating the potential for moderate volatilization from water. Distribution modeling using Mackay Level I indicates that the main target compartment will be air (94%) with smaller amounts partitioning into water (5.73%) soil (0.11%), and sediment (0.11%). Fugacity model Level III gives comparable results; the levels are: 89.4% (air), 8.24% (water), 2.39% (soil) and 0.0963% (sediment). A BCF of 13 was determined, based on a log K_{ow} of 2.38, indicating a low bioaccumulation potential. In a biodegradation assay according to OECD Guideline 301C (modified MITI-Test (I)), n-butyl acrylate was readily biodegradable (61% after 14 days). In another ready biodegradation test conducted according to ISO 14593 (identical to OECD Guideline 310), n-butyl acrylate was readily biodegradable (91 % degradation after 28 days). In acute aquatic toxicity studies, n-butyl acrylate was determined to have toxic effects in the concentration range of 2.1 to 8.2 mg/L. A measured fish 96-hr LC_{50} of 2.1 mg/L was determined in a flow-through test in *Cyprinodon variegates.* A measured aquatic invertebrate 48-hr EC_{50} of 8.2 mg/L was determined in a flow-through test in *Daphnia magna.* Finally, in algae (*Selenastrum capricornutum*) a growth-rate study using measured concentrations resulted in a 96-hr EC_{50} of 2.6 mg/L (arithmetic mean). In addition, supporting data from iso-butyl acrylate indicate toxicity values within the same ranges. For iso-butyl acrylate, the most sensitive species was the freshwater fish *Pimephales promelas* (fathead minnow) with a 96-hour LC_{50} of 2.09 mg/L (measured). The 48-hour EC_{50} for *Daphnia magna* was 9.7 mg/L (nominal), and for algae (*Desmodesmus subspicatus)* the 72-hour EC_{50}s were 3.18 mg/L (measured) for biomass and 5.28 mg/L (measured) for growth rate.

Exposure

n-Butyl acrylate is manufactured as a chemical intermediate in a closed system. Its major use is in the production of homo- and co-polymers with other monomers (i.e. acrylic acid and its salts, esters, amides, etc.) to produce emulsion polymers. The three major uses of acrylate esters are: surface coatings, adhesives/sealants and textiles. In 2000, production volumes were 250,000 – 400,000 tonnes for Europe, 581,000 tonnes for the US and 130,000 tonnes for Japan. In 2000, US TRI reporting indicated that the majority of n-butyl acrylate was released to the air compartment (94%, 233,013 pounds) where it is subject to photolysis. However, a small percentage was released to the water compartment (6%, 14,566 pounds). Impact on the environment is expected to be low due to photolysis and biodegraditive properties. Extensive occupational exposure monitoring records are available which indicate that 8 hr TWAs for a variety of operations are below the regulatory/guideline values of 2 ppm (8hr TWA). However, peak exposures were reported above the 2 ppm value and in some circumstances exceeded the NIOSH REL of 10 ppm (TWA) during sampling, cleaning, change of pump filter, check of detonation arrestors, inhibitor preparation, drumming and waste disposal. Records indicate that personnel performing these tasks wear the appropriate personal

protective equipment and therefore, exposures to pesonnel are estimated to be lower depending upon protection factors of the personal protective equipment. End-use consumer products contain only trace levels of acrylic acid and esters (as a result of polymerization). Therefore, consumer exposure to acrylate monomers is likely to be low.

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

The chemical is currently of low priority for further work. 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 a low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	144-55-8
Chemical Name	Sodium bicarbonate
Structural Formula	$NaHCO_3$

SUMMARY CONCLUSIONS OF THE SIAR

Sodium bicarbonate is a white, odourless, crystalline powder. It decomposes when heated over 50°C and therefore a melting and boiling point can not be determined. Sodium bicarbonate is an inorganic salt and therefore the vapour pressure can be considered negligible. Its water solubility is 96 g/l at 20°C. Grades with different average particle size diameters (d_{50}) are placed on the market. The average particle size diameter of the different sodium bicarbonate grades can range between 15 and 300 µm.

Human Health

Oral LD_{50} values were higher than 4,000 mg/kg bw, and an inhalation study in rats using a concentration of 4.74 mg/l inhalable dust produced no deaths.

There are no directly relevant studies on repeated dose exposure, however, knowledge of prior use and available literature does not indicate any adverse effects of long-term use of exposure via any route. *In vitro* bacterial and mammalian cell tests showed no evidence of genotoxic activity. As with other sodium salts, high doses of sodium bicarbonate promote carcinoma formation in rat urinary bladder after pre-exposure to initiator or BBN. However, when rats were only exposed to sodium bicarbonate no carcinogenic effect on the urinary bladder was found. Based on the available information there are no indications that sodium bicarbonate has carcinogenic effects.

Sodium bicarbonate has a long history of use in foodstuff, feed and industrial processes. The bicarbonate ion is a normal constituent in vertebrates, as the principal extracellular buffer in the blood and interstitial fluid is the bicarbonate buffer system. Excess sodium and bicarbonate ions are readily excreted in the urine. It is therefore assumed that normal handling and use will not have any adverse effects. The consequences of accidental or excessive oral ingestion have been described in a number of publications. Acute oral ingestion by the patients may result in a ruptured stomach due to excessive gas development. Acute or chronic excessive oral ingestion may cause metabolic alkalosis, cyanosis and hypernatraemia. These conditions are usually reversible, and will not cause adverse effects.

Environment

Acute NOEC values to fish and daphnids are higher than 1,000 mg/l. The 21-day NOEC to *Daphnia magna* is higher than 576 mg/l. The acute toxicity of sodium bicarbonate for aquatic organisms could be based on a high osmotic pressure. This is a very general effect of salts as soon as their concentration in water exceeds a certain level.

Both sodium and bicarbonate are present naturally present in aquatic ecosystems. For sodium the 10^{th}- and 90^{th}-percentile were 1.5 and 68 mg/l, respectively, based on a total number of 75 rivers. For bicarbonate the 10^{th}- and 90^{th}-percentile were 20 and 195 mg/l, respectively, based on a total number of 77 rivers. Because the natural pH, bicarbonate and sodium concentration (and also their fluctuations in time) varies significantly between aquatic ecosystems, it is not considered useful to derive a generic PNEC or $PNEC_{added}$. To assess the potential environmental effect of a sodium bicarbonate discharge, the increase in sodium, bicarbonate and pH should be compared with the natural values and their fluctuations and based on this comparison it should be assessed if the anthropogenic addition

is acceptable.

The production and use of sodium bicarbonate could potentially result in an emission of sodium bicarbonate to aquatic and terrestrial ecosystems. However, for most applications the bicarbonate will be digested (animal feeding, human food, pharmaceuticals) or treated by a waste water treatment plant (detergents and household cleaning products) and will not be directly emitted to the ecosystems. In order to determine if the production and use of sodium bicarbonate really results in a significant emission of bicarbonate, an evaluation of the complete, inorganic and organic carbon cycle would be required.

Aquatic sodium emissions originating from uses of sodium bicarbonate are probably small compared to other sources. It is clear that an environmental hazard assessment of sodium should not only evaluate all natural and anthropogenic sources of sodium but should also evaluate all other ecotoxicity studies with sodium salts, which is beyond the scope of this report.

Exposure

Sodium bicarbonate is produced on all continents of the world and the global number of production sites is estimated to be 30-50. The estimated total amount of sodium bicarbonate used in 2001 is 2 million tonnes.

Sodium bicarbonate is used as animal feed additive, human food additive and it is used in pharmaceuticals. It is also used for the production of other chemicals and it used in cosmetics and detergents and other household cleaning products. It is present in a large number of consumer products but the pure product is also available to consumers.

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 considered of low priority for further work because of its low hazard potential.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2432-99-7
Chemical Name	11-aminoundecanoic acid
Structural Formula	$HO_2C—(CH_2)10—NH_2$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Limited information indicated that 11-aminoundecanoic acid is rapidly and extensively absorbed by rats after an oral administration, distributed in the body and rapidly excreted mainly via urine.

The acute toxicity of 11-aminoundecanoic acid is negligible: oral LD_{50} in rats >14700 mg/kg, and dermal LD_0 in rats >2000 mg/kg.

11-aminoundecanoic acid induced no skin irritation and only a slight transient eye irritation in rabbits and did not induce positive response in a skin sensitisation assay in Guinea pigs performed according to the Magnusson and Kligman method.

A NOAEL of 5000 ppm in rats (equivalent to 472 mg/kg bw/d for males and 507 mg/kg bw/d for females) and 9000 ppm in mice was established based on a 4-week and a 13-week dietary toxicity study, respectively. At higher concentrations (up to 21000 ppm) administered for up to 13 weeks to rats and/or mice, 11-aminoundecanoic acid has produced histopathological lesions in the kidney in both species.

In vitro, 11-aminoundecanoic acid did not induce gene mutations on bacteria (Ames test), chromosomal aberrations on CHO cells and gene mutations on L5178Y cells. A slight increase of Sister Chromatid Exchanges (SCEs) has been observed in CHO cells. However, the results of *in vivo* assays override the SCEs increase: 11-aminoundecanoic acid was not genotoxic in a Drosophila recessive lethal test, an *in vivo/in vitro* DNA-repair test on rat hepatocytes and a micronucleus test in mice. In addition, in a DNA-binding study with 11-aminoundecanoic acid, using male and female F-344 rats, no indication of DNA alkylation was found in liver, kidneys or bladder. The overall interpretation of the results provided by *in vitro* and *in vivo* assays is that 11-aminoundecanoic acid is not mutagenic. 11-aminoundecanoic acid was tested for carcinogenicity in mice and rats by administration in the diet at 7500 and 15000 ppm. Increased incidence of transitional-cell carcinomas of the urinary bladder and neoplastic nodules of the liver were observed in male rats. Epithelial hyperplasia of the urinary bladder and renal pelvis were observed in male and female rats. No clear evidence for an increased incidence of treatment-related tumours was seen in mice. The carcinogenic effect observed in animals, involved only male rats treated with very high doses of 11-aminoundecanoic acid, and no clear evidence was found in female rats and in male and female mice. Consequently, the excess of malignant tumours of the urinary tract found in male rats are believed to have occurred through a non-genotoxic mechanism and to be associated with the non-neoplastic local tissue damages which were induced when the dose of 11-aminoundecanoic acid reached a sufficiently high level. IARC categorised 11-aminoundecanoic acid as "non classifiable as to its carcinogenicity to humans" (Category 3), due to the limited evidence provided by the animal data and the absence of epidemiological data (IARC, 1986).

No standard fertility studies are available. However, no effects on the reproductive organs (testes, seminal vesicles, and prostate for male or ovaries and uterus for female) were observed in good quality 90-day and 2-year studies in rats and mice where 11-aminoundecanoic acid was administered in feed at doses up to 21000 and 15000 ppm, respectively. Developmental toxicity studies have been carried out in the rat; 11-aminoundecanoic acid did not

produce embryotoxicity or fetotoxicity up to the dose-level of 18000 ppm, with the exception of a slight retardation of growth/skeletal development at dose-levels of 6000 ppm and particularly 18000 ppm (dose-level at which a slight reduction in fetal body weight was also noted). The No Adverse Effect Level for maternal toxicity and embryo-fetal development was established at 6000 ppm (i.e. 520 mg/kg/day). Based on the lack of toxicity on the reproductive organs of male and female rats and mice and the absence of embryo-toxicity and fetotoxicity in pregnant rats, 11-aminoundecanoic acid is unlikely to present reproductive toxicity.

Environment

A pKa (amine) of 11.15 and a pKa (carboxylate) of 4.55 have been determined for 11-aminoundecanoic acid. Therefore, at relevant environmental pH (6-8), the substance will be mainly in zwitterion form. The solubility of 11-aminoundecanoic is pH dependent. At 25°C and pH>=4, the solubility is at maximum 3.2 g/l, a typical value of 0.8 g/l having been measured at environmental pH. At pH <4, the solubility of 11-aminoundecanoic increases with decreasing pH (> 20 g/l below pH 3).

Due to the relatively high solubility (0.8 - 2 g/l), the low octanol-water partition coefficient (log Kow = - 0.16) and the low volatility (2.07 10^{-7} Pa at 25°C) of 11-aminoundecanoic acid, the substance will mainly be present in the aqueous phase. In water it is not expected to hydrolyse. It is readily biodegradable. It is not likely to bioaccumulate. Due to its ionised form, adsorption to soil or sediment with capacity of ion exchange may occur. In the atmosphere, 11-aminoundecanoic acid is rapidly photodegraded by reaction with hydroxyl radicals with an atmospheric average half-life of 4.3 h.

11-aminoundecanoic acid is slightly toxic to aquatic organisms, algae being the most sensitive species with a 72h EbC50 of 23 mg/l. (fish: 96 h LC50 > 833 mg/l; daphnid: 48 h EC50 > 355 mg/l). A PNEC of 45 µg/l may be derived from the NOEC of 4.5 mg/l available on algae applying a safety factor of 100.

Exposure

There is only one producer of 11-aminoundecanoic acid in the world. The production plant is located in the South of France. The annual production capacity is approximately 22,000 tonnes.

11-aminoundecanoic acid is exclusively used as a monomer for the production of polyamides 11 at three different sites; located in Europe (2 sites) and in the US (1 site). Polyamides 11 are used in a number of applications including automotive and aeronautics industries, offshore sector, sport sector, medical and food contact material sector.

