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

27-Feb-2012

English - Or. English

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

Cancels & replaces the same document of 13 February 2012

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

Series on Testing & Assessment
No. 166

The complete document is available in pdf format only.

JT03316624

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ENV/JM/MONO(2012)4/PART2
Unclassified

English - Or. English

OECD Environment, Health and Safety Publications

Series on Testing and Assessment

No. 166

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

Environment Directorate

ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT

Paris 2012

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

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

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

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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.	101-72-4
Chemical Name	N-Isopropyl-N'-phenyl-*p*-phenylenediamine (IPPD)
Structural Formula	$CH_3CH(CH_3)NH\text{-}C_6H_4\text{-}NH\text{-}C_6H_5$

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

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

Human Health

In a poorly reported human study, there is some evidence for uptake via the skin and bioaccumulation of IPPD. However, due to the poor quality of the study, no conclusions could be drawn on the extent of absorption. A single briefly reported animal toxicokinetic study indicated that IPPD does not readily penetrate unbroken skin, although no further information is available. IPPD is absorbed from the gastrointestinal tract, although no quantitative information is available on the extent of absorption.

There is no information on the effects of IPPD following acute inhalation, oral or dermal exposure in humans. However, IPPD is of moderate toxicity by the oral route in rats (typical LD_{50} = 800 mg/kg), and of very low toxicity by the dermal route in rabbits. No information is available regarding acute inhalation toxicity in animals. Evidence from human and animal studies suggests that IPPD is not a skin irritant. Animal studies also suggest that IPPD is not an eye irritant. Animal evidence demonstrates that IPPD is a skin sensitiser, and human evidence from volunteer studies and case-reports is consistent with this. There are no data available on respiratory sensitisation. No information was available concerning repeat exposure of humans to IPPD. No useful animal inhalation or dermal data are available. There were no findings of any toxicological significance in a 90-day oral rat study at thee highest dose, 57 mg/kg/day, and this may be regarded as a NOAEL. In a 28-day study a NOAEL of 223 mg/kg/day, the highest dose administered, was identified.

In vitro mammalian cell mutagenicity assays demonstrate IPPD has a potential to induce chromosome aberrations in the absence or presence of exogenous metabolic activation. The potential for direct acting genotoxicity was also demonstrated in a study of sister chromatid exchange. Negative results have been obtained in a number of *in vitro* genotoxicity studies (Ames, mammalian cell gene mutation, and unscheduled DNA synthesis). No carcinogenicity data are currently available. There were no fertility studies available, but in a 90-day repeat dose study there was no histological evidence of adverse effects in the reproductive organs of male and female rats exposed at the top dose of 57 mg/kg/day. In the only developmental toxicity study available, skeletal changes consistent with ossification retardation were observed at doses that did not produce maternal toxicity. NOAELs of 125 mg/kg/day and 62.5 mg/kg/day were identified for mothers and offspring, respectively. The relevance of this finding for human health hazard identification is uncertain.

Environment

Acute toxicity data are available for four fish species, three showing similar sensitivity. The lowest 96-hour LC_{50} is 0.34 mg/l for Rainbow trout (*Oncorhynchus mykiss*). A 14-day LC_{50} of 0.09 mg/l was obtained for fathead minnow (*Pimephales promelas*), which may indicate that IPPD (or its breakdown products) has cumulative toxicity. Aquatic invertebrates appear to be less sensitive, the 48-hour EC_{50} for *Daphnia magna* being 1.1 mg/l (NOEC of 0.56 mg/l). A 96-hour EC_{50} of 0.4 mg/l is reported for green algae. A PNEC of 0.34 µg/L can be derived for the aquatic environment using an assessment factor of 1000 with the acute toxicity result for rainbow trout.

IPPD hydrolyses rapidly (over timescales similar to those of the static tests), so some of the toxic effects may be due to hydrolysis products. One of the fish studies used flow-through conditions, with similar toxicity at 96 hours to that shown in the static tests. It therefore appears that IPPD is of similar toxicity to the hydrolysis products.

Exposure

Around 10,000-15,000 tonnes of IPPD are produced worldwide each year. It is used as an anti-degradant in rubber, mainly for car tyres. Potential release to the environment can occur from manufacture, the production of rubber for tyres, tyres in use and on disposal. Exposure to humans is expected to occur only via the workplace.

IPPD is a solid of low water solubility (~15 mg/l) and an octanol-water partition coefficient (log K_{ow}) of 3.9. Its atmospheric half-life is estimated to be between 23 and 54 minutes. It hydrolyses in water with half-lives between 2 and 11 hours depending on the water source. Biodegradation studies show rapid primary degradation but low ultimate degradation, indicating that the breakdown products may be persistent. IPPD has a potential to bioaccumulate in aquatic organisms (based on its log K_{ow}). It can be predicted that the substance will remain in water or soil once it reaches there, although degradation is expected to be rapid. Most of the release to air is also rapidly degraded but that which is not is quickly removed to water and soil.

NATURE OF FURTHER WORK RECOMMENDED

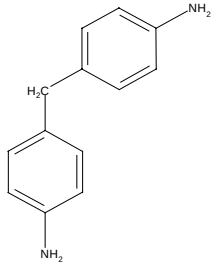
The chemical is a candidate for further work post-SIDS as follows:

1. There is some uncertainty about which chemical species produce the toxic effects on aquatic organisms. Whilst the SIDS endpoints are fulfilled, toxic effects are apparent at low concentrations and so further investigation of the nature and properties of breakdown products could be performed.

2. The hazards to the aquatic environment and to human health due to skin sensitisation are such that member states are invited to investigate the relevance of exposure conditions in their country. In this context, further information on the persistence of IPPD in tyres and the quantities leached during the lifetime of the tyre would be useful for an environmental assessment.

3. An *in vivo* bone marrow study (micronucleus) using parenteral administration would be useful to investigate the potential observed *in vitro* for direct acting clastogenicity.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	101-77-9
Chemical Name	4,4'-Methylenedianiline (MDA)
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

MDA is of moderate acute toxicity to rats: LD50oral 350-450 mg/kg, LD50dermal 1000 mg/kg and LC50inhalation >0.837 mg/l (this concentration exceeds the highest attainable concentration at room temperature). Target organs are liver and kidney (and eye in cats and dogs). MDA is slightly irritating to rabbit skin and causes mild to moderate irritation to the eyes of rabbits. Human evidence indicates that MDA is a skin sensitizer.

MDA has been shown to cause mutations both in vitro and in vivo, and to be carcinogenic. Chronic oral MDA administration to rats and mice results in tumours of the liver and thyroid, (non-neoplastic LOAEL 9 and 10 mg/kg bw/d, male and female rats, respectively). However, the available human data did not clearly demonstrate carcinogenic activity. Developmental or fertility data in animals or humans does not exist.

Environment

MDA has a log Kow of 1.59, a water solubility of 1.25 g/l and a vapour pressure of 2.87X10-8hPa. MDA is not expected to be volatile and to undergo hydrolysis. MDA is inherently biodegradable in industrial WWTPs, degradation in municipal WWTPs cannot be deduced from the actual database. The major transformation pathway in the hydrosphere is probably photolysis. MDA forms covalent bounds with the organic matter of sediments and soils. As the reaction product with humic acids is only poorly biodegraded, its accumulation in sediments has to be expected.

MDA is expected to be of low bioaccumulation potential in fish, however, accumulation of reaction products with humic substances in sediment dwelling organisms may occur, although effects data for this end point do not exist.

The following data were selected as lowest acute and long-term effect values for each algae, daphnia and fish: *Scenedesmus subspicatus:* 72h-EC50 = 11 mg/l, 72h-EC10 = 0.3 mg/l; *Moina macrocopa:* 24h-EC50 = 2.3 mg/l, 14d-NOEC = 0.15 mg/l; *Oryzias latipes* 48h-LC50 = 32 mg/l. With an assessment factor of 50, a PNEC of 3 µg/l was derived from the 14d-NOEC for *Moina macrocopa*.

Release of MDA to the environment during production is mainly via waste water. No significant releases into the atmosphere and soils are expected.

Exposure

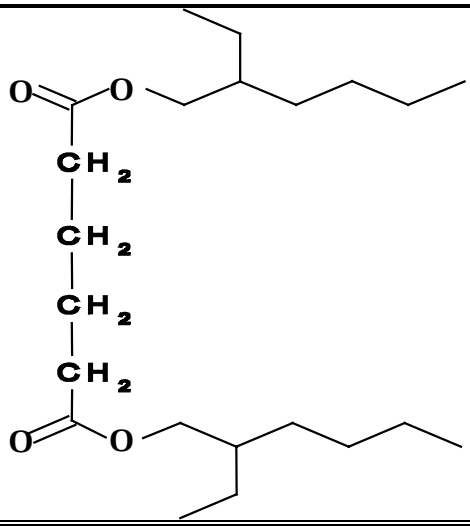
In 1993 the production volume of MDA was in the region of 430,000 tons. 4,4'-Methylenedianiline (MDA) is produced both as single compound and as the major component of a technical mixture with a varying content of tri- and polynuclear amines. More than 99% of the total production volume of MDA are used as an intermediate for the production of Methylenediphenyldiisocyanate (MDI), which is further processed to polyurethanes. Maximum 4000t MDA, per annum are used as hardners for epoxy resins and adhesives, intermediate in the manufacture of high-performance polymers and processing to 4,4'-Methylenebis(cyclohexaneamine). Significant releases of MDA into the environment occur only during production.

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 conclusions. The risk assessment shows that there is a need for specific measures to limit the risks for workers and consumers.