The substance is produced and used in closed system. Emissions of 11-aminoundecanoic acid to the environment may occur mainly from production. Aqueous effluents are treated in a waste treatment plant where 11-aminoundecanoic acid is expected to degrade to a large extent due to its ready biodegradability. There are no aqueous streams from the processing of the substance.

There is a potential for professional exposure mainly through inhalation of particles. Personnel protection equipment (mask, gloves and safety glasses) is used during production, handling and use of the substance.

There are no direct consumer uses of 11-aminoundecanoic acid. Food contact materials made of 11-aminoundecanoic acid contain low residual levels of 11-aminoundecanoic acid (< 100 ppm) and are subject to very strict regulations (EU specific migration limit = 0.05 mg/kg food). Therefore, consumer exposure to 11-aminoundecanoic acid is not expected.

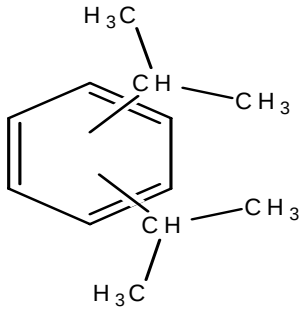
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	25321-09-9
Chemical Name	Diisopropylbenzene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

The mixture of *m*- and *p*-diisopropylbenzene (60:40/*m*-:*p*-) was assessed.

Human Health

There is no data available regarding toxicokinetics and metabolism.

No data are available for the acute toxicity of diisopropylbenzene with the composition of 60:40/*m*-:*p*-. The oral LD_{50} value of each constitutive isomer, *m*-diisopropylbenzene and *p*-diisopropylbenzene, was shown to be greater than 3,000 mg/kg b.w. in rodents. Acute toxicity studies of diisopropylbenzene with an unknown isomer ratio are available. The oral and dermal acute toxicity of diisopropylbenzene are negligible: the oral LD_{50} in rats is 5,850 mg/kg b.w., and the dermal LD_{50} in rabbits is 14,400 mg/kg b.w. In an acute inhalation study, no deaths occurred at doses below 5,300 mg/m^3 after 4h exposure in rats and after 2h exposure in mice. The weight of evidence shows that the acute toxicity of diisopropylbenzene with the composition of 60:40/*m*-:*p*- can be considered to be low.

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

In accordance with the Japanese guideline, equivalent to OECD TG 407, SD rats received diisopropylbenzene with the composition of 60:40/*m*-:*p*- by gavage at doses of 0, 6, 30, 150 and 750 mg/kg b.w./day for 28 days. Mydriasis was observed in 2 of 6 males and 2 of 6 females at 150 mg/kg b.w./day and in 10 of 12 males and all of 12 females at 750 mg/kg b.w./day. This sign was observed from about 2 to 6 hours after administration mainly during the latter half of the dosing period. On histopathological examination, centrilobular hypertrophy of hepatocytes was observed in 1 of 6 males in the 150 mg/kg b.w./day group and 1 of 6 males and 4 of 6 females in the 750 mg/kg b.w./day group. Based on mydriasis and histopathological changes in the liver at 150 mg/kg b.w./day, the NOAEL of this chemical was considered to be 30 mg/kg b.w./day.

In a reverse gene mutation assay [OECD TG 471, 472], diisopropylbenzene with the composition of 60:40/*m*-:*p*- was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *urv*A with and without an exogenous metabolic activation. In a chromosomal aberration test [OECD TG 473] with diisopropylbenzene with the composition of 60:40/*m*-:*p*-, structural chromosomal aberrations and polyploidy were not induced with and without an exogenous metabolic activation in cultured Chinese hamster lung (CHL/IU) cells.

There are no data available on carcinogenicity.

In a reproductive/developmental toxicity screening test [OECD TG 421], diisopropylbenzene with the composition of 60:40/*m*-:*p*- was administered to SD rats by gavage at doses of 0, 6, 30, 150 and 750 mg/kg b.w./day from day 14 before mating to day 14 after mating in males and to day 3 of lactation in females. This treatment produced no effect on reproductive performance and no adverse effect on offspring. In view of these findings the NOAEL for reproductive/developmental toxicity is considered to be 750 mg/kg b.w./day.

Environment

The melting points of *m*- and *p*- diisopropylbenzene are –63 and –17.1 degree C respectively. The boiling point of *m*- and *p*- diisopropylbenzene is 203 degree C. The vapour pressures of *m*- and *p*- diisopropylbenzene are 0.524 hPa and 0.328 hPa respectively at 25 degree C. Water solubility is (m-) 72.0 ug/L, (p-) 40.5ug/L at 25 degree C. Henry's law constants of *m*- and *p*- diisopropylbenzene are 1.17 and 1.30 atm m^3/moL, respectively. The partition coefficients of *m*- and *p*- diisopropylbenzene are 5.13 and 5.23 respectively.

The fugacity model (Mackay level III) suggests that if diisopropylbenzene is released to air or soil, it is unlikely to distribute into other compartments and that if it is released to water it has a tendency to go into the sediment compartment.

m- and *p*-Diisopropylbenzene are not inherently biodegradable and both of their bioconcentration potentials seems to be high (BCF= 503 – 3210, mixture). In the air, *m*- and *p*-diisopropylbenzene are expected to be photodegraded (*m*-: $T_{1/2}$=8.3 hours, *p*-: $T_{1/2}$=13 hours) by OH radicals. Hydrolysis is not expected to occur.

The acute toxicity of diisoprophylbenzene has been tested in three aquatic species belonging to three trophic levels. For algae (OECD TG 201, *Selenastrum capricornutum*, closed system) a 72hEbC50 of 1.6 mg/L and a 72hErC50 of 2.7 mg/L were determined. For daphnids (OECD TG 202 part 1, *Daphnia magna*, semistatic) a 48hEC50 of 0.39 mg/L, and for fish (OECD TG 203, *Oryzias latipes*) a LC50 of 0.71 mg/L were reported.

Regarding chronic toxicity, for algae (OECD TG 201 growth inhibition, *Selenastrum capricornutum*) a 72 h NOErC of 0.69 mg/L, a 72 h NOEbC of 0.31 mg/L, and for daphnids (TG 211 reproduction, *Daphnia magna*) a 21 d NOEC of 0.063 mg/L were reported.

Most of the toxicity results were above the water solubility limit of the substance (*m*-; 0.072 mg/L and *p*- ; 0.0405 mg/L). As the NOEC of the chronic toxicity study with daphnids is close to the solubility limit of the substance, it can be considered that this result reflects the actual toxicity of the substance.

Exposure

Diisopropylbenzenes are produced as by-products of cumene synthesis in closed systems. The production volume was ca. 30,000 tonnes/year by two companies in Japan. These chemicals are blended into gasoline, diesel and other hydrocarbon fuels, and also used for diisopropylbenzeneperoxide synthesis.

Diisopropylbenzenes are volatile liquids and consumer and worker exposure through inhalation and dermal contact is possible.

RECOMMENDATION

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

Environment: The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Diisopropylbenzene is not inherently biodegradable and is expected to have a high bioaccumulation potential and aquatic toxicity. An environmental exposure assessment and if necessary a risk assessment is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	497-19-8
Chemical Name	Sodium carbonate
Structural Formula	Na_2CO_3

SUMMARY CONCLUSIONS OF THE SIAR

Sodium carbonate has a melting point of 851°C, it decomposes when heated and therefore a boiling point can not be determined. Sodium carbonate is an inorganic salt and therefore the vapour pressure can be considered negligible. Its water solubility is 215 g/l at 20°C. The average particle size diameter (d_{50}) of light sodium carbonate is in the range of 90 to 150 µm and of dense sodium carbonate is in the range of 250 to 500 µm.

Human Health

Sodium carbonate is an alkaline substance. The acute oral LD_{50} in rats is 2,800 mg/kg bw, while the dermal LD_{50} in rats is >2,000 mg/kg bw. The LC50s for inhalation are 800, 1200 and 2300 mg/m^3 for guinea pig, mice and rat respectively. Sodium carbonate has no or a low skin irritation potential but it is considered irritating to the eyes. Due to the alkaline properties an irritation of the respiratory tract is also possible.

No valid animal data are available on repeated dose toxicity studies by oral, dermal, inhalation or by other routes for sodium carbonate. A repeated dose inhalation study, which was not reported in sufficient detail, revealed local effects on the lungs which could be expected based on the alkaline nature of the compound. Under normal handling and use conditions neither the concentration of sodium in the blood nor the pH of the blood will be increased and therefore sodium carbonate is not expected to be systemically available in the body. It can be stated that the substance will neither reach the foetus nor reach male and female reproductive organs, which shows that there is no risk for developmental toxicity and no risk for toxicity to reproduction. This was confirmed by a developmental study with rabbits, rats and mice. An *in vitro* mutagenicity test with bacteria was negative and based on the structure of sodium carbonate no genotoxic effects are expected.

Environment

The hazard of sodium carbonate for the environment is mainly caused by the pH effect of the carbonate ion. For this reason the effect of sodium carbonate on the organisms depends on the buffer capacity of the aquatic or terrestrial ecosystem. Also the variation in acute toxicity for aquatic organisms may be explained for a significant extent by the variation in buffer capacity of the test medium. In general, mortality of the test organisms was found at concentrations higher than 100 mg/l but for Amphipoda, salmon and trout lethal effects were already observed at 67-80 mg/l although these studies had a low reliability.

Individual aquatic ecosystems are characterized by a specific pH and bicarbonate concentration and the organisms of the ecosystem are adapted to these specific natural conditions. Because the natural pH, bicarbonate and also the sodium concentration (and their fluctuations in time) varies significantly between aquatic ecosystems, it is not considered useful to derive a generic PNEC or $PNEC_{added}$. To assess the potential environmental effect of a sodium carbonate discharge, the increase in sodium, bicarbonate and pH should be compared with the natural values and their fluctuations and based on this comparison it should be assessed if the anthropogenic addition is acceptable.

The production and use of sodium carbonate could potentially result in an emission of sodium carbonate and it could locally increase the pH in the aquatic environment. However, the pH of effluents is normally measured very

frequently and can be adapted easily and therefore a significant increase of the pH of the receiving water is not expected. If emissions of waste water are controlled by appropriate pH limits and/or dilutions in relation to the natural pH and buffering capacity of the receiving water, adverse effects on the aquatic environment are not expected due to production or use of sodium carbonate.

Aquatic sodium emissions originating from uses of sodium carbonate are probably small compared to other sources. It is clear that an environmental hazard assessment of sodium should not only evaluate all natural and anthropogenic sources of sodium but should also evaluate all other ecotoxicity studies with sodium salts, which is beyond the scope of this report.

Exposure

Sodium carbonate is produced on all continents of the world and the global number of production sites is estimated to be 50-70. The total world demand of sodium carbonate in 1999 was 33.4 million metric tonnes.

Sodium carbonate is used for the production of glass, soaps and detergents and other chemicals and it also used by the 'metals and mining' industry and the 'pulp and paper' industry. Sodium carbonate is not only used by industry but is also used by consumers. It may be used directly in solutions of sodium carbonate for soaking of clothes, dishwashing, floor washing and for degreasing operations but it is also present in a large number of consumer products like cosmetics, soaps, scouring powders, soaking and washing powders. Sodium carbonate is also a food additive.

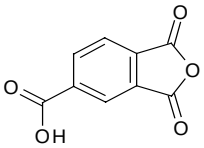
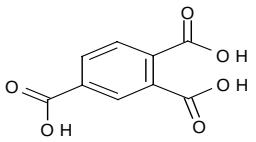
RECOMMENDATION

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. However, reversible eye and respiratory tract irritation is noted.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	552-30-7 528-44-9
Chemical Name	Trimellitic Anhydride (TMA) Trimellitic Acid (TMLA)
Structural Formula	TMA: $C_9H_4O_5$  TMLA: $C_9H_6O_6$ 

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

Trimellitic anhydride (TMA) and trimellitic acid (TMLA) are considered to be structural analogues. In addition, in aqueous environments TMA is readily converted to TMLA. TMA rapidly forms TMLA under the conditions used to test its toxicity, the toxicities of TMA and TMLA are qualitatively believed to be the similar for systemic toxicity with these two chemicals being presented as analogues. The only difference being sensitization and potentially local effects/reactions at the initial point of contact (skin, eye, and respiratory irritation). The sensitization potential of TMA, may be directly attributed to the formation of haptens following a reaction with proteins. TMLA does not react with proteins to form haptens, and therefore does not share this mode of action for sensitization.

Human Health

TMA exhibits low acute toxicity by the oral, dermal, and inhalation routes. The oral LD_{50} has been reported to range from 2,030 to 3,340 mg/kg in male and female rats, with stomach lesions appearing as the most consistent lesion upon necropsy. In rats, the inhalation LC_{50} value was reported to exceed a concentration of 2,330 mg/m^3, with lung lesions appearing as the most consistent lesion upon necropsy. The LC_{50} for TMLA was reported to be >3,750 mg/m^3, with necropsy findings considered within normal limits. A dermal LD_{50} value of 5,600 mg/kg was reported for TMA. Because TMA rapidly converted to TMLA in the body, the acute toxicity of TMLA is expected to be similar to that of TMA. Both chemicals are considered to have mild skin and severe eye irritation potential. Studies on TMA suggest that these materials may also be respiratory sensory irritants. TMA but not TMLA should be considered a dermal sensitizer.