The toxicity of the reaction product of MDA with humic acids on sediment organisms is unknown. Thus no PNECsed could be estimated, and a risk assessment for this sub-compartment is not possible. A test on *Lumbriculus variegatus* with pre-incubated MDA should be performed.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	103-23-1
Chemical Name	Bis(2-ethylhexyl)adipate
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

DEHA exhibits low acute mammalian toxicity as seen by reported oral and dermal LD50s in rats of greater than 2 g/kg and no mortality in rodents exposed via inhalation for eight hours at levels up to saturation. Available data show that DEHA is not irritating to skin or eyes in animal studies and was not a dermal sensitizer in guinea pigs. Repeated-dose toxicity studies (up to 90-days) in rats and mice with DEHA in feed showed reduced body weight gains at levels of approximately 400 mg/kg and higher in rats and approximately 600 mg/kg and higher in mice (NOAELs of 189 mg/kg in rats and 451 mg/kg in mice). *In vitro* genotoxicity studies have been negative for mutations, unscheduled DNA synthesis and DNA interactions in bacterial and mammalian systems. *In vivo* genotoxicity studies have also been negative (two mouse micronucleus assays). DEHA has been evaluated for carcinogenicity in mice and rats, and there was no evidence of carcinogenicity in rats but there was evidence of liver cancer in female mice (significant incidence) and male mice (less significant). Tumors in mice were observed at high concentrations (3222 mg/kg for females and 2659 mg/kg in males). A one-generation reproductive toxicity test was performed in rats and there were no effects on reproduction although the body weight gains of pregnant dams and first generation pups was reduced at a dose level of approximately 3222 mg/kg. A developmental toxicity performed with DEHA in rats (animals treated orally via DEHA in feed on days 6-15 of gestation) demonstrated reduced maternal body weight gain at the highest dose (1080 mg/kg/d). There was evidence of pre-implantation fetal loss at the highest dose, but no gross, skeletal, or visceral abnormalities. A NOAEL for developmental toxicity was determined in rats at an estimated oral dose of 170 mg/kg/d, based on slight fetotoxicity from reduced ossification which was not statistically significant.

Environment

Experiments show that DEHA has no acute toxicity effects to aquatic organisms and a low bioaccumulation potential, and is readily degradable via abiotic (hydrolysis) and biotic processes. No acute aquatic toxic effects were noted at the apparent limit of DEHA solubility (0.0032 mg/L) and no effects were noted at concentrations several orders of magnitude greater than the solubility for most species. A chronic daphnid study did show effects at concentrations slightly above the water solubility limit. There were no effects observed at the lowest concentration tested (0.014 mg/L). An *acceptable toxic concentration* of 0.035 mg/L was derived as the geometric mean of the NOEC (0.024 mg/L) and the LOEC (0.052 mg/L). A PNEC of 0.0035 mg/L has been established (0.035 divided by an assessment factor of 10).

Tests on terrestrial organisms (earthworm) have also been performed (LC50s of >1000 mg/kg and 865 mg/kg were reported after exposures of 7 and 14 days, respectively.

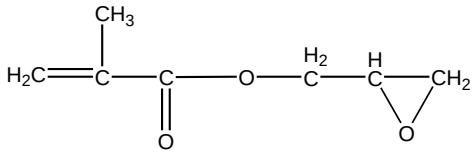
Exposure

DEHA is a plasticizer used primarily in food-contact wrapping. Approximately 10,000 to 50,000 tonnes are produced each year in closed systems. It is estimated that only 25-50 individuals in the US are involved in the manufacturing and handling process. Occupational exposures are low based on production in a closed system and its low vapor pressure. The estimated exposure levels to the general population via consumer products (migration of DEHA from food wraps – estimated exposures of 117 ug/kg/d) and the environment (highest measured surface water concentration was 0.001 mg/L) are considered to be quite low in several countries.

NATURE OF FURTHER WORK RECOMMENDED

Because of the potential chronic hazard to the aquatic environment an exposure assessment is recommended with subsequent risk assessment, as appropriate.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-91-2
Chemical Name	Glycidyl methacrylate
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acute lethal toxicity of glycidyl methacrylate is low via the oral administration route. No mortality was observed in rats following inhalation exposure up to 2,394 mg/m^3, the highest practically attainable vapor concentration. This chemical is considered both highly irritating (including necrosis, degeneration and hyperplasia) to the skin, eyes and respiratory tracts and a skin sensitizer. In an oral (via gavage) OECD combined repeat dose and reproductive/ developmental screening toxicity test (TG 422) in rats at doses of 10, 30, 100 mg/kg/day, squamous hyperplasia in forestomach was induced at 30 and 100 mg/kg/day. Thus, the NOAEL was 10 mg/kg/day. In many repeated inhalation studies, the changes were observed only in respiratory tract (necrosis, inflammation etc. in nasal tissues), and were likely due to irritation. The lowest NOAEL was 0.5 ppm (equivalent to 0.26 mg/kg/day) in a rabbit study. In the OECD combined study (TG 422), the NOAEL for reproductive toxicity was considered to be 30 mg/kg/day, based on a decrease in the fertility index (number of delivered animals/ number of mated animals) at 100 mg/kg. In developmental toxicity studies, teratogenic effect**s** were not induced either by oral administration at 108 mg/kg for rats or inhalation at 291 mg/m^3 for rabbits. Most *in vitro* genotoxicity studies showed positive results. In an *in vivo* micronucleus test, oral administration of glycidyl methacrylate increased the frequency of micronucleated polychromatic erythrocytes only at the highest dose (750 mg/kg in males and 1000 mg/kg in females), although mostly negative results were shown in other *in vivo* genotoxicity studies including micronucleus tests by intraperitoneal administration. Therefore, the genotoxic potential of this chemical can not be ruled out. There was no available data on carcinogenicity of this chemical.

Environment

Glycidyl methacrylate is readily biodegradable (OECD 301C: 100 % after 28-d) and readily hydrolyzed ($T_{1/2}$ = 3.66 days at pH 7). This chemical has a low bioaccumulative potential judging from the low log Pow value, 0.96 at 25 °C.

The lowest acute and chronic aquatic toxicity data reported were 14d LC_{50} (1.9 mg/l) of fish (Medaka; *Oryzias latipes*) and 21d NOEC (1.02 mg/l) of *Daphnia magna*, respectively. An assessment factor of 100 was chosen and applied to the chronic toxicity data to determine PNEC, which is 0.01 mg/l.

Exposure

About 3,000 tones/year of glycidyl methacrylate is produced as intermediate for resins in the closed system in Japan, and ca. 3.3 tones (ca. 0.1%)/ year is released into rivers. Release to air phase is negligible. A generic fugacity model (Mackey level III) shows this chemical will be distributed mainly to water phase (99.1%) when it is discharged into water.

NATURE OF FURTHER WORK RECOMMENDED

There is a need for limiting the risk; risk reduction should be taken into account because of the high irritation, sensitization, and the genotoxic potential.

Occupational exposure information should be collected by individual member countries.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-02-8
Chemical Name	Acrolein
Structural Formula	$CH_2 = CH – CHO$

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acrolein is very reactive and conjugates easily with glutathione or other thiol-containing molecules, with protein sulfhydryl groups and primary and secondary amine groups. As a consequence of its high reactivity the acrolein molecule will bind primarily at the application site. Toxicokinetic data on absorption, distribution, metabolism and excretion for the dermal route are lacking. Assessment of the available acute toxicity data indicates that acrolein is toxic by the oral and dermal route, and very toxic after exposure by inhalation. Acrolein is corrosive and irritating to skin and eyes in laboratory animals and humans. Despite the fact that the study designs and descriptions do not allow clear conclusions on human (no) effect levels for irritating effects after short-term inhalation exposure to acrolein vapours, the risk assessment was based on the LOAEL of 0.14 mg/m^3 from the study of Darley et al. (1960) for subjective symptoms, and the NOAEL of 0.34 mg/m^3 from the study of Weber-Tschopp et al. (1977) for measurable effects (increase in eye blinking rate at 0.59 mg/m^3). Based on the data available acrolein should be considered as sensitising to the skin.

The results of the repeated-dose inhalation studies do not permit establishment of a NOAEL. Intermittent exposure (6-7 hours per day, 5 days per week for a total period of 62 days - 13 weeks) to 0.9 mg/m^3 (0.4 ppm, DCV: 0.16 mg/m^3) acrolein vapour (the lowest concentration examined) resulted in slight, but treatment-related changes in rats, but not in hamsters and rabbits. Continuous exposure (24 hours per day, 7 days per week for 90 days) to 0.5 mg/m^3 (0.22 ppm) acrolein (the lowest concentration examined) resulted in treatment-related effects in guinea pigs, monkeys, and dogs, but not in rats. The effects found at the lowest-observed adverse effect concentrations, consisted of histopathological changes in the epithelium of the respiratory system and changes in respiratory tract function; they were minimal to slight and were found in one animal or a few animals only. Effects at higher concentrations included signs of chronic inflammatory changes, and epithelial metaplasia and hyperplasia of the respiratory tract, and at even higher concentrations increased mortality.

The overall NOAEL for oral toxicity amounted to 0.05 mg/kg bw/day and was found in a 102-week rat study. The discriminating effects for establishing NOAELs in the oral studies comprised decreased survival in rats (NOAEL 0.05 mg/kg bw), decreased survival and decreased body weight gain in mice (NOAEL 2 mg/kg bw), and an increased incidence of vomiting accompanied by a decrease in total serum protein, calcium and albumin at the highest dose level (1.5-2 mg/kg/bw) in dogs (NOAEL 0.5 mg/kg bw). Effects at higher dose levels included severe gastric lesions and increased mortality. Acrolein has been found to impair pulmonary antibacterial defence mechanisms upon inhalation exposure *in vivo* and *in vitro* Acrolein is a mutagen for bacteria and may induce gene mutations and sister chromatid exchanges, but no chromosome aberrations in mammalian cells *in vitro*. The mutagenicity/genotoxicity of acrolein in bacteria and mammalian cells *in vitro* is restricted to a narrow dose range that is near to or overlaps the cytotoxic dose range. Acrolein did not induce dominant lethal mutations in mice or

chromosome aberrations in bone marrow cells of rats. There is evidence that acrolein is not an oral carcinogen. The available data do not allow a conclusion with regard to possible carcinogenicity upon exposure by inhalation. However, none of the available repeated-dose inhalation study meets the generally accepted requirement for adequate carcinogenicity testing. On the basis of the experimental data it cannot be excluded therefore, that respiratory tumours may be induced at non-cytotoxic concentrations. No dermal carcinogenicity studies were available.