In repeated dose inhalation studies, the principal effects of TMA are on the immune system and the lung. In a 13-week inhalation repeat dose study, elevated antibody levels and lung foci were observed in rats following exposures to relatively low concentrations of TMA (0.002 – 0.054 mg/m^3), however a NOAEL was not identified. Elevated antibody levels, asthma, allergic rhinitis, and a late respiratory systemic syndrome (LRSS) are associated with

occupational exposures to TMA in some workers. The toxicity of TMA following repeated oral exposures is low, based on NOAELs of approximately 500 mg/kg-day identified for both rats and dogs. In a 13 week inhalation study, immunological and pulmonary effects were not associated with repeated exposures to TMLA; the NOAEL was determined to be 300 $\mu g/m^3$ (the highest dose tested). *In vivo* genotoxicity data are not available however, three *in vitro* assays with TMA were negative. Although a reproductive toxicity test has not been conducted for TMA, histopathological changes to reproductive tissues have not been observed in rats following subchronic exposures, and it has been found to be neither teratogenic nor fetotoxic in developmental toxicity studies.

Environment

TMA has a melting point of 165ºC, a boiling point of 390ºC, a vapor pressure of 7.6×10^{-5} Pa @ 25ºC, and assuming no hydrolysis a log K_{ow} of 1.95 and a water solubility of 1,036 mg/L. TMLA has a melting point of 219ºC, an unknown boiling point, a vapor pressure of 3.8×10^{-6} Pa @ 25ºC, a log K_{ow} of 0.95 and a water solubility of 21,000 mg/L. The half-life of TMA and TMLA in air is estimated to be 13.4 and 6.6 days, respectively, due to direct reactions with photochemically generated hydroxyl radicals. In the presence of water, TMA rapidly hydrolyzes (within 10 minutes) to form TMLA. Based on both chemicals physical chemical properties, TMA and TMLA are likely to partition to the water compartments in the environment. Acute toxicity testing in fish, invertebrates, and algae indicate a very low order of toxicity with measured No-Observed-Effect-Concentrations (NOECs) of 896, 792 and 739 mg/L, respectively. TMA and TMLA are readily biodegraded under aerobic conditions in sewage sludge, and are expected to biodegrade in soil and water as well. TMA and TMLA are not expected to bioaccumulate in food webs based on a BCF of 3.2.

Exposure

Approximately 100,000 metric tonnes/year TMA are produced worldwide, the majority of which (65,000 metric tonnes/year) are produced in the U.S. Most of the TMA produced (65%) is used in the synthesis of plasticizers for PVC resins, while smaller amounts (30%) are used as a reactant in wire and cable insulation enamels and polyester resins for powder coatings. When TMA is processed into the above materials, it is fully consumed and therefore, is not readily available for releases to the environment. All TMLA produced is used to make TMA. Occupational exposures to TMA and TMLA are likely to occur by the inhalation and dermal routes in settings where TMA is produced or used. Historical monitoring data have revealed mean concentrations ranging from 0.00051 to 0.77 mg/m^3. Because TMA is rapidly hydrolyzed to form TMLA in the presence of water, consumer and environmental exposures to TMA are not anticipated. Data regarding these potential exposures to TMLA are largely lacking, but exposures are expected to be low outside of the workplace.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Although a reproductive toxicity study and an *in vivo* genotoxicity are not available for TMA or TMLA, sufficient data are available to address these endpoints. Therefore, no additional studies are recommended to meet the SIDS data set.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	68186-90-3
Chemical Name	C.I. Pigment Brown 24
Structural Formula	Complex inorganic coloured pigment based on titanium oxide; in the rutile lattice, titanium ions are partially replaced by chromium (III) and antimony (V) ions. (Ti, Cr, Sb) O_2

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

In some circumstances, available data for C.I. Pigment Yellow 53 (CAS No. 8007-18-9, a nickel antimony doped rutile) may be presented to assist the weight of evidence approach for C.I. Pigment Brown 24, since it is closely related structurally and similar regarding its non-bioavailabilty. Its toxicological profile was also essentially similar to C.I. Pigment Yellow 53, therefore, analogy considerations can be made where the non-bioavailability is the determining parameter of non-toxicity. This was the case for reproductive and developmental toxicity.

Human Health

The acute toxicity of C.I. Pigment Brown 24 after oral exposure is negligible: oral LD50 in rats > 10000 mg/kg body weight.

C.I. Pigment Brown 24 is minimally irritating to the rabbit skin and may cause slight particle mediated irritating effects after instillation into the rabbit eye. Coloration of the skin occurred within the first 3 days after application. No data are available on sensitisation; the substance contains chromium, but no evidence for its bioavailablity was seen in a repeat oral study in the rat (see below).

No signs of clinical toxicity or histopathological changes were seen in a 90-day dietary study in the rat. A NOAEL of 500 mg/kg was identified from this study. In this study there was no evidence for chromium accumulation in the liver or kidney of rats, and traces of antimony (below 30 µg/kg tissue) were found only in the high dose group. These traces of antimony may be available from the acid-soluble impurities of the pigment. The small amount of antimony is considered to have no toxicological significance.

C.I. Pigment Brown 24 induced no gene mutation in bacteria nor in mammalian cells and no clastogenic or aneugenic effects in mammalian cells with or without addition of a metabolic activation system. Therefore, the *in vitro* data indicates that C.I Pigment Brown 24 would not exhibit a genotoxic potential *in vivo*.

There are no specific studies on carcinogenicity available.

No effects on gonads were observed in the 90 day feeding study on rats at doses of up to 500 mg/kg b.w./day (see above). A developmental toxicity study is not considered necessary because the substance showed no bioavailability with toxicological relevance after oral exposure (see above). In analogy to C.I. Pigment Yellow 53 where no reproductive or developmental effects were seen in a screening test conducted in rats tested up to 1000 mg/kg bw according to OECD Guideline 422, no effects are expected with C.I. Pigment Brown 24.

Environment

C.I. Pigment brown 24 is a solid, complex inorganic coloured pigment, based on titanium dioxide with chromium (III) and antimony (V) ions partially replacing titanium ions in the rutile lattice. It is practically inert and has a melting point above 1000°C. The vapour pressure is estimated to be negligible. C.I. Pigment brown 24 has an extremely low solubility in water; the concentration of chromium and antimony in filtrates (10 g/l) has been measured by atomic absorption to be <0.01 mg/l.

The following aquatic effect concentrations (nominal) are available:

Leuciscus idus: LC_{50} (96 h)> 10,000 mg/l; *Daphnia magna*: EC_{50} (48 h) > 100 mg/l; *Desmodesmus subspicatus*: EC_{50} (72 h)> 100 mg/l; *Pseudomonas putida*: EC_{50} (30 min) > 10,000 mg/l.

The substance is not acutely toxic to aquatic organisms (fish, invertebrates and algae) in tests with either aqueous eluates or suspensions prepared with nominal concentrations far exceeding its water solubility.

No data are available on terrestrial organisms.

The substance is inorganic and thus not biologically degradable. According to the low water solubility and the structural properties of the pigment, bioaccumulation is not expected.

Exposure

Pigment brown is used for coloring plastics, ceramics, building materials and coatings. The estimated world production amounts to 10,000 – 15,000 tonnes.

No data are available concerning exposure. Pigments released from production sites and not having been eliminated mechanically, will probably absorb to sewage sludge. In the end products, the pigments are fixed in the matrix and a release into the environment during use phase 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 is currently of low priority for further work based on a low hazard potential.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	74-87-3
Chemical Name	Chloromethane (Methyl chloride)
Structural Formula	H_3C-Cl

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Chloromethane is a gas, unless it is under pressure. Inhalation is the major route of exposure in the occupational setting. Most inhaled chloromethane is metabolized and rapidly excreted via urine and expired CO_2. Because of high volatility and rapid metabolism, chloromethane does not accumulate in the tissues. The blood clearance is rapid and biphasic. Chloromethane metabolism involves conjugation with reduced glutathione in the ultimate transformation to formate and CO_2.

Chloromethane exhibits low acute toxicity by the oral and inhalation routes. The rat oral LD_{50} is 800 mg/kg bw. Studies illustrate species, strain and sex differences in sensitivity following acute inhalation, such that male mice appear to be most susceptible (6-hour LC_{50} = 4500-4600 mg/m^3), followed by rats (4-hour LC_{50} = 5300-5400 mg/m^3), and then female mice (6-hour LC_{50} = 17,000-17,500 mg/m^3).

In a 90-day inhalation study with rats and mice exposed to 375, 750 and 1500 ppm (750, 1500 and 3000 mg/m^3) the NOAEL and LOAEL were 750 ppm (1500 mg/m^3) and 1500 ppm (3000 mg/m^3), respectively. The LOAEL is based on the observation of significant increases in SGPT activity (male mice) with histological hepatic changes, hepatic infarction (one male mouse and one female rat), increased liver weights, and lower body weights (male and female rats.) In a two-year, inhalation bioassay, rats and mice were exposed to 50, 225 and 1000 ppm (100, 450, 2000 mg/m^3) with interim sacrifices at 6, 12 and 19 months. The NOAEL and LOAEL for systemic effects in rats and mice were 225 ppm (450 mg/m^3) and 1000 ppm (2000 mg/m^3), respectively. In rats, at 1000 ppm (2000 mg/m^3), increased relative heart weights (males and females), relative kidney and liver weights (males), decreased absolute and relative testes weights and decreased absolute liver weights (females) were seen. Histopathology of testes showed bilateral and diffuse generation and atrophy of the seminferous tubules at 6 months and their severity increased until the 18-month sacrifice. Mice were more affected than rats, severe effects were seen at 1000 ppm. Effects at 1000 ppm included: neurofunctional impairment (females); depressed growth, clinical signs suggestive of CNS disturbance, significantly elevated SGPT levels, and increased relative heart weights (males and females); increased relative liver weights (females); decreased absolute brain weights (males and females); and decreased absolute and relative testes weights. In addition, hepatocellular degeneration (males and females); renal tubule epithelial hyperplasia, and cerebellar lesions characterized by degeneration and atrophy of the cerebellar granular cells occurred at 1000 ppm and was treatment related (males). Splenic atrophy and lymphoid depletion were noted at 1000 ppm (males and females). In a 12-day inhalation study in rats (4000, 7000 or 10000 mg/m^3) and mice (1000, 2000 or 4000 mg/m^3), deaths occurred in both rats and mice at the highest concentration tested. Primary effects were CNS related with lesions also occurring in the liver, kidney and brain. Rats were evaluated for testicular degeneration in which a clear exposure-concentration related response was observed. Lesions did not affect all seminiferous tubules equally with the principle affects being a reduction in late-stage spermatids, separation of spermatocytes and early-stage spermatids, with sloughing of the cells into the lumen, formation or irregular, apparently membrane-bound vacuoles in the germinal epithelium and variable formation of the giant cells. In a 93-95 day multi-species inhalation study, CNS, liver, kidney and testes were evaluated in dogs, rats and mice. No specific target organ toxicity or unequivocal toxic manifestations of chloromethane were observed in rats, mice and dogs exposed to concentrations as high as 800 mg/m^3. The NOAEL for the study was determined to be 800 mg/m^3

(the highest dose tested). In an a-typical repeated dose inhalation study, female mice were continuously exposed (22 hrs/day for 11 days) to 15, 50, 100, 150, 200 or 400 ppm (30, 100, 200, 300, 400 or 800 mg/m^3), the NOAEL was determined to be 100 mg/m^3 (50 ppm) and the LOAEL = 200 mg/m^3 (100 ppm) based on the presence of cerebellar lesions. In the same study, female mice were intermittently exposed (5.5 hrs/day for 11days) to 150, 400, 800, 1600 or 2400 ppm (300, 800, 1600, 3200 or 4800 mg/m^3) the NOAEL and LOAELs were 300 mg/m^3 (150 ppm) and 800 mg/m^3 (400 ppm), respectively.

The weight of evidence indicates that chloromethane, at high concentrations, is a direct-acting mutagen in bacteria and human cells in culture (*in vitro*) however, *in vivo* genotoxic effects were not seen due to cytotoxicity occuring at high doses. Existing information indicates that chloromethane exposure does not result in DNA alkylation.

In a 2-year bioassay, there were no statistically significant increases in tumors in rats exposed to 100, 450 or 2000 mg/m^3. A similar exposure in mice caused increased mortality at 2000 mg/m^3, and an increased incidence of kidney tumors in male mice only. Male mice exposed to 450 mg/m^3 had a slightly increased incidence of kidney tumors. Exposure of 100 mg/m^3 did not cause any increases in the tumor incidence in either sex of mice.

In a two-generation reproduction study in rats, repeated 6-hour exposures to 3000 mg/m^3 (1500 ppm) resulted in sterility (decreased spermatogenesis) that is consistent with the testicular degeneration and granulomas seen in the epididymis of male rats after seven weeks. Exposures to 950 mg/m^3 (475 ppm) also caused a decrease in fertility, but no effects were seen in rats exposed daily to 300 mg/m^3 (150 ppm) for two generations. Exposures of 300 mg/m^3 did not cause inflammation of the epididymis and did not effect reproduction in rats. The NOAEL was 300 mg/m^3 for both adults and offspring. Teratological studies have shown possible differences between species. In rats, severe maternal toxicity was seen at 3000 mg/m^3 (1500 ppm), but no teratological response was observed following repeated 6-hour daily exposures to 200, 1000, or 3000 mg/m^3 (100, 500 or 1500 ppm) during gestation. In two studies, an increased incidence of heart malformations in mice were reported at exposures that were not maternally toxic. In both studies, the NOAELs for maternal toxicity were 1000 mg/m^3 (500 ppm.) The NOAELs for developmental toxicity in these studies were 200 mg/m^3 (100 ppm) and 500 mg/m^3 (250 ppm).