Developmental effects in mammals *in vivo* were only seen at dose levels that also resulted in maternal toxicity. The overall NOAEL in the oral teratogenicity studies amounted to 2 mg/kg bw or higher for developmental and 0.75 mg/kg bw per day for maternal effects. Except for a slight reduction in *F1* pup weights at 6 mg/kg bw, no effects on reproduction parameters were found in oral 2-generation rat studies. The overall NOAEL amounted to 3 mg/kg bw for developmental and 1 mg/kg bw per day for parental effects.

Environment

Acrolein may be released into the environment during its production and processing of intermediates. This release, however, is very low compared to emissions from several non-industrial diffuse sources (e.g. formation of acrolein during automobile fuel combustion). Acrolein emissions will occur via water, but predominantly via air.

Acrolein does not contain any hydrolysable groups, but it does react with water in a reversible hydration reaction to 3-hydroxypropanal (HPA). The stability of acrolein in the atmosphere is limited by the rapid gas-phase reactions with the hydroxyl radical and ozone. DT50 is less than one day. Based on the entire data set on biodegradation and the QSAR estimates, acrolein is considered as ready biodegradable. Henry's Law constants indicate that volatilisation of acrolein from surface waters and moisty soil is expected to be high. Acrolein is expected to be moderately to highly mobile in soil. No bioaccumulation is expected.

Both short-term and long-term acrolein toxicity data are available for aquatic organisms. There are also a number of studies with bacteria and protozoans. Short term LC50-values for fish range from 14-250 µg/l. NOEC for fish: 11.4 µg/l. Daphnia magna 48 h EC50 values range from 22 to 93 µg/l. NOEC daphnids: 16.9 µg/l. NOEC algae: 10 µg/l. The $PNEC_{water}$ is set at 0.1 g/l, based on an acute *Xenophus laevis* study (LC50 7 µg/l) using an assessment factor of 100 (instead of 1000) as a several acute and long-term studies were available. There is a limited number of studies in which the phytotoxicity of airborne acrolein is investigated. An indicative $PNEC_{plant-air}$ of 2 g/m^3 is derived.

Exposure

In the EU Acrolein is only used as an intermediate in the chemical industry. The main fraction of the isolated acrolein is reacted via the intermediate product methylmercapto-propionaldehyde (MMP) to the amino acid D,L-methionine, which is used as an animal feed additive. In the EU no consumer exposure was dentfed. Outside the EU (e.g. Egypt, Argentina, Australia, Canada and USA) acrolein is used as an effective broad-band biocide. It is applied in process water circuits, irrigation canals, cooling water towers and water treatment basins. The total EU production volume for 1994 was estimated to be between 20,000 to 100,000 tonnes per annum.

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.

This substance has been agreed in the European Union Risk assessment program under Regulation EEC/793/93. The EU risk assessment concludes that there are need for specific measures to limit the risks for workers. No use of acrolein in consumer products has been identified.

It was considered to examine the potential genotoxic effect (gene mutation) of acrolein at the first site of contact after exposure by inhalation. However, at this moment, a validated test system or a system that giving sufficiently reliable results for the target cells of concern i.e. cells of the respiratory tract, does not exist.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	109-55-7
Chemical Name	3-Aminopropyldimethylamine
Structural Formula	$H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}N(CH_3)_2$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

3-Aminopropyldimethylamine has been found to be harmful following oral administration to rats. Based on the results of the sensitisation test on the skin 3-Aminopropyldimethylamine has been classified as having a sensitising effect. 3-Aminopropyldimethylamine showed strong irritating or corrosive effects. In an oral 28-day subchronic toxicity study with rats, the no-observed-adverse effect-level (NOAEL) was 50 mg /kg bw/day. In the oral reproduction/developmental toxicity screening test the no-observed-adverse effect-level (NOAEL) was 200 mg/kg bw/day. 3-Aminopropyldimethylamine was not mutagenic in the Ames Test and in a mouse micronucleus assay. The corrosive property of the compound prompts workers to limit the potential exposure to this chemical.

Environment

3-Aminopropyldimethylamine has a log Kow of –0.35, a vapour pressure of 8 hPa and is miscible in water.. The substance is strongly basic. The pK_1 value is 9.9 and the pK_2 value 7.7. Therefore, it can be assumed that under environmental conditions the compound is completely protonated. The log Kow of -0.35 measured for the neutral 3-Aminopropyldimethylamine is not useful for modelling the environmental distribution properties of the ionized form.

Experimental data about adsorption of 3-Aminopropyldimethylamine onto soils or sediments are not available. However, due to the physical chemical properties soil sorption via ion-exchange and chemisorption are possible. As 3-Aminopropyldimethylamine in aqueous solutions is always protonated, no volatilisation from treatment plants or surface waters is expected. Based on the physico-chemical properties, the preferred environmental compartment of 3-Aminopropyldimethylamine is the hydrosphere (Mackay I: ca. 97 %).

3-Aminopropyldimethylamine can be classified as readily biodegradable without fulfilling the 10-day window criterion.

No bioaccumulation studies with DMAPA are available.

In short-term tests with fish, daphnids and algae the following results were found: *Leuciscus idus*: 96 h-LC_{50} = 122 mg/l; *Daphnia magna*: 48h-EC50 = 60 mg/l; *Scenedesmus subspicatus*: 72h-EC50 = 56 mg/l. With these data the substance can be classified as moderately toxic. With an assessment factor of 1000 a PNECaqua of 56 µg/l can be calculated from the EC50 for green algae.

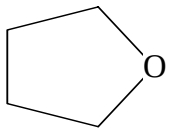
Exposure

In Germany 3-Aminopropyldimethylamine is produced by two companies. In 1994 the total production volume was about 15 000 t. 3-Aminopropyldimethylamine is used as an intermediate in the production of binding agents, ion-exchange materials, flocculating agents (water treatment), cosmetic agents, washing and cleaning agents (betaines), additive for petrol and other fuels, polyurethane fibres and lubricants, dyes, agrochemicals, agents used in the photographic and textile industries, etc. 3-Aminopropyldimethylamine is also used directly as a hardener in epoxy resins in the plastics industry, as a cross-linking agent for cellulose fibres in the paper industry and as an anti-shrinking agent for leather.

NATURE OF FURTHER WORK RECOMMENDED

No need for further work.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	109-99-9
Chemical Name	Tetrahydrofuran
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In short-term tests with fish, daphnids and algae the following results were found: *Pimephales promelas*: 96h-LC50=2160 mg/l; *Daphnia magna*: 24h-LC50=5930 mg/l; *Scendesmus quandricauda*: NOEC(8 days)=3700 mg/l. A fish early life stage test with the fathead minnow was performed and showed a NOEC of 216 mg/L. With an assessment factor of 50 a PNEC of 4.32 mg/l can be calculated from the fish early life stage test.

THF has low acute toxicity by all routes of exposure. In rats the LC50 (4hr) is 53.9 mg/l (18,271 ppm). It is irritating to the skin, mucous membranes and the eyes. Repeated exposures to THF in laboratory animals has produced mainly transitory narcosis and mild adaptive responses – respiratory and mucous membrane irritation, exacerbation of nephropathy in male rats, adrenal and liver toxicity all at high dose levels (lowest oral NOEL in a 90-day study of 400 mg/kg body weight, and lowest inhalation NOEC in a 90-day study of 200 ppm). In animals, no effects on reproductive performance was observed (two-generation oral study in rats with a NOEL of 300 mg/kg body weight), and signs of developmental toxicity were observed at levels (inhalation NOECs of 500 ppm for maternal effects in rats and 610 ppm for fetal effects in mice) which also produced effects in the maternal animals. The fetal effects observed were intrauterine mortality, early resorptions, and slight reduction in breastbone ossification. No teratogenic effect was seen. All *in vitro* genetic toxicity studies were negative for mutational/chromosomal effects, both with and without metabolic activation. Four *in vivo* genetic toxicity studies in mammals were conducted. Two were negative (an unscheduled DNA synthesis study in rats and a bone marrow chromosomal aberration assay in mice), and two were equivocal (sister chromatid exchange assay in mice and the male response in a mouse micronucleus test, the female response was negative). The weight of evidence indicates that THF is non-genotoxic.

In rodents, THF produced some evidence of carcinogenicity in male rats (renal tubule epithelial adenoma or carcinoma combined) and clear evidence of carcinogenicity in female mice (hepatocellular neoplasms) following inhalation exposures to 600 ppm and 1800 pm, and to 1800 ppm, respectively. The doses used in both experiments were 0, 200, 600, and 1800 ppm. Studies designed to further understand these findings are underway.

Environment

Tetrahydrofuran (THF) is a liquid at room temperature and boils at 66°C. Fugacity models suggest that THF would

be found in the environmental compartment where it would be released. Estimation of photodegradation by hydroxyl radicals in air is rapid and hydroxyl radical reaction half-life is estimated at 7.3 hours. THF released to the environment could partition to the water compartment, where it is readily biodegradable but would not degrade through hydrolysis. Bioaccumulation of THF is not expected because of its very low octanol/water partition coefficient. Based upon physical and chemical properties, production, use patterns, and environmental monitoring levels in the low ppb range, the environmental exposure potential is expected to be low.