In humans, the most common consequence of single or repeated exposures $\geq$ 400 mg/m^3 is functional changes in the CNS, which can involve unsteadiness, dizziness, etc. The liver, kidney, testes, epididymis and lungs can also be affected by these exposures, but most of these effects are secondary, as pronounced CNS changes occur in the presence of these effects being observed.

Environment

Chloromethane has a vapor pressure of 4800 hPa at 20^{o}C, a melting point of -97.7^{0}C, a boiling point of -24.22^{0}C (at 1013 hPa), a log K_{ow} of 0.91 and a water solubility of 4800 to 5325 mg/l at 25^{0}C. Chloromethane's atmospheric residence time is estimated to be about 1 year. The major removal process for chloromethane is reaction with hydroxyl radicals with an estimated half-life of approximately one year. Natural environmental levels are about 700 parts per trillion in ambient air. The stratospheric steady-state ozone depletion potential (ODP) of methyl chloride has been determined to be 0.02 relative to CFC 11 (ODP=1). Hydrolysis of chloromethane in water is relatively slow (does not readily hydrolyze) with a half-life of about 1.1 years at pH 7 and 25^{o}C. Considering its solubility, volatility and resultant Henry's Law Constant, chloromethane is expected, under equilibrium conditions, to exist principally in the air and is not expected to be present in the aquatic or terrestrial compartments. Fugacity (Level III) modeling performed based upon release data to the respective compartments, indicates that about 99.8% of the total, steady state mass of chloromethane will reside in the air compartment and about 0.1% will reside in each of the soil and water compartments. However, when chloromethane is released only to the water compartment it is predicted to remain primarily in that compartment (80% water and 20% air). Chloromethane is not readily biodegradable but may be degraded by adapted bacteria and under anaerobic conditions. The calculated BCF ranges from 2.98 to 3.16.

Based on the chemical's volatility, results based on nominal concentrations may be considered an underestimation of the actual toxicity; however, this may be mitigated by the chemical's high water solubility and dependent upon test conditions. The LC_{50} from the 96-hr fish study using nominal concentrations is 270 mg/L. In daphnia, the 48-hr reported EC_{50} based on nominal concentrations is 200 mg/L. The algal toxicity thresholds of 550 and 1450 mg/L were 7 day tests using nominal concentrations. Due to the possibility that the algae may not have been in the

exponential growth phase throughout the tests, the ECOSAR predicted 96-hour EC_{50} value of 231 mg/L is preferred. In addition, the predicted acute toxicity of chloromethane (ECOSAR; version 0.99g) is in good agreement with the experimental data as indicated above for green algae along with acute toxicity for fish (96-h LC_{50} = 396 mg/L) and daphnia (48-h LC_{50} = 394 mg/L.). In combination with the chemicals environmental fate characteristics, the chemical is considered to be a low concern for the environment.

Exposure

Chloromethane is used almost entirely as a chemical intermediate to make other chloromethanes, silicone intermediates, pesticides, quaternary amines and surfactants, and as a methylation reactant for various other processes. The various uses of chloromethane were estimated at the following percentages in 1987: 74% silicones, 7% agricultural chemicals, 6% methyl cellulose, 5% quaternary amines, 2% butyl rubber, 2% miscellaneous, 4% exports. These estimates do not recognize captive use for other chloromethane production. Most chloromethane is released to the air from non-anthropogenic sources (forest fires and releases from the ocean). The natural levels of chloromethane are about 700 parts per trillion in ambient air. Monitoring near non-industrial anthropogenic sources have shown much higher levels. Chloromethane has been observed at low concentrations (< 222 ng/l) in water. The total global production from sources other than manufacture is estimated at about 4.5×10^9 tonnes. The 1997 global manufactured production of chloromethane was estimated at 1.54×10^6 tonnes. This estimate is based on the assumption that the U.S. produces 35-45% of the total global estimate and the 1997 U.S. production volume of 6.3×10^5 tonnes. Under the US EPA Toxic Release Inventory, 109 U.S. facilities reported in 1998, that approximately 1.2×10^6 kgs were released to air, representing approximately 90% of the total on-and of-site releases of chloromethane. People who smoke or use wood as a heat source are likely exposed to much higher than normal background concentrations of chloromethane. Higher exposures may also occur in or near industrial plants producing or using this chemical. Individuals engaged in chloromethane production may be exposed to concentrations greater than background; however, most U.S. industries have maintained their worker-exposure levels well below the ACGIH guideline of 50-ppm TWA, which was adopted by OSHA in 1989. Chloromethane is not used in any commercial product currently manufactured.

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. Based on data presented by the Sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently a low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7647-01-0
Chemical Name	Hydrogen chloride
Structural Formula	H-Cl

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Hydrogen chloride will rapidly dissociate and its effects are thought to be a result of pH change (local deposition of H^+) rather than effects of hydrogen chloride/hydrochloric acid.

The acute oral LD_{50} values were determined to be 238-277 mg/kg bw for female rats, and the inhalation LC_{50} values were determined to be 23.7-60.9 mg/L/5min, 5.7-7.0 mg/L/30min and 4.2-4.7 mg/L/60min for rats, 20.9 mg/L/5min, 3.9 mg/L/30min and 1.7 mg/L/30min for mice. Hydrogen chloride is corrosive to the skin and severe effects can be expected from exposure to the eyes. No skin sensitisation has been reported.

There are few detailed studies reported for human exposure. The irritation of hydrogen chloride to mucous is so severe that workers evacuate from the work place shortly after detecting its odor. A relation between concentrations from accidental exposure and health effects have not been reported in detail.

For repeated dose toxicity, local irritation effects were observed in the groups of 10 ppm and above in a 90-day inhalation study in compliance with FDA-GLP. The NOAEL for systemic toxicity has been determined to be 20 ppm for rats and mice.

For genetic toxicity, a negative result has been shown in the Ames test. A positive result, which is considered to be an artifact due to the low pH, has been obtained in a chromosome aberration test using Hamster ovary cells. The effects of low pH in *in vitro* studies are not a problem *in vivo* as the proton level is regulated systemically.

For carcinogenicity, no pre-neoplastic or neoplastic nasal lesions were observed in a 128-week inhalation study with SD male rats at 10 ppm hydrogen chloride gas. No evidence of treatment related carcinogenicity was observed either in other animal studies performed by inhalation, oral or dermal administration. In humans, no association between hydrogen chloride exposure and tumor incidence was observed.

No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. Because protons and chloride ions are normal constituents in the body fluid of animal species, low concentrations of hydrogen chloride gas/mist or solution do not seem to cause adverse effects to animals. In fact, the cells of gastric glands secrete hydrochloric acid into the cavity of the stomach and orally administered sulfuric acid, which results in pH change as well, did not cause developmental toxicity to laboratory animals. These facts indicate that hydrogen chloride/hydrochloric acid is not expected to have developmental toxicity. In addition, no effects on the gonads were observed in a good quality 90-day inhalation study up to 50 ppm.

Environment

Hydrogen chloride is a colourless gas which has a pungent odor, and has a vapour pressure of 42,200 hPa at 20°C and a water solubility of 823 g/L at 0°C, 673 g/L at 30°C. Its aqueous solution (called hydrochloric acid) possesses

strong acidity, and reacts with most metals producing explosive hydrogen gas. Hydrogen chloride is readily dissociated in water into hydrated protons and chloride ion.

The physico-chemical properties indicate that hydrogen chloride released into the environment is distributed into the air and water.

Hydrogen chloride can react with hydroxyl radicals to form chloride free radicals and water and its half-life time is calculated as 11 days. No accumulation of hydrogen chloride *per se* in living organisms is expected due to its high solubility and dissociation properties.

The toxicity values to *Selenastrum capriornutum* 72h-EC_{50} is pH 5.1 (0.780 mg/L) for biomass, pH 5.3 (0.492 mg/L) for growth rate and the 72h-NOEC is pH 6.0 (0.097 mg/L) for biomass and growth rate. The 48h-EC_{50} for *Daphnia magna* is pH 5.3 (0.492 mg/L) based on immobilization.

The hazard of hydrochloric acid for the environment is caused by the proton (pH effect). For this reason the effect of hydrochloric acid on the organisms depends on the buffer capacity of the aquatic ecosystem. Also the variation in acute toxicity for aquatic organisms can be explained for a significant extent by the variation in buffer capacity of the test medium. For example, LC_{50} values of acute fish toxicity tests varied from 4.92 to 282 mg/L.

It is not considered useful to calculate a PNEC for hydrochloric acid because factors such as the buffer capacity, the natural pH and the fluctuation of the pH are very specific for a certain ecosystem.

There is a possibility that the emission of hydrochloric acid could locally decrease the pH in the aquatic environment. Normally, the pH of effluents is measured very frequently to maintain the water quality. In addition to that, water quality including the range of pH could be managed properly to prevent adverse effects on the aquatic environment based on the criteria of the pH in rivers and lakes. Therefore, a significant decrease of the pH of the receiving water is not expected. 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 anthropogenic or naturally occurring hydrochloric acid.

Exposure

The production volume of hydrogen chloride in 1999 was 1,155,259 tonnes (Production; 1,144,779 tonnes, import; 10,480 tonnes) in Japan and approximately 7,150,000 tonnes (6,500,000 metric tonnes) in the U.S.A. The production capacity in the U.S.A. in 1999 was approximately 2,242,000 tonnes excluding the capacity for by-product HCl that is generated and recycled in integrated systems such as ethylene dichloride/vinyl chloride monomer (EDC/VCM) production plants. The market of the aqueous solution occupies only about 20% of the total demand in the U.S.A.

Hydrogen chloride is produced by the direct reaction of hydrogen and chlorine, by reaction of metal chlorides and acids, and as a by-product from many chemical-manufacturing processes such as chlorinated hydrocarbons. A large quantity of hydrogen chloride is recycled in a same line for other material production processes such as ethylene dichloride production.

Hydrogen chloride/hydrochloric acid is commercially available in a gaseous form and solutions at various concentrations. The anhydrous hydrogen chloride is mainly used for ethylene dichloride and vinyl chloride monomer production etc. In aqueous form, there are various uses such as oil well acidising and steel pickling.

Hydrogen and chlorine, which is the source of formation for hydrogen chloride, are commonly found in the environment. Thus, hydrogen chloride occurs in nature through the reaction of sea salt aerosol and acidic sulphate in the ocean, and through atmospheric or aquatic (hydrolysis or biodegradation) degradation of organo-halogens etc. Volcano eruption injects hydrogen chloride of 400,000-11,000,000 tonnes into the atmosphere. Additionally mammalian constantly secrets the gastric juice, which contains H^+ concentration equivalent to 0.17 N HCl (pHs as low as 0.87) into the stomach cavity.

Hydrogen chloride may be released into air from artificial source such as production and use sites. Unwanted

hydrogen chloride is released into the environment from garbage incineration plants and by open burning or fire. Practically, the emission of hydrogen chloride into air is controlled, for instance, by the absorption in water and neutralisation before the emission into the environment if significant release is expected.

For workers, a maximal concentration of hydrogen chloride in the atmosphere at the working place of 5 ppm (7.5 mg/m^3) is established by ACGIH (TLV-ceiling limit). Since hydrogen chloride/hydrochloric acid is irritating or corrosive depending on the concentrations, exposure control such as ventilation should be provided and acid resistant protective equipment for eyes and skin, respiratory protective equipment and face shield should be ready to use.

The products using hydrochloric acid as food-processing agents are neutralized or buffered in the products, and no effects of the pH are expected. Action to reduce consumer exposure has also been taken for products such as toilet cleaners containing high-level hydrochloric acid which produce hydrogen chloride gas or cause irritancy.

Hydrogen chloride which occurs in nature and exists in the atmosphere could be inhaled by the general population. Also, indirect expose to hydrated protons and chloride ions occur via drinking surface water or food consumption occurs since both ions are commonly found in the environment. The significant acidic effect as hydrochloric acid, however, is not expected due to the buffering capacity in the environment.

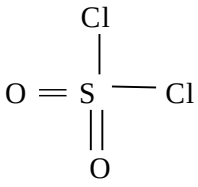
RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses corrosive properties indicating a hazard for human health and the environment. No further work is recommended if sufficient control measures are in place to avoid significant human exposure and environmental impact, including prevention of accidental exposure. In situations where this is not the case, risk assessment and if necessary, risk reduction measures are recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7791-25-5
Chemical Name	Sulfuryl chloride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute toxicity of sulfuryl chloride following inhalation is high. In male Sprague-Dawley rats with head-only exposure to vapor a 4 h-LC50 of 878 mg/m^3 was calculated. Clinical signs included nasal discharge and eye irritation.

In humans, pulmonary edema of delayed onset has been reported after inhalation of sulfuryl chloride vapor.

Sulfuryl chloride hydrolyzes slowly in moist air and reacts violently with water, forming chlorosulfonic acid, hydrochloric acid and sulfuric acid. Due to this hydrolytic reaction, sulfuryl chloride is corrosive to the skin, eyes and respiratory tract.

Studies with sulfuryl chloride concerning sensitizing properties are not available. The hydrolysis products sulfuric acid and hydrochloric acid gave no indication for a sensitizing potential in humans and experimental animals.

From a 14-day inhalation study with sulfuryl chloride in rats, a NOAEC could not be derived, since pneumonitis was still observed at the lowest exposure level of 17 mg/m^3. The reported effects are in line with all other evidence regarding the chemical and biological properties, i.e. corrosivity of sulfuryl chloride and its hydrolysis products hydrochloric acid, sulfuric acid, and chlorosulfonic acid. Studies performed with sulfuric acid gave LOAECs in the range of 0.3 mg/m^3, the LOAEC found in a 90-day study with hydrochloric acid was 15 mg/m³. All findings were confined to the site of first contact and can be explained by the irritating/corrosive properties of the acid.