Exposure

Tetrahydrofuran is a chemical used mainly in the production of polytetramethylene ether glycol (PTMEG), a component of synthetic polymers. It is also used as a solvent, an intermediate and in adhesives. Germany has also reported the use of THF as both a stain remover and for use to delete mordant dyes in products available to consumers. Total production for 1999 was 551 million pounds of which 78% were for PTMEG synthesis in closed systems; the remainder was used for intermediates, agriculture, industrial chemicals, pharmaceuticals and solvents. Worker exposure at production and use facilities shows air levels (on average less than 10 ppm) well below any designated exposure limits. Consumer exposure is rare and occurs on a sporadic basis during the use of plastic pipe solvent cements. Plumbers who use these materials also can have exposures. Workplace exposure monitoring is well below current US OSHA and ACGIH standards/guideline, of 200 ppm, 8 hour daily values and short-term value of 250 ppm (15 minutes, STEL). Monitoring of THF exposure of plumbers during use of THF as a solvent cement for plastic pipe did not exceed the above values. However, it may be noted that the substance seems to be an efficient skin penetrant. Release to the environment from PTMEG is no more than 1% of the THF produced or handled. Other environmental exposures during regular use would also be low.

NATURE OF FURTHER WORK RECOMMENDED

Work is currently underway to determine the mechanism of the carcinogenic response in the rat (by measuring alpha –2u globulin in kidneys of THF-treated-rat) and mouse (cell proliferation studies in liver of THF-treated mice). There are also experiments planned to assess the metabolic fate of THF in both rats and mice.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-63-4
Chemical Name	1,4-Butanediol
Structural Formula	$HO\text{-}CH_2CH_2CH_2CH_2\text{-}OH$

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Acute lethal toxicity of 1,4-butanediol is low via all administration routes. Major toxicity by oral administration is respiratory failure and catalepsy. This chemical is a slight irritant to the skin, eyes and respiratory tract, but not a skin sensitizer. As 1,4-butanediol is rapidly absorbed and metabolized to gamma-hydroxybutyric acid in animals and humans, neurotoxic effect of 1,4-butanediol such as depression of central nervous system is considered to be caused by the metabolite, gamma-hydroxybutyric acid. 1,4-Butanediol seems to show a competitive inhibition of alcohol dehydrogenase and increase the toxic effect of alcohol.

In an OECD combined repeat dose and reproductive/developmental screening toxicity test (OECD TG 422), rats were administered by gavage at doses of 200, 400 and 800 mg/kg/day for 45 days in males and from 14 days before mating to day 3 of lactation in females. Neurobehavioral toxicity (i.e. hyperactivity and coma after hypoactivity and recumbency) and pathological changes (diffuse transitional epithelial hyperplasia and fibrosis in the lamina propria of the urinary bladder) were observed. The transient hyperactivity only just after administration was observed at the lowest dose of 200 mg/kg/day. This neurotoxicity in dams was also observed in developmental toxicity study of mice at doses of 300 and 600 mg/kg/day by gavage during gestational days 6-15 but not at 100 mg/kg/day. This study was conducted by NTP test guideline under GLP. Therefore NOAEL of 100 mg/kg/day for oral repeated toxicity is sufficiently reliable.

In a 2 week inhalation rat study at 1.1 g/m^3 (6 hours/day, 5 days/week), no changes including neurotoxicity were observed. Therefore, 1.1 g/m^3 was considered to be inhalation NOAEL. Repeated intraperitoneal administration induced narcotic effect at more than 500 mg/kg/day, but NOAEL was not established.

From repeated dose studies, it is evident that critical effect is neurotoxicity. However, the nature of the data does not allow for the identification of the dose-response and NOAEL for this effect.

As for reproductive toxicity, a reduction in fetal body weight of rats was observed in the above OECD combined repeat dose and reproductive/developmental screening toxicity test (OECD TG 422) but this effect was considered to be secondary to maternal toxicity. NOAEL for reproductive toxicity is the highest dose of 800 mg/kg/day. In the developmental toxicity study of mice at 100, 300 and 600 mg/kg/day described above, the only definitive expression of developmental toxicity was a reduction in average fetal body weight at doses of 300 and 600 mg/kg/day (92% and 83% of control weight, respectively). However, this effect against foetal development was considered to be secondary to maternal toxicity. No teratogenicity was observed at any doses. Thus, 600 mg/kg/day is the developmental NOAEL. Genotoxicity of this chemical may be negative because of neither bacterial mutation in *S.*

Typhimurium TA100, TA98, TA1535, TA1537, and *E.coli* WP2 *uvr*A with and without metabolic activation (OECD TG 471 and 472), nor chromosomal aberration *in vitro* in CHL/IU cells with or without metabolic activation system OECD TG (473).

Environment

1,4-Butanediol is a liquid at 20 °C, and this chemical is classified as a readily biodegradable chemical (OECD 301C: 100 % after 14-day). Bioconcentration factor may be low judging from a low P_{ow} value (0.50 at 25 °C).

The lowest acute and chronic toxicity data were 14d LC50 (>100 mg/l) of fish (Medaka; *O. latipes*) and 21d NOEC (> 85 mg/l) of *Daphnia magna*, respectively. Assessment factor of 100 was used to chronic toxicity data to determine PNEC, because chronic toxicity data for fish were not available. Thus, PNEC of this chemical is >0.85 mg/l. Toxicity of this chemical to aquatic organisms is low, because all toxicity data are higher than 85 mg/l.

Exposure

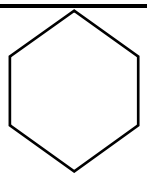
The production volume of this chemical was 29,717 tones in 1993 in Japan. This chemical is used as an intermediate for resins and/or solvents in closed system, and not included in consumer products of Sponsor county. The potential environmental distribution of this chemical obtained from a generic fugacity model (Mackey level III) shows that this chemical will be distributed mostly in water (99.6 %) and partly in sediment (0.4%) when it is discharged into water. The route of occupational exposure is inhalation and skin with a limited numbers of workers. As for consumer use, this chemical is used as an ingredient in deodorants in European countries, and marketed as dietary supplement in US.

NATURE OF FURTHER WORK RECOMMENDED

Human health

Further exposure information should be collected in each member country**.**

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-82-7
Chemical Name	Cyclohexane
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Cyclohexane is readily absorbed via inhalation and oral route, rapidly eliminated and not accumulated in the tissues. Absorption via dermal route varies from 50 % to 5 % depending on the physical form and concentration of cyclohexane. Metabolisation occurs in the liver and cyclohexane is mainly transformed in humans in 1,2- and 1,4-cyclohexanediols (which can be used as biological markers). Induction of CYP 2E1 and CYP 2B1/B2 can occur in humans. Pulmonary elimination is the major route of excretion and a urinary excretion is also possible. Cyclohexane has been found in human milk too.

Cyclohexane has a low acute oral, dermal and inhalation toxicity. In human volunteers, no effects were seen at concentrations ranging from 27 to 274 ppm for a 4-hour inhalation exposure. Another study in human volunteers showed no effects for a 8-hour inhalation exposure to 290 ppm. Cyclohexane is a skin irritant due to its defatting properties. It is a slight ocular and respiratory irritant. A very low sensitising potential can be anticipated.

No repeated-dose tests were available via oral route. Repeated-dose administration via dermal route caused irritation lesions due to defatting effects. Recent 90-day inhalation studies in both rats and mice (OECD TG 413) led to a NO(A)EL of 500 ppm (1,750 mg/m^3). Effects observed at higher doses were transient narcotic properties. This effect is considered to be an acute effect and is common to a large majority of solvents. Other signs of neurotoxicity were described in various studies at high doses (28,000 mg/m^3 and possibly at 8,000 mg/m^3) but were limited to acute and reversible behavioural effects. Slight hepatic toxicity was also noted for doses between 6,000 and 7,000 ppm in rats and mice leading to a NOAEL of 2,000 ppm for this effect.

Cyclohexane is not genotoxic *in vitro*, this was demonstrated in a series of studies including Ames test, mouse lymphoma assays, sister chromatid exchange assay, Unscheduled DNA synthesis assay and DNA binding to *E coli*. An *in vivo* rodent bone marrow cytogenetic assay was considered negative.

An old study (with questionable results) showed that cyclohexane was a weak tumour promoter (particularly stage II tumour promoter). No reliable chronic/carcinogen studies were available.

No overt effect was noted in a two-generation study in rats (OECD TG 416). Cyclohexane does not impair fertility at doses as high as 7,000 ppm.

No developmental effects were induced in rats and rabbits studies (performed according to OECD TG 414) at doses up to 7,000 ppm. Maternal toxicity, limited to narcotic effect was seen from 2,000 ppm.

Environment

Cyclohexane is highly volatile (Henry's law constant H = 14900 $Pa.m^3/mol$). The substance is readily biodegradable and has a medium potential for bioaccumulation (BCF for fish: 31 - 129).

Acute toxicity results are available for fish, invertebrates or algae. L(E)C50 values range from 0.9 to 4.5 mg/l. Due to the non-specific mode of action, a low assessment factor (AF = 100) was chosen and a PNEC of 9 µg/l was derived. No studies with soil or sediment organisms were performed.

Exposure

The consumption of cyclohexane in the EU is estimated to be 900000 t/a. It is mostly used as a chemical intermediate for the production of nylon (approx. 96 %). Remaining uses are as a solvent in adhesives and coatings as well as solvent in chemical production processes.

NATURE OF FURTHER WORK RECOMMENDED

Based on the use pattern and hazard assessment of cyclohexane, a detailed risk assessment is recommended for both human health (narcotic effects and chronic toxicity) and the environment. Especially the risk from the use as a solvent should be evaluated due to the higher exposure compared to the other uses.

This substance is under discussion in the European Union Risk Assessment program under Regulation EEC/793/93.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	116-15-4
Chemical Name	1-Propene, 1,1,2,3,3,3, hexafluoro (Hexafluoropropylene; HFP)
Structural Formula	$F_3C\text{-}CF{=}CF_2$

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Hexafluoropropylene (HFP) has been tested in various acute and repeat-dose toxicity tests and genotoxicity tests. Results indicate that HFP causes kidney damage in rats, mice, guinea pigs, and rabbits under both acute and subchronic inhalation exposure conditions. Kidney effects include changes in urinary output (increased volume and decreased osmolality) as well as pathological changes including regeneration of cortical tubules, cytomegaly of tubular epithelium, and necrosis. All changes appear reversible in male and female rats and female mice, but not in male mice, at concentrations of 50 ppm and above in 13-week studies. A 13-week NOEL of 10 ppm has been established for human health in this hazard assessment. Genotoxicity studies with HFP show that it does not cause gene mutations in *in vitro* tests, is not a heritable mutagen based on a negative dominant lethal test in rats, but does cause chromosomal aberrations in both *in vitro* and *in vivo* tests. The latter positive results were seen at high exposure levels (*in vitro* – 0.29 to 1.40% of the atmosphere above plates; and at a single, six-hour inhalation concentration of 1200 ppm, the highest concentration tested in the *in vivo* micronucleus test). An unscheduled DNA synthesis study in rats was also negative.

The only SIDS endpoint not fulfilled at this time is the reproductive/developmental toxicity endpoint. It is recommended that this be filled (see below for rationale).

Environment

HFP by virtue of its physical form as a gas will be found mainly in the air compartment. Estimations of abiotic degradation via reactions with hydroxyl radicals is a half-life of 5-25 days in air. HFP is not likely to partition into water, soil, sediment, suspended sediments or biota. HFP is also not likely to bioaccumulate based on estimated partition coefficients. The environmental exposure potential is low since relatively small quantities are released into the environment.

Because HFP's distribution is almost exclusively into the air compartment, there are no aquatic hazard data available or needed for this assessment. The only potential hazard is the possible effects of HPF in terms of global warming potential. Neither HFP or its breakdown products (COF_2 and C_2F_4O) following reaction with hydroxyl radicals, are listed as individual contributors to global warming potential in the U.S.

Exposure

HFP is a gas that is a chemical intermediate manufactured in closed system and used primarily in the synthesis of

fluropolymers, fluoroelastomers and fluorolubricants. Total production ranges from 10,000 to 20,000 metric tonnes each year in closed systems. HFP is normally utilized in the synthesis process. However, it can be sold and transported as a compressed, non-flammable gas in 1 to 15 ton pressurized containers or via pipelines to other processing/production facilities.

Measured occupational exposure data at U.S. production sites exist from the mid-1980's. The data indicate predominantly low exposure (below the limit of detection – between 0.3 to "less than 1.0" ppm), with occasional, rare variances up to 6.3 ppm (highest reported level). There is no known direct consumer use and so consumer exposure is limited to HFP at the impurity level in the marketed end-use products.

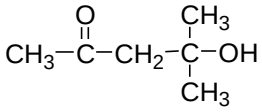
Release to the environment from regular use is anticipated to be negligible. However, computer modeling of a U.S. facility from which estimated fugitive emissions were reported resulted in a "fenceline" air level of 0.017 mg/m^3, or 2.7×10^{-3} ppm. This level can be considered a PEC for the environment.

NATURE OF FURTHER WORK RECOMMENDED

The OECD SIDS test plan for HFP was approved in 1993, indicating there was no need for a reproductive/developmental toxicity test because HFP is a gas and a closed-system intermediate. Following subsequent review (SIAM 8), it was decided that HFP needed to be evaluated for potential developmental toxicity based on the possibility of a single exposure to a pregnant woman during an industrial accident.

In order to evaluate the developmental toxicity, a reproductive/developmental test is needed for this chemical. Based on similarity of chemical structure and comparable repeat dose toxicity data it is recommended that this data gap be filled by using information on a surrogate chemical – tetrafluoroethene (TFE) before the conduct of additional animal experiments. TFE is currently being investigated in the U.S. HPV Challenge Program.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-42-2
Chemical Name	Diacetone Alcohol
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Oral LD_{50} of diacetone alcohol is more than 4,000 mg/kg. This chemical is moderately irritating to skin and irritating to eyes but there is no available data for sensitisation. In oral rat study by an OECD combined repeated dose and reproductive/developmental toxicity screening test [TG 422] at doses of 0, 30, 100, 300 and 1,000 mg/kg/day for at least 44 days, decreased locomotor activity and less response to stimulation by knocking sounds or palpation were observed in males and females of the 300 and 1,000 mg/kg groups. Histopathological examination revealed increases of deposition of hyaline droplets in the proximal tubular epithelium at doses of 100 mg/kg or more, basophilic tubules at doses of 300 and 1,000 mg/kg and dilatation of the distal tubules at dose of 1,000 mg/kg in male kidneys. Slight but no significant increases of dilated distal tubules and fatty degeneration of the proximal tubular epithelium were observed in female kidneys at doses of 300 and 1,000 mg/kg. Furthermore, hepatocellular hypertrophy was evident in both sexes of the 1,000 mg/kg group, and vacuolization of the cells of the zona fasciculata in the adrenals of males receiving 1,000 mg/kg. Based on renal toxicity in male, NOAEL by oral administration was considered 30 mg/kg/day. An inhalation rat study conducted for 6 hr/day, 6 day/week, 6 weeks at doses of 0.232, 1.035 and 4.494 g/m^3 demonstrated the histologic changes in the proximal tubules of the kidneys toxicity in males at the highest dose. As only liver weight was increased at mid dose, NOAEL was considered at 1.035 g/m^3 for 6 hr/day, 6 day/week. The daily intake is roughly calculated as 156 mg/kg/day. In a reproductive/developmental toxicity study [OECD TG22] there were no statistically significant adverse effects noted at any doses. However the composite data at the 1000 mg/kg dose group suggests that there may be chemically related adverse effects such as decreased tendency in the fertility index, number of implantations, and implantation index. Two mothers were not able to normally carry the litter. Therefore a NOAEL for reproductive/developmental toxicity was considered to be 300 mg/kg/day. Evidence of malformations was not observed at any dose. This chemical was not genotoxic in bacterial test and chromosomal aberration test *in vitro* [OECD TG 471 & 473]. The lowest reported concentration to cause adverse symptoms in humans is 0.475 g/m^3, although the reliability of the study is not clear because of insufficient information.

Environment

Diacetone alcohol is readily biodegradable (OECD TG 301C: 100% after 14-day). The lowest acute and chronic toxicity data were 96h LC_{50} (420 mg/l) of fish (Bluegill; *Lepomis macrochirus*) and 21d NOEC (>100 mg/l) of *Daphnia magna*, respectively. Assessment factor of 100 was used to chronic toxicity data to determine PNEC, which is >1.0 mg/l. Toxicity of this chemical to aquatic organisms is low, because all toxicity data are higher than 100 mg/l.

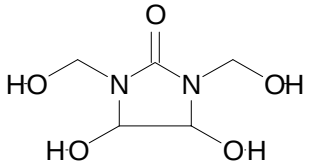
Exposure

The production volume is 3,236 tonnes/year in 1995 in Japan. All of this chemical produced in Japan is used as solvent. A generic fugacity model (Mackey level III) shows this chemical would be distributed mainly to water. As this chemical is contained as a solvent for specific paint products and used in industrial sites, user exposure may take place at using sites in the industry.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1854-26-8
Chemical Name	4,5-Dihydroxy-1,3-bis(hydroxymethyl)imidazolidin-2-one
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

DMDHEU has a very low acute toxicity and does not cause primary irritation.

With regard to the wide spread use, the incidence of contact dermatitis from specific textile-finishing resins is regarded to be very low. Products containing the substance and formaldehyde in concentrations of $\geq$ 0.2% may induce skin sensitization.

Repeated dose toxicity in rats and mice revealed also a very low toxic potential for oral application over 90 days with NOAELs of 3,000 mg/kg in rats and 6,000 mg/kg in mice.

No indication of toxic effects on reproductive function in subchronic studies in rats and mice nor embryotoxicity in rats was found (NOAEL > 640 mg/kg/day).

In bacterial tests, DMDHEU did not show mutagenicity. Whereas in *Drosophila melanogaster* a four-fold increase in the sex-linked recessive lethal events was found, there was no indication of induction of reciprocal translocation. In an *in vivo* micronucleus test the substance did not show clastogenicity. Therefore, there is no evidence for DMDHEU to possess a relevant mutagenic or clastogenic activity.

The chemical exhibits a very low toxic potential, and no local or organ-specific effects were detected.

Environment

Dimethylolglyoxalmonoureine has a log Kow of –2.2, a vapour pressure of 26 hPa and is miscible with water. Based on the physico-chemical properties of dimethylolglyoxalmonoureine the preferred compartment is the hydrosphere.

Dimethylolglyoxalmonoureine can be classified as inherently biodegradable. In a sewage treatment plant simulation test a mean DOC elimination of 27 % was found.

No bioaccumulation study is available. The log Kow indicates no potential for bio- or geoaccumulation.

Short-term tests with fish, daphnids and algae and a long-term test with daphnids are available. The following effect values were found: *Leuciscus idus:* 96h-LC_{50} = 2200 mg/l; *Daphnia magna*: 48h-EC50 > 500 mg/l, 21d-NOEC = 100 mg/l; *Scenedesmus subspicatus*: 96h-EC_{50} = 28.4 mg/l, 96h-NOEC = 15 mg/l. However, in the tests the content of active substance was 40 % for the short-term tests and 70 % for the daphnia reproduction test. The most sensitive species was the green algae *Scenedsmus subspicatus*. A NOEC for the pure substance of 15 mg/l * 0.4 = 6 mg/l was found. With an assessment factor of 10 a $PNEC_{aqua}$ of 600 µg/l was derived from this value.