Sulfuryl chloride as well as the hydrolysis products hydrochloric acid, sulfuric acid and chlorosulfonic acid are all classified as corrosive and hydrochloric acid and chlorosulfonic acid are classified as irritant to the respiratory tract. No primary systemic effects were reported.

Sulfuryl chloride did not show mutagenic activity in Ames tests with *Salmonella typhimurium*. A slight mutagenic activity was observed in only one tester strain without metabolic activation. However, this result was found to be not reproducible in further tests. As sulfuryl chloride decomposes to acids, the resulting change in pH may induce genotoxic effects such as chromosomal aberrations and other DNA damage *in vitro* and *in vivo* at the portal-of-entry.

No carcinogenicity studies with sulfuryl chloride were identified. The hydrolysis products hydrochloric acid and sulfuric acid gave no clear indications for an increased tumor incidence after life-time exposure in laboratory animals.

Studies with sulfuryl chloride concerning effects on fertility and development were not available and there were also no data on fertility effects for the hydrolysis products sulfuric acid and hydrochloric acid. Concerning developmental toxicity, the hydrolysis product sulfuric acid gave no indication for adverse effects in mice and rabbits after exposure via inhalation. Because sulfuryl chloride 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 sulfuryl chloride by any route.

In humans, several epidemiological studies have suggested a relationship between exposure to strong inorganic acid mists containing sulfuric acid and an increased incidence of laryngeal cancer. IARC (1992) has concluded that "occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic to humans" (Group 1). Concerns have been raised that confounding factors could not be fully excluded. The effects might be a secondary finding to be expected after prolonged exposure to strong acid due to the cytotoxicity and consequent stimulus to increased cell proliferation.

Environment

Sulfuryl chloride is a moisture/water sensitive fluid which hydrolyses completely and decomposes on heating above the boiling point (69°C) from 100°C on. It reacts violently with water. The vapor pressure is given with 148 hPa at 20°C, the log Kow cannot be determined due to hydrolysis.

If sulfuryl chloride is released to water, degradation occurs through hydrolysis to sulfuric and hydrochloric acid. A guideline test on hydrolysis at room temperature under stirring shows the substance to be completely hydrolyzed within 5 min. For assessment of the environmental impact of the hydrolysis products it is referred to the validated results of the hazard assessments on sulfuric acid (CAS-No. 7664-93-9) and hydrochloric acid (CAS-No. 7647-01-0) within the OECD HPV Chemicals Programme. Both acids are strong mineral acids, which dissociate readily in water to sulfate or chloride ions resp. and the hydrated protons, and they are miscible with water. The total ionization will imply also that both acids themselves, will not adsorb on particulate matters or surfaces, and will not accumulate in living tissues.

The hydrolysis products of sulfuryl chloride have been tested in a number of aquatic species. All effects are accounted to acidification.

Lepomis macrochirus showed an acute toxicity (96 h LC50) when a pH value of 3.5 to 3.25 was reached. Chronic testing with early life stages of fish gave NOECs at pH 6.0 (*Jordanella floridae*, exposure for 45 d) and 5.56 (*Salvelinus fontinalis* , exposure for 10 months).

Exposure

About 10,000 to 20,000 t/a sulfuryl chloride were produced by about 7 producers world wide in 2001. Sulfuryl chloride is a basic chemical which is processed chemically to other intermediates in different fields of application. A direct use besides in hermetically sealed batteries for special uses is not known. Due to the production and processing conditions, as well as the rapid hydrolysis property of sulfuryl chloride, no emission to the environment has been identified at the production site in the Sponsor country. There is no information about environmental emission at other production and processing sites.

Sulfuryl chloride is produced in closed systems. To protect workers from exposure during maintenance and repair work precautionary measures like engineering controls and personnel training is used. Sulfuryl chloride has a high vapour pressure and may react violently with water. Hence, workers may potentially be exposed through the inhalation of vapour or dermally by splashing from liquid.

There is no exposure of the general public 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

Human Health: The corrosive properties indicate a hazard for human health. No further work is recommended, if sufficient control measures are in place to avoid significant human exposure, including prevention of accidental exposure. In situations where this is not the case, risk assessment and, if necessary, risk reduction measures are recommended.

Environment: The chemical is currently of low priority for further work as it hydrolyses very fast and therefore environmental releases of sulfuryl chloride are not likely to occur. The degradation products sulfuric acid and hydrochloric acid have already been assessed within the OECD SIDS-Program.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-34-5
Chemical Name	1,1,2,2-Tetrachloroethane
Structural Formula	$Cl_2HC - CCl_2H$

SUMMARY CONCLUSIONS OF THE SIAR

1,1,2,2-Tetrachloroethane is a colourless volatile liquid with chloroform-like odour.

Human Health

Based on the large body of past human experience, 1,1,2,2-tetrachloroethane can be considered as very toxic to humans exposed acutely. It is irritating to skin and eye. Repeated exposure observations in laboratory animals and cases reported in humans indicate that it is mainly toxic to the liver and the kidney; it can also damage the nervous system and the hematological system. No standard reproductive toxicity studies in laboratory animals are available. The available data are conflicting and no conclusion can be made regarding effects of 1,1,2,2-tetrachloroethane on reproductive organs. The database for developmental toxicity is poor and adverse developmental effects were reported in rats and mice at doses known to be clearly toxic to pregnant females. It is not possible to draw a valid assessment from these studies on developmental toxicity. Some potential for genotoxicity of 1,1,2,2-tetrachloroethane has been demonstrated *in vitro.* The overall results observed *in vivo* and *in vitro* indicate that 1,1,2,2-tetrachloroethane might have some genotoxic potential. In an oral long term bioassay, 1,1,2,2-tetrachloroethane has been shown to induce hepatocellular carcinoma in mice but it was not carcinogenic in rats.

From the past experience, the threshold chronic toxicity by inhalation in human has been estimated around 70 mg/m^3, a value ten time higher than the current occupational exposure limit and several thousand times higher than the ambient and indoor air for the general population. The lowest oral threshold dose in rats was found around 3 mg/kg bw/day indicating large margins of safety when comparing with the trace levels of 1,1,2,2-tetrachloroethane when it is detected in food or drinking water in northern America.

Environment

Based on its physico-chemical properties, (vapor pressure: 6 hPa; solubility: 2.9 g/l) 1,1,2,2-tetrachloroethane released to the environment will mainly partition into the atmosphere. It has an average atmospheric lifetime of 92 days. Its impact on stratospheric ozone, its greenhouse effect and its contribution to the formation of tropospheric ozone is expected to be low. Observed intermediate products formed during the atmospheric oxidation are phosgene, C(=O)ClH and dichloroacetylchloride. Decomposition in the atmosphere of phosgene and C(=O)ClH should lead to the formation of HCl and CO_2 by hydrolysis in atmospheric water whereas, dichloroacetylchloride will form HCl and dichloroacetic acid which will be further removed from the atmosphere by rain water.

If released to water, 1,1,2,2-tetrachloroethane will be removed rapidly by volatilization. It is not readily biodegradable. It is expected to undergo dehydrochlorination under hydrolytic alkaline conditions to trichloroethylene (see SIDS for trichloroethylene: CAS No. 75-01-6) and to biodegrade under anaerobic conditions. Based on its partition coefficient (logKow = 2.39) and its bioconcentration factor (BCF = 4.2-13.2), it is not likely to bioaccumulate. Due to its low Koc value of 46, it is not expected to adsorb to suspended solids, sediments and soils.

1,1,2,2-Tetrachloroethane is toxic to aquatic organisms, *Daphnia magna* being the most sensitive species with a 48h EC50 of 9.3 mg/l. On the basis of the NOEC determined from the chronic tests (32 day NOEC *Pimephales promelas*

= 1.4 mg/; 28 day NOEC *Daphnia magna* = 6.9 mg/l; 72h EC10 *Scenedesmus subspicatus* = 9.8 mg/l), a PNEC of 140 µg/l is proposed applying a factor of 10 to the lowest NOEC available with fish.

Exposure

The historic production level of 1,1,2,2-tetrachloroethane in the 1960–70's was over a hundred thousand tonnes/year. Since then, because of its disappearance as a solvent, the production has dramatically decreased. The substance is no longer on the market but it is exclusively produced and consumed on site. There are no publicly available production data but it is estimated that the current production level is between 10,000 and 100,000 tons/year. According to the Sponsor country, 1,1,2,2-tetrachloroethane is only used in OECD countries as a feedstock in closed system for the production of other chlorinated hydrocarbons. It may also be an incidental by-product of other production processes for chlorinated hydrocarbons such as the production of vinyl chloride.

Personal exposure monitoring conducted during production, processing and maintenance activities shows that potential for exposure of workers to 1,1,2,2-tetrachloroethane is extremely low. The available monitoring data range from 0.01 to 0.2 ppm. These values are well below the Occupational Exposure Limit (TWA/8h) of 1 ppm (7 mg/m^3).

The recent data from the US and the European Union show that the release of 1,1,2,2-tetrachloroethane into the environment through its production and uses is low. Its concentration in surface water was found far below the Predicted No Effect Concentration (PNEC) of 140 µg/l proposed for the substance.

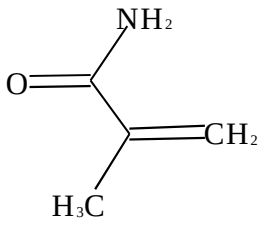
RECOMMENDATION

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. 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.	79-39-0
Chemical Name	Methacrylamide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

After i.v. administration of ^{14}C-methacrylamide (15% solution in water) , most of the radioactivity (86 % of the dose) was excreted with the urine within 24 hours in rabbits. Following 15 to 30 minute dermal exposure to male rabbits and male rats, 23-52% and 3.7-5.7% of the administered radioactivity, respectively, were excreted in urine after 24 hours. Phenobarbital induction increased the reaction rate about 2-fold suggesting a cytochrome P-450 dependent metabolism.

Acute oral toxicity of methacrylamide in rats is: LD_{50} = 1653-1938 mg/kg [OECD TG 401]. In one study, tremor was found at 1315 mg/kg and higher. Salivation, staggering gait, irritability, soiled perioral fur, sitting position and orange-yellow urine in cage trays were observed at 1512 mg/kg and higher. Histopathological changes were observed in the testes and epididymides in males at 1512 mg/kg and higher. Necrosis of neurocyte cell in cerebellum was observed at 1315 mg/kg and higher of both sexes. Degeneration of sciatic nerve fibers was observed in males at 1512 mg/kg and in females at 1739 mg/kg. In the other study, sedation, ataxia, mortality, ruffled fur, ventral/curved/or latero-abdominal body position, somnolence, emaciation, and lacrimation were observed. Methacrylamide was not to slightly irritating to skin in rabbits [OECD TG 404] and moderately irritating to eyes in rabbits [OECD TG 405]. There is no available information on skin sensitization.

In a 28 day repeated dose study in rats [OECD TG 407] by gavage at the dose levels of 0, 30, 100 and 300 mg/kg/day, body weight gain and food and water consumption were decreased in both sexes at 300 mg/kg/day. A decrease in body weight gain was also observed in females at 100 mg/kg/day. Some clinical and functional changes (decrease in muscle tone, ataxia and decrease in grip strength) were found at 300 mg/kg/day. Males at 100 mg/kg/day and higher and females at 30 mg/kg/day and higher showed a decrease in locomotor activity. These functional changes were observed continuously throughout the recovery period. Histopathological examination revealed a degeneration of the sciatic nerve fibers and axonal swelling in the cerebellar peduncle at 300 mg/kg/day of both sexes. At 300 mg/kg/day, a decrease in hematocrit, hemoglobin, MCH, urea nitrogen, creatinine, alpha1-globulin, alpha2-globulin and ALP, and an increase in albumin and triglyceride were noted. At 100 mg/kg/day, a decrease in hemoglobin and MCH were noted. At the end of the recovery period, an increase in absolute and relative testis weights was found. NOAELs were considered to be 30 mg/kg/day for males and less than 30 mg/kg/day for females.

A 12 month repeated dose toxicity study in male rats and male mice given methacrylamide in drinking water (200, 400, 800 and 1200 ppm corresponding to ca. 4.6, 9.1, 19.5 and 31.6 mg/kg for rats, and ca. 24.3, 49.6, 120 and 220.6 mg/kg/day for mice) was also conducted. For rats, at 800 ppm (ca. 19.5 mg/kg/day) and higher, reduction in

the rotarod performance, distension of the urinary bladder, shrinkage and loss of myelinated fibers of sciatic nerve, and atrophy of gastrocnemius muscle were observed. Symptoms of peripheral neuropathy including decrease in grip strength and abnormal gait were noted in the highest dose group. Serum total cholesterol and phospholipid content were increased significantly at the highest dose. In mice, reduction in the rotarod performance, symptoms of peripheral neuropathy including decrease in grip strength and abnormal gait, atrophy of gastrocnemius muscle, distension of the urinary bladder and decrease in body weight gain were seen at 800 ppm (ca. 120mg/kg/day) and higher. At 400 ppm (ca.49.6 mg/kg/day) and higher, paralysis of hindlimb, shrinkage and loss of myelinated fibers of sciatic nerve were observed. The NOAELs for the 12 month repeated dose study were considered to be ca. 9.1 mg/kg/day (400ppm) for rats and ca. 24.3 mg/kg/day (200ppm) for mice.