Exposure

The production level of dimethylolglyoxalmonoureine (DMDHEU) in Germany was 10,000-15,000 t in 1991. The major part is produced at one site. The production volume at this site decreased continually during the last years to a capacity of 1,000-5,000 t/a. All the produced dimethylolglyoxalmonoureine was used in the textile industry to produce easy care fabrics by crosslinking the cellulose molecules.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	590-86-3
Chemical Name	3-Methylbutanal (Isovaleraldehyde)
Structural Formula	CH_3-CH(CH_3)-CH_2-CHO

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Isovaleraldehyde is an irritating fluid of unpleasant odor, which at excessive doses may be absorbed into the body via all routes of exposure (oral, dermal and inhalation). Under practical conditions the irritation potential and chemical reactivity, however, would preclude significant systemic absorption. Biotransformation occurs through the usual oxidative pathway, mediated by aldehyde dehydrogenase to isovaleric acid, which may be incorporated into the intermediary metabolism. Furthermore, isovaleric acid and – transiently - also isovaleraldehyde may arise from isovaleric alcohol (3-methylbutanol). For that reason, toxicity data from this alcohol and also from isovaleric acid may help in the assessment of potential systemic effects of isovaleraldehyde (i.e. this part of toxicity which is not mediated by the protein-reactive aldehyde function).

Isovaleraldehyde is low in general acute toxicity after oral, dermal or inhalation exposure, is clearly irritating to the eyes and is strongly irritant to the skin under occlusive conditions. The material is not regarded as a potent sensitizer which is a common experience for aliphatic aldehydes with a single aldehyde function in the molecule supported by the negative animal data from the structural analogous aldehydes n-butyraldehyde, n-valeraldehyde and 2-methylbutanal. Studies with repeated exposure in animals (subchronic toxicity) do not exist with isovaleraldehyde. However, the relatively uniform toxicity profiles of aldehydes allow an estimation of these endpoints on the basis of data and results, which have been obtained during the investigation of other structurally related aldehydes, such as propionaldehyde, n-butyraldehyde and isobutyraldehyde. For systemic effects in the tested aldehydes the NOAEL for oral uptake is 300 mg/kg in rats, with effects on blood at > 600 mg/kg bw (n-butyraldehyde). For inhalation, the NOAELs with respect to systemic toxicity are $\geq$ 150 ppm. Effects observed were reduced food consumption in females rats at 750 ppm (propionaldehyde); no systemic effects were found up to the highest concentration of 2,000 ppm in rats (n-butyraldehyde). At 4,000 and 8,000 ppm body weight depression and mortality were observed in 13-week and 2-year studies in rats (isobutyraldehyde). In the metabolic precusor (3-methylbutanol-1) the only effects at the highest dose of 1,250 mg/kg (drinking water, rats) were blood effects. With respect to irritation, there is a clear dependency on molecule size, water solubility and Log Pow, indicating a NOAEL for isovaleraldehyde of > 51 ppm; butyraldehydes show a distinct lower irritating potential than propionaldehyde. The genotoxicity of isovaleraldehyde was investigated in-vitro with negative results in the Ames test and questionable results on SCE-rate in human lymphocytes. The substance did not show DNA-damaging activity in a Bacillus subtilis study (Rec-Assay). A mouse micronucleus test after intraperitoneal administration in doses up to 100 mg/kg body weight was clearly negative with respect to clastogenicity

and impairment of chromosome distribution in the course of mitosis. Thus, there is no concern with respect to genotoxicity. At present, there is no concern for carcinogenic effects of isovaleraldehyde. The experiments with isobutyraldehyde indicate a LOAEL for non-neoplastic effects of 500 ppm with weak local effects in female rats. Prenatal toxicity investigations have been carried out with propionaldehyde in rats and isobutyraldehyde in rats and 3-methylbutanol-1 in rats and rabbits. In these studies no prenatal defects and no high systemic toxicity was observed; hence, also isovaleric acid is not expected to exert prenatal toxicity. Isovaleric acid is, furthermore, also physiologically formed during the catabolism of leucine.

The NOAELs derived from the toxicological endpoints show no concern for the workplace, consumers and in relation to direct and indirect exposure from the environment.

Environment

3-Methylbutanal has a log Kow of 1.3, a water solubility of 20 g/l and a vapour pressure of 61 hPa. Based on the high vapour pressure of the substance isovaleraldehyde tends to pass from water to air. The compound does not tend to adsorb on sediment/soil or accumulate in biota. According to Mackay I the target compartment for this substance is the atmosphere.

It can be concluded that 3-methylbutanal is biologically readily degradable from a BOD5/COD ratio > 60 %.

Short-term tests with fish, daphnids and algae are available. For *Daphnia magna* EC50-values of 210 mg/l (24 h) and 177 mg/l (48 h) based on nominal concentrations were found. For *Scenedesmus subspicatus* a EC50 of 80 mg/l and a EC10 of 33 mg/l based on nominal concentrations was obtained in a 72h test. In a flow-through study with *Pimephales promelas* a 96h-LC50 of 3.25 mg/l was found based on measured concentrations. With an assessment factor of 1000 a $PNEC_{aqua}$ of 3.3 µg/l was derived.

Exposure

The production level of 3-methylbutanal (isovaleraldehyde) in Germany is in the range of 1000 - 5000 t/a. A certain amount is exported (no data about volumes). There is no information about import volumes. The chemical is used as an intermediate for pharmaceuticals, pesticides, solvents and softeners. Consumer exposure is not expected.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	62-53-3
Chemical Name	Aniline
Structural Formula	∅-NH_2

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Aniline is absorbed through the skin and the lungs with formation of methaemoglobin leading to cyanosis as main toxic effect. Acute intoxication of humans with aniline/aniline vapours is reported frequently. The average lethal inhalation dose for humans is reported to be 25 mg/l air or 0.35-1.43 g/kg body weight.

The acute toxicity of aniline in experiments to rats and rabbits is moderate: In rats oral LD50-values of 442 and 930 mg/kg bw in males and of 780 mg/kg bw in females were determined. Inhalation LC50 values in rats are different depending on the kind of exposure: head-only exposure 3.3 mg/l/4 hours and whole-body exposure 1.86 mg/l/4 hours. Acute dermal toxicity of aniline is characterized by LD50 values of 1540 mg/kg bw for rabbits and 1290 mg/kg bw for guinea pigs. Cats, however, react much more sensitive, with a dermal LD50 of 254 mg/kg bw and death following oral application of approximately 50-100 mg/kg.

Aniline causes weak irritation to the skin but long lasting severe irritation with pannus formation to the eyes of rabbits. Aniline has no local corrosive properties, but causes mild to moderate skin sensitization in guinea pigs. In humans aniline causes contact allergy, often associated with para-group cross reactivity.

Repeated aniline administration to rats has been shown to damage erythrocytes followed by haemolytic anaemia, cyanosis and methaemoglobinemia. Corresponding effects were haemosiderin deposits in the spleen, kidneys and liver as well as increased erythropoeitic activity in the bone marrow and spleen. Congestion of the red pulp sinuses, increased spleen weight, excessive fibrosis and fatty metamorphosis of splenic stroma and chronic capsulitis were demonstrated. Adverse effects of minor relevance were also reported in the adrenals (cortical hyperplasia) and ovaries (reduced organ weights).

Aniline shows positive results in mammalian cell cultures with respect to chromosomal effects, sister chromatid exchanges and possibly for gene mutations. In general, stronger effects are induced in the presence of an exogenous metabolic activation system than in the absence. *In vivo*, aniline is an inducer of micronuclei in mouse and rat bone marrow cells. The mutagenicity *in vitro* and *in vivo* of aniline is supported by *in vivo* studies showing DNA strand breaks and DNA adduct formation in different organs.

Aniline is carcinogenic in rats, however, no clear tumor response could be associated with aniline exposure to humans. Taking into account positive *in vivo* genotoxicity tests and metabolic information a carcinogenic hazard cannot be excluded.

Concerning reproductive toxicity (fertility), data from animal studies (sperm-morphology, repeated exposure) did not give evidence of an impairment of parameters related to male fertility. The significance of incidental findings

concerning female sex organs (ovaries, uterus) for reproductive capacity and/or performance was not further evaluated. The available developmental studies did not give evidence for a specific embryotoxic, fetotoxic or teratogenic potential of aniline. As far some effects on fetuses and on postnatal development were observed, these findings were associated with dose levels resulting in maternal toxicity over an extended period.

Environment

Aniline has a log Kow of 0.9, a water solubility of 35 g/l and a vapour pressure of 0.4 hPa. With a Henry's law constant in the range of 0.1-0.2 $Pa.m^3.mol^{-1}$, the substance is not expected to be volatile from aqueous solution.

Aniline does not undergo hydrolysis. Aniline is readily biodegradable in treatment plants and in the hydrosphere. In surface water photolysis occurs to but this degradation mechanism is of minor importance compared to biodegradation. In soils and sediments, aniline reacts with humic acids. This reaction product is immobile and only slowly degraded (half-life of 350 days). In the atmosphere, the substance is readily removed by reaction with OH-radicals, with a half-life of 3.2 h.

In agricultural soils, aniline is formed by biodegradation of plant protection agents. Within some days, aniline forms covalent bonds with soil organic matter. The reaction product is extremely slowly biodegraded and accumulates in soils when the agents are periodically applied.

In a bioaccumulation study with fish a BCF of 2.6 was found. Because aniline forms covalent bounds with the organic matter, the substance may accumulate in sediment and soils. Therefore, bioaccumulation via the route sediment/soil – sediment/soil-dwelling organisms – bird or mammal may occur.

For aniline short- and long-term tests with fish, daphnids and algae are available. Daphnids are the most sensitive species to aniline in short- and long-term tests. For *Daphnia pulex* a 48h-EC_{50} of 0.1 mg/l was found. For *Daphnia magna* the 21d-NOECs from three reproduction tests are in the range of 4 µg/l to 24 µg/l. From these data an average value of 15 µg/l can be calculated. With an assessment factor of 10 a PNECaqua of 1.5 µg/l can be derived. There are no data available on effects on benthic and terrestrial organisms for the reaction product of aniline with organic matter. For aniline two 14d-EC50 for *Lactuca sativa* of 33 mg/kg and 56 mg/kg were found.