The lowest NOAEL for repeated dose toxicity was considered to be ca. 9.1 mg/kg/day obtained from the 12 month repeated dose toxicity study based on clinical signs, rotarod performance and histopathological changes of the nervous system.

In a preliminary Reproduction Toxicity Screening Test by oral administration in Rats [OECD TG 421], this substance was administered at 0, 12.5, 50 and 200 mg/kg/day. A decrease in the maternal copulation rate, delayed parturition and abnormal nursing were found at 200 mg/kg/day. Furthermore low body weights and decreased viability of the pups were also found at 200 mg/kg/day. 50 mg/kg/day was considered to be the NOAEL for reproductive and developmental toxicity in this study. However, the changes observed in pups might be related to severe maternal toxicity.

A two-generation reproductive toxicity study with mice given methacrylamide in drinking water was conducted according to the modified RACB (the National Toxicology Program's Reproductive Assessment by Continuous Breeding Protocol). In this study, F_0 and F_1 animals were dosed for approximately 100 days (24 – 240 ppm corresponding to 4.5 – 49 mg/kg/day) and 74 days (24-240 ppm corresponding to 6.8 - 71.3 mg/kg/day), respectively. No maternal nor reproductive toxicity was observed in both generations. The NOAELs of methacrylamide are considered to be 49 mg/kg/day for F_0 and 71.3mg/kg/day for F_1.

Based on the results of the two studies, the lowest NOAEL of methacrylamide for reproductive toxicity was considered to be 49 mg/kg/day.

In a developmental toxicity study, methacryamide was administered to pregnant mice from gestation day 6 to gestation day 17 at the dose levels of 60, 120 and 180 mg/kg/day. Increased postimplantation death per litter at 180 mg/kg/day and reduction of fetal body weight at 120 mg/kg/day and higher were found. External anomalies in offspring were not observed. 60 mg/kg/day was considered to be the NOAEL for developmental toxicity in this study.

In the two-generation reproductive toxicity study (4.5 - 49 mg/kg/day for F_0 and 6.8 - 71.3 mg/kg/day for F_1), the hindlimb grip strength was reduced in three- week- old male and female F_1 offspring in all dose groups. However, this effect became insignificant when animals grew older at 6.8 and 23.8 mg/kg/day.

Based on these results, the NOAEL of methacrylamide for developmental toxicity was considered to be less than 6.8 mg/kg/day.

As mentioned above, methacrylamide has neurotoxic effects.

Methacrylamide was not mutagenic in bacteria up to 5,000 ug/plate [OECD TG 471] and not clastogenic in CHL/IU cells up to 900 ug/mL (10 mM) [OECD TG 473]. It also gave a negative response in a dominant lethal assay conducted as a part of a modified reproductive assessment. Males after treatment of methacrylamide (4.5 – 49 mg/kg/day) for approximately 100 days were cohabited with untreated females. No dominant lethal effects were observed. However, with reference to the structural similarity with acrylamide, uncertainty remains with regards to mutagenicity.

The available data are insufficient to judge the carcinogenicity potential of this chemical.

Environment

Methacrylamide is soluble in water (>=100g/L at 25°C). Its vapor pressure is estimated to be low (1.3×10^{-4} hPa at 25 °C). This substance is readily biodegradable and has a low bioaccumulation potential based of its log Pow (-0.15). Methacrylamide will react in the atmosphere with photochemically-produced hydroxyl radicals with a half life of 0.5 day. The fugacity model (Mackay level III) suggests that if released to the environment, the majority of this substance would distribute into water and soil.

In acute toxicity studies, the EbC_{50} and ErC_{50} for green algae [OECD TG 201] and the EC_{50} for Daphnia [OECD TG 202] were greater than 1000 mg/L. LC_{50} for fish were greater than 100 mg/L [OECD TG 203] and 2730 mg/L [other method], respectively. In a chronic toxicity study with Daphnia [OECD TG 211], the NOEC was greater than 100 mg/L. As for chronic toxicity in green algae, the NOEbC and NOErC were 556 mg/L and greater than 1000 mg/L, respectively.

Exposure

The production volume of the substance in 2001 is estimated at ca. 3500 tonnes/year in Japan and the production capacity in the EU is ca. 5000 tonnes/year.

It is mainly used as a raw material for polymerized compounds such as emulsions (liquid that includes many minute floating particles) or latex, whose applications are textile-finishing agent, paper finishing agent, coating agent, condensing agent, etc. The residual monomer content in polymers is ca. 0.5% or less. Typical residual monomer contents are 0.001% to 0.01%. Migration of residual unpolymerized methacrylamide from polymer articles is very low, as typified by migration into food simulants under EU food regulations for plastic materials (Directive 90/128/EEC relating to plastic materials and articles intended to come into contact with foodstuffs). The Specific Migration Limit (SML) is below 0.02 mg/kg. Hence exposure of this substance to consumers is very low.

Because of its use limited to industries and its low vapor pressure, release of this substance into air and soil is very low. At the production sites waste and residues of the production process are incinerated. It is considered that release to water through sewage treatment system is the most important exposure route to the environment. The concentrations of methacrylamide in the influent of the sewage treatment plant was 2100 mg/L. In the effluent and the river water downstream from the outfall of the industrial site the concentration was below 1 mg/L. Measurement data at ca. 400 meters down stream from the outfall of the industrial site show concentrations of below 0.1 mg/L – 0.3 mg/L

Based on usage and properties of methacrylamide, only occupational exposure via inhalation and dermal routes is considered to be possible, and consumer exposure is not expected.

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 environmental hazard potential and because it is anticipated based on data presented by the Sponsor country that the exposure to humans is low. However, the substance has properties indicating hazards for human health (developmental toxicity and neurotoxicity) and uncertainty regarding mutagenicity. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. It is noted that a micronucleus assay will be conducted.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	8007-18-9
Chemical Name	C.I. Pigment Yellow 53
Structural Formula	Complex inorganic coloured pigment based on titanium oxide; in the rutile lattice, titanium ions are partially replaced by nickel (II) and antimony (V) ions. (Ti, Ni, Sb) O_2

SUMMARY CONCLUSIONS OF THE SIAR

C.I. Pigment yellow 53 is a solid, complex inorganic coloured pigment, based on titanium dioxide with nickel (II) and antimony (V) ions partially replacing titanium ions in the rutile lattice. It is practically inert and has a melting point above 1000 °C. The vapour pressure is estimated to be negligible. C.I. Pigment yellow 53 has an extremely low solubility in water; the concentration of nickel and antimony in filtrates (10 g/l) has been measured by atomic absorption to be <0.01 mg/l.

Human Health

No mortalities or clinical signs of toxicity were observed in male and female rats in an acute oral study; LD50 > 2000 mg/kg body weight [OECD TG 401].

C.I. Pigment Yellow 53 is minimally irritating to the rabbit skin immediately after application due to mechanical effects and slightly irritating to the rabbit eye for the same reason. No data are available on sensitisation. The substance contains nickel, however, which has been shown to be not biologically available following repeated inhalation and oral exposure in rats.

No signs of clinical toxicity or histopathological changes were seen in a 90 day feeding study in rats tested up to 450 mg/kg bw or in a combined repeat dose and/reproductive screening study conducted according to OECD TG 422. A NOAEL of 1000 mg/kg was identified in rats for repeated oral toxicity from the OECD 422 study. In a rat inhalation study, exposure to 60 mg/m^3 for 6 hr/day for 5 days produced no clinical signs of toxicity. However, the absence of histological examination prevents identification of a reliable NOAEC.

In *in vitro* genotoxicity tests no gene mutation in bacteria or mammalian cells and no clastogenic or aneugenic effects in mammalian cells were observed. There are no data available for *in vivo* genotoxicity. However, based on the *in vitro* data, there is no indication that C.I. Pigment Yellow 53 would exhibit genotoxic potential *in vivo*.

There are no specific studies on carcinogenicity.

No adverse effects on reproduction and development were observed in a reproductive/developmental toxicity screening test conducted according to OECD Guideline 422 using male and female rats treated via gavage up to 1000 mg/kg bw/day. The NOAEL for fertility for males and females = 1000 mg/kg bw/day (highest dose tested), the NOAEL for maternal toxicity = 1000 mg/kg bw/day (highest dose tested), and the NOAEL for development = 1000 mg/kg bw/day (highest dose tested). No histological changes on the gonads were observed in rats in the 90 d feeding study tested up to 450 mg/kg.

As for bioavailability of C.I. Pigment Yellow 53, in the same 90 day feeding study (see above) in rats, traces (below

30 µg/kg) of antimony were detected in liver and kidney of rats, but exclusively in the high dose group. These traces most likely originate from acid-soluble impurities. Anyhow, the traces of antimony detected in liver and kidney are considered to have no toxicological significance. No treatment related increase in nickel concentration was detected in liver and kidney at any dose level and exposure duration. The nickel and antimony concentration of liver and kidney in rats after inhalation exposure to 60 mg/m³ C.I. Pigment Yellow 53 was within the range of quantification limit or below. A bioavailability of nickel and antimony from the pigment was not demonstrated. The pigment dust is eliminated from the lungs with a half-life of about 50 days which is typical for nuisance dusts.

Environment

The following aquatic effects concentrations (nominal) are available:

Tests with *Oryzias latipes*, *Daphnia magna* and *Selenastrum capricornutum* each show no toxic effects in the range of water solubility.

Investigations well above the water solubility show the following results:

Leuciscus idus: LC_{50} (96 h) > 10,000 mg/l; *Daphnia magna*: EC_{50} (48 h) > 100 mg/l; *Desmodesmus subspicatus*: EC_{50} (72 h)> 100 mg/l; *Pseudomonas putida*: EC_{50} (30 min) > 10,000 mg/l.

In a reproduction study with *Daphnia magna* a NOEC (21 d) >1 mg/l has been derived.

The substance is not acutely toxic to aquatic organisms (fish, invertebrates and algae) in tests with either aqueous extracts or suspensions prepared with nominal concentrations far exceeding its water solubility. Furthermore, no chronic effects towards *Daphnia magna* were observed.

No data are available on terrestrial organisms.

The substance is inorganic and thus not biologically degradable. According to the low water solubility and the structural properties of the pigment, bioaccumulation is not expected.

Exposure

Pigment yellow 53 is used for coloring plastics, ceramics, building materials and coatings. In 2001 the estimated world production amounts to 5,000 – 10,000 tonnes.

No data are available concerning exposure. Pigments released from production sites and not having been eliminated mechanically, will probably absorb to sewage sludge. In the endproducts, the pigments are fixed in the matrix and a release into the environment during use is not expected.

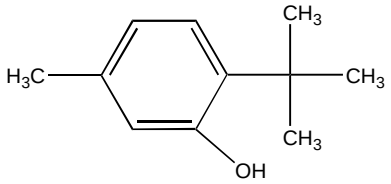
RECOMMENDATION

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 based on a low hazard potential.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-60-8
Chemical Name	6-*tert*-Butyl-*m*-cresol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics and metabolism of 6-*tert*-Butyl-*m*-cresol. The LD50 values for acute toxicity of this substance were between 320 and 800 mg/kg in males and between 130 and 320 mg/kg in females for rats, and 580 mg/kg in males and 740 mg/kg in females for mice. This substance is corrosive to skin and eyes in rabbits. But no irritation problem has been reported at any production site where workers wear proper clothing and equipment. In a repeated toxicity study in rats (combined repeat dose and reproduction toxicity screening test [OECD TG 422]), suppression of the body weight and decrease in food consumption were observed in females of the 60 mg/kg group. Liver was the primary organ for toxic effect. Hypertrophy of centrilobular hepatocytes was observed in both sexes of the 60 mg/kg group. Based on the above results, the NOAEL for repeated dose toxicity is considered to be 12.5 mg/kg/day for both sexes.

This substance was not genotoxic in a gene reverse mutation test [OECD TG 471,472]. A chromosomal aberration test in CHL/IU cells [OECD TG 473] was positive for short-term treatment with an exogeneous metabolic activation system. However, a mouse micronucleus assay conducted *in vivo* [OECD TG474] was negative.

A reproductive toxicity study in rats [OECD TG 422] revealed that this substance was toxic to the dams at 60 mg/kg, causing depression of body weight gain and a slight decrease in the number of corpora lutea and implantations. This effect in the dams influenced the outcome of pregnancy, seen as a decrease in the number of live births and depression of weight gain in the offspring. These effects were not seen at 12.5 mg/kg/day. No evidence of gross malformations was observed at any dose. Based on these findings, the NOAEL for reproductive toxicity is considered to be 12.5 mg/kg/day for both female parents and pups. Evidence of malformations was not observed at any dose.

Environment

The substance has a solubility in water of 0.42 g/L at 25°C and a vapour pressure of 3.3 Pa at 25°C. The Henry's law constant is 1.3 $Pa \cdot m^3 \cdot mol^{-1}$ at 25°C.

The potential distribution of the substance was estimated using a Fugacity Mackay level III model. The results suggest that the majority of the substance distribute into soil if released to soil or air or equally to each compartment, and into water and sediment if released to the aquatic compartment.

The substance is not readily biodegradable ([OECD TG 301C]; 1% after 28 days). Abiotic degradation by hydrolysis does not occur at pH4, 7 and 9 [OECD TG 111]. The substance has a high logPow (4.11), but the measured BCF is low ([OECD TG 305]; BCF = 41-92 at 10 µg/L and 39-93 at 1 µg/L). The calculated Koc is 3.2×10^3. The acute EC_{50} values for algae were 0.900 mg/L and 1.84 mg/L (24to 48hr, i.e. within the exponential growth phase of the

controls) for biomass and growth rate, respectively [OECD TG 203]. The acute EC_{50} for daphnids was 2.77 mg/L [OECD TG 202] and the LC_{50} for fish was 2.72 mg/L [OECD TG 203]. The chronic NOEC values for green algae were 0.248 mg/L and 0.622 mg/L for biomass and growth rate, respectively [OECD TG 201]. The chronic NOEC for daphnids was 0.241 mg/L [OECD TG 211, draft April, 1997].