Exposure

In the European Union, 500,000 t aniline (1990) were produced by hydrogenation of nitrobenzene. Aniline is exclusively used as an intermediate in chemical industry for the synthesis of 4,4'-methylenedianiline (71%), dyes, caoutchouc chemicals, pesticides, pharmaceuticals, fibres and others. During production and processing, aniline is released via waste water into the hydrosphere and into the atmosphere. Further releases in both compartments are expected during processing of caoutchouc chemicals, and from coal and oil industry. In Europe, consumer exposure is unlikely to occur.

NATURE OF FURTHER WORK RECOMMENDED

There is a need for further information and further consideration of exposure and risk assessment. Depending on review by national and regional authorities risk reduction measures may need to be reviewed.

- missing emission data into atmosphere and hydrosphere for several aniline production and processing sites have to be completed;
- emissions into atmosphere by the caoutchouc industry have to be clarified;
- effect tests with terrestrial and benthic organisms with pre-incubated soil and sediment should be conducted;
- a nitrification inhibition test with domestic and industrial sludge should be conducted;
- depending on emission data into atmosphere the conduction of plant fumigation test should be considered;
- genotoxic effects of aniline in combination with its carcinogenic properties causes concern for human health.

This substance is under discussion in the European Union Risk Assessment Program under Regulation EEC/793/93.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7664-39-3
Chemical Name	Hydrogen Fluoride
Structural Formula	H - F

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In the data set for HF animal as well as human studies were available. With respect to reproduction toxicity, mutagenicity and carcinogenicity data from studies carried out with sodium fluoride have been taken into account, since these studies provide insight in the possible hazard of fluoride and thus HF as has been explained in the sections on toxicokinetics.

HF is very toxic by inhalation, in contact with skin and if swallowed.

When applied to skin and eye HF produces severe lesions, even at low concentrations. The substance is considered corrosive.

Sensitisation studies with HF are not available. It was agreed that HF and F^- are not expected to react with proteins and therefore it is assumed that the substance has no sensitising properties.

Signs of acute fluoride intoxication in humans resemble those observed in animals. Dermal contact with HF either as liquid or as gas produces severe dermal lesions. Dermal contact with HF may result in systemic (cardiac) effects including death. Inhalatory exposure is highly damaging to the respiratory tract. Exposure to HF in a concentration of 1.16 mg/m^3 will possibly result in some irritation. Prolonged oral intake of excess fluoride results in skeletal fluorosis, an effect for which indications were also found after inhalatory exposure.

The available animal data set for HF permits the derivation of a NOAEL for repeated subchronic inhalatory exposure. No suitable studies are available to derive a NOAEL for HF for other routes of exposure. In a study with rats, changes in body and organ weights as well as haematological and clinical signs and death were seen at actual concentrations of 7.52 mg/m^3; 6 hr/d; 5 d/w for 90 days. This value is equal to a duration corrected value (DCV) of 1340 µg/m^3. Based on actual exposure levels a NOAEL of 0.72 mg/m^3 is established. Because at higher dose levels apart from irritation also systemic effects occur, a duration corrected equivalent of this NOAEL is calculated. This duration corrected value (NOAEL) amounts to 128 µg/m^3.

In epidemiological studies with workers exposed to 0.48 mg total fluoride/m^3 (of which 0.2 mg gaseous fluoride) no fluorosis was observed. This level can be considered as an inhalatory NOAEL for fluoride in humans. At this level slight respiratory effects were observed, but these effects were not attributable to HF, because simultaneously, exposure to other air-way irritants occurred.

It is concluded that fluoride does not induce chromosomal damage *in vivo*. However, genetic damage is observed in *in vitro* studies. Carcinogenic studies with HF are not available. From studies with sodium fluoride in rats and mice it is concluded that fluoride is not considered to be carcinogenic in animals.

Reproduction studies with HF are not available. The LOAEL for these effects was 2.26 mg F^-/kg b.w./d. In a two-generation study (leading to a NOAEL of 250 mg NaF/l; equivalent to 11 mg/kg bw./d) and in an intratesticular injection study, fluoride did not induce any sign of impaired testicular functioning. There are very strong indications from the two-generation study that fluoride does not affect male or female fertility. This cannot be stated with certainty because the study has not been fully reported, yet. Despite this limitation, the NOAEL of about 10 mg/kg b.w./d derived from the two-generation study has been used in the risk assessment.

From three well-performed embryo- and developmental toxicity studies with NaF an overall NOAEL for maternal toxicity and developmental effects of 11.12 mg F^-/kg b.w./d can be derived.

Environment

HF may enter the environment from both natural (volcanoes, weathering of minerals and marine aerosols) and anthropogenic sources. The latter includes production of HF itself, but HF is also formed as a by-product during other industrial processes (phosphate fertiliser, aluminium and steel production, ceramic industry etc.).

Once released in the environment HF is unlikely to remain in its original form for very long. In air, water and soil HF is transformed to a variety of other F-compounds.

Both short and long term toxicity data (NaF) are available for fish, crustaceans, algae and micro-organisms.

The PNEC for the freshwater compartment is extrapolated from the calculated mean NOEC-value for *Daphnia magna* (8.9 mg/l) using an extrapolation factor of 10. The extrapolation leads to a PNEC for the freshwater environment of 0.9 mg/l ($PNEC_{aqua}$). Long-term ecotoxicity data with fluoride for terrestrial organisms, including microbial processes, are available. The lowest available NOEC, i.e. 106 mg/kg for nitrification, was selected for deriving the PNEC for the terrestrial compartment. Applying an assessment factor of 10 gives a PNEC of 11 mg/kg.

Many experiments are available in which all kinds of plants (bean, barley, corn, garden flowers, strawberries, pine, shrubs, grass, rice etc.) are exposed to HF in fumigation experiments. Sensitive species are tulip, gladiolus, fruit crops, conifers and grasses, which are affected at concentrations ranging from 0.4 to 1.0 $\mu g/m^3$ after exposure for several days. The $PNEC_{plant-air}$ is set at 0.2 $\mu g/m^3$.

Cattle were shown to be the most sensitive of domestic animals to dietary fluoride, particularly young animals. Observed effects all eventually lead to a loss of body weight and diminished meat and milk production. Atmospheric NOECs for livestock (and plants) of 0.8 µg and 0.3 $\mu g/m^3$ (daily averages) were calculated for the grazing season and winter season, respectively. It is concluded that wild herbivores are or may be more susceptible to fluoride toxicity than domestic live stock, on a dietary F content basis. Thus the atmospheric NOECs derived for livestock may provide an insufficient guarantee for the protection of wild fauna.

Exposure

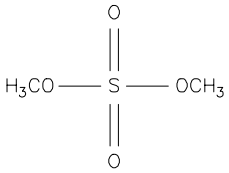
Anhydrous HF and hydrofluoric acid is used for the production of organofluor compounds and inorganic fluorides, as well as a catalyst of alkylation reactions in the petrochemical industry. It is also used for etching of glass and pickling of stainless steel. The quantitative estimate currently available for the industrial and use category distribution of HF is 60% for the synthesis of organofluor compounds, 30% as intermediate in chemical synthesis of inorganic fluorides, 4% as pickling agent of metal surfaces, 3% for etching of glass surfaces, and 2% as catalyst in alkylation reactions in the petrochemical industry (CTEF 1995). The maximum total production of HF in the European Union for 1994 is 245,000 tonnes. Consumer exposure was found in rust cleaning and stone and wood cleaning agents.

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.

This substance has been agreed in the European Union Risk assessment program under Regulation EEC/793/93. The EU risk assessment concluded that there are need for specific measures to limit the risks for workers and consumers and for exposure via the environment for some sites.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	77-78-1
Chemical Name	Dimethyl sulphate
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Dimethylsulphate (DMS) is a methylating agent, which is found to react with nucleic acids. No data on interference with other nucleophilic macromolecules, e.g. proteins, are available.

Data on dermal absorption are limited and insufficient to draw conclusions. DMS can be absorbed via respiratory and oral routes. For oral absorption this is concluded from toxicodynamic data. Rapid respiratory absorption is observed in rats exposed to dose levels up to 50.3 mg/m^3. At higher dose levels uptake was decreased, probably due to a decreased minute volume. No information is provided on the metabolism of DMS in animals following oral administration. The information on metabolism after inhalatory or dermal exposure is limited. DMS may be hydrolysed to methanol, sulphuric acid, and methyl sulphate, and may be metabolised to a lesser extent to formaldehyde and formate. The toxicokinetic studies do not allow derivation of quantitative figures on absorption that can be used in risk characterisation.

The available acute toxicity data indicate that DMS is toxic after oral administration, and very toxic after exposure by inhalation.

DMS is corrosive to the skin and should be considered to cause risk of serious damage to eyes in laboratory animals. Irritation of the respiratory tract was observed in a poorly reported inhalation experiment with rats.

Local effects of DMS after dermal and respiratory exposure were also seen in humans.

Based on the results of the local lymph node assay, it is concluded that DMS has sensitising properties.
The repeated-dose inhalation studies do not permit the establishment of a NOAEL. No oral and dermal repeated dose toxicity studies are available.

DMS is a potent direct-acting genotoxicant in bacteria and mammalian cells *in vitro*, it is positive in tests for primary DNA damage, gene mutations, and chromosome aberrations *in vitro*. DMS appears genotoxic in various *in vivo* tests in Drosophila, i.e., in tests for somatic mutations and recombination, for sex-linked recessive lethals, and for sex chromosome loss. From the results of the tests with mammals it is concluded that DMS may have clastogenic activity in somatic cells *in vivo*, but there are no indications for the induction of gene mutations *in vivo*. No tests are available to assess the genotoxicity of DMS in germ cells in mammals.