Exposure

Production volume of the substance is estimated to be ca. 1,500 tonnes/year in Japan. As the substance is used solely as a chemical intermediate of antioxidants, the exposure of the substance is limited to the production and industrial use in Japan. Although the substance is registered in the EU as a flavoring agent, there is no information to confirm the actual usage in the EU.

Consumer exposure: In consideration of the application of the substance (mostly for industrial use as an intermediate to synthesize antioxidants added to polymers and rubbers.), consumer exposure is considered to be negligible because residual contents of the substance in these products is not expected.

Occupational exposure: During production, processing and use, occupational exposure by inhalation and skin contact at the production and industrial use sites is the only case for consideration. The margin of safety for the exposure by inhalation is very high and workers wear proper protective equipment during these operations.

Exposure to the environment: During production, processing and use in Japan, only the aquatic release of the substance at the production site seems to be possible. But the estimated emission amount at the production site where the greatest amount of release is expected, is practically negligible.

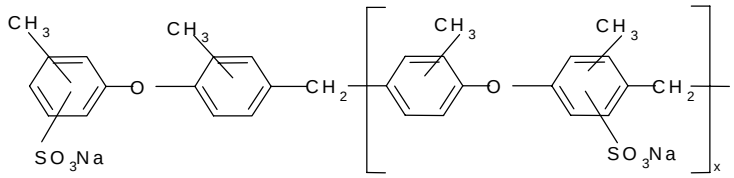
RECOMMENDATION

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 the Sponsor country.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	90387-57-8
Chemical Name	Formaldehyde, reaction products with sulfonated 1, 1'-oxybis[methylbenzene], sodium salts (= FSD-Na)
Structural Formula	 X ≥ 1

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute toxicity of formaldehyde, reaction products with sulfonated 1,1'-oxybis (methylbenzene), sodium salts, (FSD-Na) is very low. The LD_{50} is above 5000 mg/kg after oral exposure in rats (clinical signs: apathy and reduced activity at 5000 mg/kg bw). FSD-Na is well tolerated after single application to the skin of rats. The dermal LD_{50} is above 500 mg/kg.

FSD-Na was not irritating to the skin of rabbits in a test performed according to OECD Guideline 404, but induced slight effects when a 23-25 % aqueous preparation was applied for 24 hours under occlusive conditions. There was no evidence for irritation from limited and not well-documented human volunteer studies. FSD-Na was slightly irritating to the eyes of rabbits in two studies performed in accordance with OECD Guideline 405.

FSD-Na is well tolerated by rats and dogs after repeated oral exposure. The NOAEL for rats is ca. 500 mg/kg bw/day (3 months) and for dogs ca. 620 mg/kg bw/day (6 months). Effects on the kidneys were seen at higher doses in rats (1500 mg/kg bw/day: increased kidney weights, dilated tubuli, changes in the tubular epithelial cells, tubular cell necrosis).

There is no evidence indicating a potential of FSD-Na to induce gene mutations or chromosome aberrations *in vitro*.

There is no study on the effects of FSD-Na on fertility. In a three months rat and a six months dog oral repeat dose study, histological examination of the testes, epididymides, prostate glands and seminal vesicles (rat only) did not reveal any treatment related effects. In females, no treatment related effects on the uterus and ovaries were observed. No developmental or maternal effects were observed in a teratogenicity study performed in accordance with OECD Guideline 414 at the maximum recommended dose of 1000 mg/kg bw/day (NOEL for maternal and developmental effects: 1000 mg/kg bw/day).

Environment

The substance is soluble in water with 79 g/l. A log Kow of 2.79 and a vapor pressure of $5.39 \cdot 10^{-22}$ Pa was calculated with a simplified molecular structure. As the substance is ionized under environmental conditions, the calculation of a Mackay model is not appropriate. On the basis of the physico-chemical properties of FSD-Na, at equilibrium, one can expect water to be the main target compartment. The substance is neither readily nor inherently

biodegradable. In an OECD confirmatory test performed with adapted activated sludge, no biodegradation was observed. However monitoring data showed the substance to be removed > 85 % at the industrial biological sewage treatment plant of the production site. Based on the EU TGD (Simpletreat model) it can be estimated that this removal cannot be transferred to other sewage treatment plants due to possibly different waste water composition and adaptation mechanisms. Based on the chemical structure, hydrolysis is not expected under environmental conditions. Calculation of the indirect photodegradation in air according to Atkinson with a simplified molecule structure, lead to a rough estimation of the half-life $t_{1/2}$ = 3.5 hours for reaction with OH radicals. Measured data on bioaccumulation show the substance not to be bioaccumulative. The BCF on fish was determined to be about 6.5 (mean value; highest single value = 13).

The acute toxicity has been determined for *Brachydanio rerio* with a 96 h-LC_0 of >=100 mg/l, for *Leuciscus idus* with a 48 h-LC50 between 200 and 500 mg/l and for *Daphnia magna* with a 48 h-EC_0 of >= 100 mg/l. For the growth rate of algae (*Scenedesmus subspicatus*) a 72 h-EC_{50} = 29 mg/l and a 72 h-NOEC of 6.3 mg/l has been determined. For the inhibition of the respiration of activated domestic sludge a 3 h-EC_{50} has been determined with > 100 mg/l. A PNECaqua of 0.029 mg/l is derived from the test on the alga, using an assessment factor of 1000.

Exposure

FSD-Na currently is produced in the range of 1,000 to 5,000 t/a worldwide by one company. The substance is used worldwide as an emulsifying agent in the dyestuff producing industry (30 %) and as a syntan (synthetic tanning agent) in the leather industry (30 %). In several countries the substance is licensed as a dispersion agent in plant protection agents (40 %). Releases into the environment may occur during production, during use in the textile and leather industry, during formulation and use of plant protection agents and in minor amounts from products containing the substance (washing out from textiles and leather during cleaning processes). Releases into the atmosphere may not occur as the substance is a salt. Due to the use in plant protection agents, releases into terrestrial compartments may occur.

RECOMMENDATION

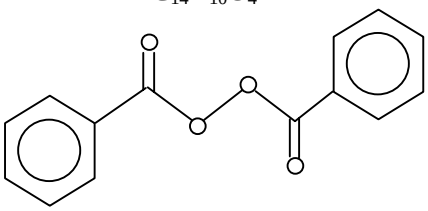
The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: No recommendation for further work within the context of the OECD SIDS program since adequate information is available on all SIDS endpoints and because no particular hazard to human health could be identified.

Environment: High releases are to be expected from the use of the substance in the textile and leather industry. As no elimination can be expected in non-industrial sewage treatment plants according to the EU TGD (Simpletreat model), high local concentrations in surface waters may occur. However, no information about emissions is currently available. In addition, no information is available about releases into the terrestrial compartment from the use of plant protection agents that contain FSD-Na as dispersing agent. Therefore, an exposure assessment is recommended. If then indicated, further tests with aquatic and/or terrestrial organisms may be considered.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	94-36-0
Chemical Name	Benzoyl peroxide
Structural Formula	$C_{14}H_{10}O_4$ 

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The dry chemical becomes explosive above 105°C and when subjected to impact or friction.

The acute oral toxicity of benzoyl peroxide is very low: LD50 >2,000 mg/kg bw in mice, and 5,000 mg/kg bw in rats. No deaths occurred in male rats following inhalation of 24.3 mg/L. Visible effects included eye squint, dyspnea, salivation, lacrimation, erythema and changes of respiratory rates and motor activity.

Benzoyl peroxide was slightly irritating to skins in 24 hr-patch tests. Benzoyl peroxide was not irritating to the eyes of rabbits if washed out within 5 minutes after instillation, however, if the chemical was not washed out until 24 hours later, it proved to be irritating.

Positive results from sensitisation tests in guinea pigs and mice, and from a maximization test in human volunteers, indicate that benzoyl peroxide is a skin sensitizer.

In the combined repeated dose and reproduction/developmental toxicity study (OECD TG 422), benzoyl peroxide did not produce hematological or biochemical adverse effects. Repeated administration by oral gavage up to 1,000 mg/kg bw/day for 29 days resulted in decreased weights of testes and epididymis in male rats. The NOAEL for repeated dose toxicity was 500 mg/kg bw/day.

This substance did not cause gene mutation in bacteria (OECD TG 471 & 472) and *in vitro* chromosomal aberration in CHL (Chinese Hamster Lung) cells. An *in vivo* mammalian erythrocytes micronucleus test (OECD TG 474) produced negative result. The available evidence supports the conclusion that benzoyl peroxide is not a mutagen.

There is no evidence to suggest that benzoyl peroxide is a carcinogen. However, there is some evidence from non-guidelines studies that benzoyl peroxide is a skin tumour promoter.

In the combined repeated dose and reproduction/developmental toxicity study [OECD TG 422], no treatment-related changes in precoital time, rate of copulation, fertility and gestation were noted in any treated group. Adverse effects were shown at the highest dose of 1,000 mg/kg bw/day in parental male rats with the reduction of reproductive organ weight and slight testes degeneration. In parental female rats, no adverse effects were observed during the test period. The NOAEL for reproduction toxicity in male rats was 500 mg/kg bw/day. In the offspring, the only effect seen was that body weight gain of pups at dose of 1,000 mg/kg bw/day was significantly decreased. The NOAEL for developmental toxicity was 500 mg/kg bw/day.

Environment

Benzoyl peroxide is commercially produced as a white granule with purities ranging from 22 to 95%. It has a melting point of 104 -106 °C, vapor pressure of 0.00929 Pa, solubility of 9.1 mg/L in water at 25 °C, and log P_{ow} of 3.43 at 25 °C. For indirect photolysis in the atmosphere, the half-life is estimated to be 3 days with the AOPWIN model. The substance is readily biodegradable (OECD TG 301C: 83% by BOD after 21 days) and hydrolyses rapidly in water [OECD TG 111] with a half-life of 11.87 hrs at pH 4.0 and 5.20 hr at pH 7.0 at 25 °C. The main hydrolysis product of benzoyl peroxide is benzoic acid (a SIDS assessment of benzoic acid is available: CAS No. 65-85-0). The estimated BCF of 92 with the BCFWIN model suggests that the chemical has a low potential for bioaccumulation.

The following studies for aquatic organisms are available:

Green algae (*Selenastrum capricornutum)*: 72 hr-E_bC_{50} is 0.07 mg/L (biomass) and 0.44 mg/L (growth rate).
Invertebrates (*Daphnia magna)*: 48 hr-EC_{50} is 0.07 mg/L.
Fish (*Oryzias latipes*): 96 hr-LC_{50} is 0.24 mg/L.
Microorganism (*activated sludge)*: 30 min.-EC_{50} is 35 mg/L.

The toxicity observed is assumed to be due to benzoyl peroxide rather than benzoic acid, which shows much lower toxicity to aquatic organisms. One can assume that effects occur before hydrolysis takes place.

A generic fugacity model (Mackay level III) was used for environmental fate estimation. If the most realistic emission pattern to water is assumed then the substance will remain in the aquatic compartment.

Exposure

In Korea, the total production volume of benzoyl peroxide was 1,357 tonnes in 2001, and the chemical is produced in only one company. The amounts of import and export were estimated as 268 and 293 tonnes/year, respectively. 75% benzoyl peroxide is mainly used in the manufacture of expandable styrene polymer and other resins as initiators of polymerization. Benzoyl peroxide has also been used in the treatment of acne vulgaris and the medical product contains mainly 5-10 % benzoyl peroxide. A very small portion of benzoyl peroxide is used as flour bleaching agent.

The Danish, Norwegian and Swedish product register indicates that this substance is used in adhesives, cosmetics, dental products, process regulators, fillers, construction materials and paints. These products may contain 2-80 % of the substance depending upon the product.

The major routes of occupational exposure are inhalation and dermal. Limited data on exposure are available. At a production facility monitoring its workplace for the worker exposure annually, the concentration of airborne aerosols at personal sampling has been less than 1 mg/m^3.

RECOMMENDATION

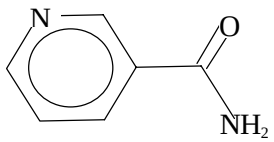
The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating hazards to human health (sensitisation, effect on testes weight, fetal body weight and skin tumour promotion activity) and is a candidate for further work, i.e. exposure assessment, and if considered necessary, risk assessment.

Environment: It is expected that the possibility of any environmental releases of benzoyl peroxide is low in the sponsor country. However, this substance is a candidate for further work, even if it hydrolyses rapidly and has a low bioaccumulation potential. The substance shows high acute toxicity to aquatic organisms and some information indicates wide-dispersive use of this substance. This could lead to local concern for the aquatic environment and therefore environmental exposure assessment is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-92-0
Chemical Name	3-Pyridinecarboxamide (nicotinamide)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Nicotinamide is a vitamin, an essential constituent for the synthesis of pyridine coenzymes in mammalian systems. The substance can be synthetised directly in the body from the aminoacid tryptophan. In humans exogeneous nicotinamide is easily absorbed from the gastro-intestinal tract. In other species it may be deamidated to nicotinic acid by intestinal micro-organisms before entering the systemic circulation. The substance can be incorporated into NAD(P) either directly or after deamidation or metabolised and excreted in urine. The primary metabolite in both humans and rats is N-methylnicotinamide.

The acute toxicity of nicotinamide after oral administration or dermal application is very low: oral LD_{50} 3-7 g/kg bw in rodents and dermal LD_{50} >2000 mg/kg bw in rabbits. Skin irritation studies indicate that nicotinamide has no potential to irritate the skin. Nicotinamide is an eye irritant. Evidence from human exposure indicates that nicotinamide is not a skin sensitiser.

In a 4-week oral toxicity study male rats dosed with 215 and 1000 mg/kg bw showed a significant decrease in body weight gain and food consumption during part of the treatment period. Liver weight was increased accompanied histopathologically by mild liver centrilobular hypertrophy in all treated animals. These effects were considered to be an adaptive response to nicotinamide treatment. In females at the high dose group extramedullary haematopoiesis was reported. The NOAEL derived from this study is 215 mg/kg bw. In this study no effects on male and female gonads were found.

A developmental toxicity test was performed in rats with nicotinic acid, which has a similar physiological function as nicotinamide and comparable kinetics as nicotinamide in rats. The NOAEL for maternal toxicity derived from this study was 200 mg/kg bw/d based on effects on body weight (equivalent to 198 mg/kg bw/d for nicotinamide). The NOAEL on reproduction toxicity and developmental toxicity is 200 mg/kg bw/d (equivalent to 198 mg/kg bw/d nicotinamide) based on the significantly decreased placental and pup body weight (males only). No teratogenic effects were observed.

Nicotinamide is considered not mutagenic in bacterial strains. No chromosomal effects in mammalian cells were reported. In an *in vivo* micronucleus test no clastogenic effects were seen. Thus nicotinamide is not mutagenic.

In humans nausea with or without vomiting was the main effect after acute exposure and generally seen after doses in excess of 5 g/day. No persisting effects were reported.

Environment

Nicotinamide is a solid with a vapour pressure of 31.4 hPa (at 25ºC), a water solubility of 691-1000 g/L and a Log

K_{ow} of -0.38 (at 22°C). It has a calculated half-life for photo-oxidation of 2.23 days in the atmosphere. Nicotinamide will partition primarily to water (Mackay level III modelling). No hydrolysis is expected based on the stability of the amide bond. Nicotinamide is readily biodegradable (100% within one week). Based on the log K_{ow} nicotinamide is not expected to bioaccumulate (calculated BCF 3.162). It has a low potential for sorption to soil (predicted log Koc 0.97).

The 96-hour LC_{50} in fish for nicotinamide is >1000 mg/L The 24-hour EC_{50} for daphnia is >1000 mg/L. In a test with algae (*Scenedesmus subspicatus*, 72-hours exposure) virtually no growth was seen during the first 24 hours. The 72-hour E_bC_{50} and E_rC_{50} were >1000 mg/L. The EC_{10} for the inhibition of micro-organisms is 4235 mg/L.

Exposure

Nicotinamide can be found as a dietary supplement in food and feed and in cosmetics. Consumers may be exposed to nicotinamide by the oral and dermal routes of exposure. There is a potential for occupational exposure through inhalation and skin contact.

There is potential exposure for the aquatic compartment arising from the production and processing of nicotinamide.

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 a low hazard potential. However it is noted that the substance is an eye irritant.

SIDS INITIAL ASSESSMENT PROFILE

High Boiling Ethylene Glycol Ethers Category

CAS No.	143-22-6 23783-42-8 1559-34-8
Chemical Name	Triethylene glycol butyl ether Tetraethylene glycol methyl ether Tetraethylene glycol butyl ether
Structural Formula	$HO(CH_2CH_2O)_nR$ n= 3 or 4; R=methyl or butyl Note: Both tetraethylene glycol methyl ether and tetraethylene glycol butyl ether are available as mixtures with other glycol ethers and some other compounds. Therefore, the molecular and structural formulas for tetraethylene glycol methyl ether and tetraethylene glycol butyl ether presented represent structures for only a portion of the compounds in the methyl and butyl high boiling streams.

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The category contains three structurally related, high boiling glycol ethers:

- Triethylene glycol butyl ether (TGBE; CAS No. 143-22-6);
- Tetraethylene glycol methyl ether (TetraME; CAS No. 23783-42-8); and
- Tetraethylene glycol butyl ether (TetraBE; CAS No. 1559-34-8).

TGBE is available as a relatively pure product, with a purity of ≥85 percent. TetraME and TetraBE are not commercially available as pure compounds, but as components of mixtures that contain glycol ethers of various chain lengths.

Data for these glycol ethers are supplemented with data from compounds that are closely related to the category members in molecular structure, and physicochemical properties, and toxicity. These compounds are:

- Triethylene glycol methyl ether (TGME; CAS No. 112-35-6);
- Triethylene glycol ethyl ether (TGEE; CAS No. 112-50-5);
- Polyethylene glycol methyl ether (MPEG350; CAS No. 9004-74-4);
- Polyethylene glycol butyl ether (CAS No. 9004-77-7); and
- Brake Fluid DOT 4.

TGME and TGEE were both reviewed at SIAM 4. Polyethylene glycol monobutyl ether (CAS No. 9004-77-7) is used only for the melting point. (Details of the composition of category members and analogs are provided in Section 1 and Appendix I of the SIAR.)

Human Health

Based on structural and physical similarities of TetraME and TetraBE with the other glycol ethers, it is likely that they will also exhibit similar toxicity.

Results of several acute toxicity studies are available. The oral LD_{50} values are 5,300 mg/kg and 6.73 ml/kg for TGBE and > 15,000 mg/kg for TetraME. In an inhalation study, an 8-hour exposure to a saturated solution of TGBE resulted in no deaths. Two dermal LD_{50}s were estimated for TGBE: > 2000 mg/kg and 3.54 ml/kg. Data for the surrogate compounds are comparable.

In general, repeated dermal or oral exposures to moderate to high doses of TGBE and the surrogate compounds are well tolerated. In a 21-day dermal study, a systemic toxicity NOAEL of 1000 mg/kg/day (single dose tested) was established for TGBE. The repeated dose oral NOELs or NOAELs of TGME, TGEE and Brake Fluid DOT4 in rats range from 150 to 750 mg/kg/day. Systemic effects (other than reproductive effects) noted at an oral dose of approximately 1,000 mg/kg/day TGME or Brake Fluid DOT4 are reduced weight gain, slight hepatocellular centrilobular hypertrophy, and increased relative liver weight (TGME). All rats survived oral exposure to 3,300 mg/kg/day TGEE for 30 days, and 19/20 survived oral exposure to 4,000 mg/kg/day TGME for 90 days. Changes observed in rats treated orally with 3,300 mg/kg/day TGEE for 30 days were decreased weight gain, slightly increased high blood urea concentrations, and "congestion and cloudy swelling of the liver (6/10) and kidney (1/10)." Rats administered 4,000 mg/kg/day TGME orally for 91 days exhibited reduced weight gain and food consumption, and microscopic changes in the liver (hepatocellular cytoplasmic vacuolization and/or hypertrophy and cholangiofibrosis). The severity of the lesions was minimal or mild (with the exception of moderate or marked hepatocellular cytoplasmic vacuolization in 4/15 males). In a 2-week intravenous toxicity study with 1,000 mg/kg/day MPEG350, there was no effect of treatment on body or organ weights, hematological values, or pathology of the heart, liver, spleen, kidneys, adrenal glands or gonads.

Reproductive toxicity of the surrogate chemicals is limited to high doses. Male rats orally administered 4,000 mg/kg/day TGME for 91 days exhibited testicular toxicity characterized by mild to moderate degeneration and/or minimal to moderate atrophy of the seminiferous tubules (spermatocytes or developing spermatids). In the same study, testicular toxicity was observed in 1/15 males at 1200 mg/kg/day and no testicular effects were noted at 400 mg/kg/day. A NOAEL for reproductive toxicity between 400 and 1200 mg/kg/day was derived from this study. A 91-day repeated-dose dermal toxicity study in rats given 400, 1,200 or 4,000 mg TGME/kg/day showed severe testicular toxicity in 1/10 animals given 4,000 mg/kg/day and minimal decreases in developing germ cells in 1/10 rats given 1,200 mg/kg/day. No testicular effects were seen at 400 mg/kg/day. A NOAEL between 400 and 1200 mg/kg/day was derived from this study. Results of a 90-day dermal toxicity study found that doses of up to 338 mg/kg/day MPEG350 did not produce toxicity to reproductive organs. In a 21-day dermal toxicity study, testicular degeneration (scored as trace in severity) was observed in one rabbit given 1,000 mg TGEE/kg/day and another treated with 1,000 mg TGME/kg/day. Results of a 2-week study indicate that dermal administration of up to 4,000 mg TGME/kg/day did not produce testicular toxicity.

The bulk of the evidence from developmental toxicity experiments conducted with the category member TGBE and the surrogates TGME, TGEE and Brake Fluid DOT4 indicates that fetal toxicity was not noted at doses < 1,000 mg/kg/day. The single oral exposure study in rats resulted in maternal and developmental NOAELs of 1000 mg/kg/day (highest dose tested). Of the surrogates, TGME has been studied most extensively. In one oral study in rats, the developmental NOAEL for TGME was 625 mg/kg/day based on decreased body weight and skeletal variations, with a maternal NOAEL of 1,250 mg/kg/day based on decreased body weight and food consumption. Another oral study in rats with TGME resulted in developmental and maternal NOAELs of 1000 mg/kg/day (highest dose tested). In an oral study in rabbits with TGME, the developmental NOAEL was 1000 mg/kg/day based on presence of angulated hyoid alae and reversible delays in ossification of the xiphoid. The maternal NOAEL was 500 mg/kg/day based on maternal deaths, abortion, clinical signs of treatment, gastrointestinal lesions, and reduced uterine weight. Finally, the developmental NOAEL for TGEE from an oral study in rats was determined to be 1000 mg/kg/day.

All *in vitro* and *in vivo* genotoxicity studies on the category member TGBE and surrogates (TGME, MPEG350, and Brake Fluid DOT 4) were negative at concentrations up to 5,000 micrograms/plate and 5,000 mg/kg, respectively,

indicating that these chemicals are not genotoxic at these concentrations.

Environment

In most cases, measured and predicted environmental fate parameters among category members and surrogates are similar. Ether groups are generally stable to hydrolysis in water under neutral conditions and ambient temperatures. OECD guideline studies indicate ready biodegradability for TGBE and inherent biodegradability for TetraME. However, an APHA comparative biodegradation study of TGME, TGEE and TGBE indicates somewhat slower biodegradation of TGBE. No glycol ethers that have been tested demonstrate marked resistance to biodegradative processes. Due to the structural and physical similarities with the other glycol ethers in the category, TetraBE is likely to be biodegradable. Upon release to the atmosphere by evaporation, high boiling glycol ethers are estimated to undergo photodegradation (atmospheric half lives = 2.4-2.5 hr). When released to water, the category members undergo biodegradation (47-92% after 8-21 days) and have a low potential for bioaccumulation (log Kow ranges from –1.73 to +0.51).

Based on the structural and physical similarities with TGBE and TGME, it is likely that the toxicity of TetraBE and TetraME to aquatic species will be similar. Aquatic toxicity data indicate that the tri- and tetra ethylene glycol ethers are "practically non-toxic" to aquatic species. For the category member TGBE, the LC_{50} values for fish and *Daphnia*, are 2,400 mg/l, 2,210 mg/l, respectively, and the EC_{50} for algae is > 500 mg/l. No major differences are observed in the order of toxicity going from the methyl- to the butyl ethers.

Exposure

In the United States, three manufacturers produced 20,900 metric tonnes (46 million pounds) of TGBE in 1999. Production is projected to increase slightly to 22,300 metric tonnes (49 million pounds) in the year 2004. In 1998, > 454 – 4,540 metric tonnes (> 1-10 million pounds) of TetraGME and > 4,540 – 22,700 metric tonnes (> 10-50 million pounds) of TetraGBE were produced in the United States. In Western Europe consumption of triethylene glycol ethers was 40,000 metric tonnes (88 million pounds), but this is a total for combined methyl, ethyl and butyl ethers of triethylene glycol. Although Japan may produce significant amounts of TGBE, other regions (including Canada, Mexico, South America and Eastern Europe) do not produce significant commercial amounts of TGBE.

Although inhalation and oral exposure is possible, the most likely route of human exposure to high boiling ethylene glycol ethers (liquids with boiling points ranging between 235-350°C) is via dermal contact. Workplace exposure during manufacture and storage is limited by the enclosed nature of the manufacturing processes and equipment. The major known use of high boiling ethylene glycol ethers is as components of automotive brake fluids. Although exposure is limited during the formulation of these glycol ethers into brake fluids (which is done in closed systems in an industrial setting) greater exposure potential exists in automotive plants and brake service/repair shops, where brake lines and cylinders are filled with fluid, or brake systems are serviced. Exposure is more limited in automotive plants than in local shops by automated processes. Occasional consumer exposure via brief dermal contact may occur when car owners top off their brake master cylinders from a container of fluid and possibly spill some liquid. Environmental releases are limited by the enclosed nature of industrial processes and the low volatility of the material. Releases are best characterized as usually occurring in very small amounts, but releases are possible wherever brakes are serviced.

RECOMMENDATION

The High Boiling Ethylene Glycol Ethers Category is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The High Boiling Ethylene Glycol Ethers category is currently of low priority for further work based on a low hazard potential.