Given the results of the mutagenicity studies, it is assumed that the carcinogenicity of DMS is based on a genotoxic mode of action. Evidence on human carcinogenicity is inadequate. The conclusion of IARC is that DMS produces mainly local tumours in rats following inhalation or subcutaneous injection and that there is sufficient evidence to classify DMS as an animal carcinogen (2A). This conclusion is in agreement with the conclusion of the sponsor country. The sponsor country could not verify IARC's statement on tumours of the nervous system after prenatal exposure of laboratory animals. The study design of the carcinogenicity study of Schlögel does not fulfil the requirements of OECD 451. However, the results of this study can be used to give a indication of the carcinogenic potency of DMS.

The toxicological database of DMS has gaps with respect to systemic toxicity after repeated exposure, and with respect to effects on reproduction. There are no data available on toxicological parameters such as haematology and clinical chemistry. Furthermore, no data are available on fertility effects of DMS.

It is concluded that DMS did only induce slight developmental toxicity after inhalation at maternal toxic concentrations.

Environment

DMS may enter the environment during its production and industrial use (processing), and in emissions from power plants that are burning sulphur-containing coal/fuel. DMS has an estimated atmospheric half-life of 84 days for the reaction with photochemically produced hydroxyl radicals, hydrolysis quickly in water (DT50 < 1day), is readily biodegradable, has a relatively low Henry constant of 0.39 $Pa.m^3/mol$ indicating that the compound shows no tendency to evaporate from water and has a relatively low log Kow of 0.16. From the log Kow a log K_{oc} of 1.38 is calculated indicating that DMS has a low adsorption potential and thus a high mobility/leaching potential. No bioaccumulation of DMS is expected.

Short-term aquatic toxicity data are available for fish, daphnia and algae. Since DMS is known to hydrolyse quickly into monomethylsulphate and methanol the observed toxicity concerns the toxicity of DMS and its hydrolysis products. The PNEC for the aquatic compartment is extrapolated from the lowest short-term toxicity result, i.e. 14 mg/l for the goldfish, using an extrapolation factor of 1000. This results in a PNEC of 14 µg/l. No ecotoxicity data are available for the terrestrial and atmospheric compartment.

Exposure

In the EU, DMS is mainly used as a chemical intermediate. Its major applications are as a methylating agent of many organic chemicals (e.g. amines, carbon acids, thiols and phenols) both in industry and laboratories. The total EU production volume for 1994 was estimated to be between 20,000 and 30,000 tpa. Production and processing in large quantities occur in closed systems in the EU. At these sites no release waste water occurs and emission to air is theoretically assumed to be zero. No use of Dimethyl sulphate in consumer products has been identified.

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.

A detailed risk assessment for this substance has been agreed under the European Union Risk Assessment Program under Regulation EEC/793/93. The risk assessment concludes that there are need for specific measures to limit the risks for workers. Dimethyl sulphate has not been tested for reproductive toxicity, because it is considered to be a non-threshold carcinogen.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	85535-84-8
Chemical Name	Alkanes, C10-13, chloro-
Structural Formula	CxH(2x-y+2)Cly (Where x = 10-13 and y = 1-17)

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

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

Human Health

Very little toxicological information is available from studies in humans. The available animal data do not allow a direct comparison from every toxicological endpoint of the effects of SCCPs. However, the information available from acute studies and skin irritation studies indicates that the intensity and nature of effects for these endpoints are independent of chain length and degree of chlorination. It would appear unnecessary to attempt to fill these gaps with further testing.

There is very limited information on toxicokinetics. No information is available on absorption via the inhalation route. A study in animals via the oral route indicates that significant absorption (60%) does occur. Studies in animals (on a longer chain substance) and humans indicate that absorption via the dermal route will be low.

Assessment of the available data clearly indicates that SCCPs are of low acute toxicity in animals. Limited information indicates that they do not cause skin irritation in humans and in animal studies, at most, minimal skin and mild eye irritation were reported. More pronounced skin irritation was observed in animals following repeated exposure presumably because of defatting.

No conclusions can be drawn from the information available on skin sensitization in humans. However, well-conducted studies in animals have shown that SCCPs do not have the potential to produce skin sensitization. Although there is no information on respiratory sensitization in humans or animals, it is significant that no such effects have been reported in humans of repeated exposure. The principal signs of toxicity in animals were effects in the liver and thyroid. However, mechanistic information has indicated that these effects are probably not relevant to human health. NOAELs of 100 and 1000 mg/kg/day were identified in rats and mice respectively for other signs of toxicity, such as decreased body weight gain and increased kidney weight, which may be relevant to human health.

SCCPs were mutagenic in bacterial cell systems. No standard *in vitro* cytogenetics studies were available but a gene-mutation assay was negative. Well-conducted *in vivo* studies indicate that SCCPs do not produce mutagenicity in somatic or germ cells. Overall the evidence indicates that SCCPs are not mutagenic.

No information is available on carcinogenicity studies in human populations potentially exposed to exclusively SCCPs. In rodent carcinogenicity studies, dose-related increases in the incidence of ademomas and carcinomas were

observed in the liver, thyroid and kidney. Other cancers seen were dismissed as not significant. The characteristic patterns in the results and probable underlying mechanisms indicate that in the liver chronic tissue damage was caused by peroxisome proliferation and that in the thyroid there was long-term hormonal stimulation, potentially consequent to the liver effects. Consideration of the likely underlying mechanisms for these tumours suggests that they are not relevant to human health.

The kidney adenomas (benign) were seen exclusively in male rats. It is considered likely that the underlying mechanism is the male rat-specific phenomenon of hyaline droplet nephropathy, although this has not been clearly demonstrated. The EU Specialised Experts concluded that there was insufficient evidence to conclude a male rat specific event and that the consequences for humans could not be ruled out. Given that SCCPs are not genotoxic, it is considered that there would be no risk of kidney tumour development associated with exposures lower than those required to produce chronic toxicity in this target organ. The NOAEL for kidney toxicity in male rats, identified at 100 mg/kg/day will therefore be used ass the NOAEL for kidney carcinogenicity [N.B. this appraisal of carcinogenicity data reflects the position at the time the risk assessment was agreed (1997)].

There are no data available in humans or animals on fertility although no changes were seen in the reproductive organs in rats and mice treated for 13 weeks with up to 5000 and 2000 mg/kg/day, respectively. There are no data available on developmental effects in humans. Developmental effects were produced in rats at a dose which also cause maternal toxicity (2000 mg/kg), but no developmental effects at lower doses (at and below the NOAEL of 500 mg/kg and below). No developmental effects were observed in a study in rabbits, although maternally toxic doses were not tested.

Overall, SCCPs are of low toxicity with the principal toxicological issue being for general non-specific toxicity following repeated exposure. NOAELs for general toxicity of 100 and 1000 mg/kg/day were identified in rats and mice respectively.

Environment

SCCPs appear to be of low acute toxicity to fish with 96-hour LC_{50}s in excess of water solubility. The lowest no observed effect concentration (NOEC) in chronic toxicity studies was <0.04 mg/l (based on sublethal effects on rainbow trout over 60 days). Several aquatic invertebrate species have been tested, and all show similar sensitivity. *Daphnia magna* is the most sensitive species, with 24-hour EC_{50}s of 0.3 – 11.1 mg/l, and 21-day NOECs of 0.005-0.05 mg/l. For algae, acute toxicity studies give 96-hour EC_{50}s of 0.043 – 3.7 mg/l. A 96-hour NOEC of 0.012 mg/l is reported for the marine alga *Skeletonema costatum*. SCCPs are therefore very toxic to the aquatic environment, especially during longer-term exposure and a PNEC of 0.5 µg/l has been derived by applying an assessment factor of 10 to the lowest Daphnia NOEC.

Toxicity data for soil-dwelling organisms are not available, but an extrapolation from aquatic toxicity data can be made using the equilibrium partitioning method for screening risk assessment purposes (giving a provisional PNEC for the soil compartment of 0.8 µg/kg wet weight), and consequently actual data are currently not required. The NOAEL from a 22-week avian reproduction study was 166 mg/kg food for mallard duck (*Anas platyrhynchos*).

Exposure

C_{10}-$_{13}$ chloroalkanes – generally known as short chain length chlorinated paraffins or SCCPs – are a complex mixture of components. Up to 15,000 tonnes are manufactured annually in Europe (1995 figures). They are used mainly as additives in meal working fluids, with minor uses in rubbers, paints and coatings, sealants/adhesives, leather processing and textiles.

The substance is a viscous liquid of low volatility and low water solubility (0.15-0.47 mg/l at 20 degree Celsius), with a log octanol-water partition coefficient (log K_{ow}) of 4.4 – 8 (depending on the degree of chlorination). The components do not hydrolyse in water, and are not readily or inherently biodegradable in standard tests.

The high log K_{ow} values imply a high potential for bioaccumulation, strong sorption to sewage sludge, soils and sediments and very low mobility in soil. A small but not insignificant fraction is predicted to distribute into water

and air and so SCCPs may be slightly mobile in the environment. High bioconcentration factors (whole body values ranging from 1,000 to 50,000, with high values for individual tissues) have been reported with a variety of freshwater and marine organisms.

The main route of worker or consumer exposure is via skin contact. Exposure to vapour is generally considered insignificant due to the low vapour pressures involved. However, there is a potential for significant inhalation exposure to SCCPs during the formulation of hot melt adhesives and in the use of metal working fluids.

NATURE OF FURTHER WORK RECOMMENDED

A national environmental risk assessment is recommended to identify the need for risk reduction and for further work to characterise hazards to the sediment and soil environments (as a post-SIDS activity).

A detailed risk assessment for this substance has been agreed under the European Union Risk Assessment Programme under Regulation EEC/793/93. The assessment concludes that risk reduction measures need to be considered for the formulation and use of SCCPs in metal working and leather finishing fluids. Consequently, risk reduction activity is being discussed at OECD level. SCCPs have also been raised as a concern with regard to long range atmospheric transport, and this is being considered by the appropriate international fora.

The mechanism of kidney adenoma formation in male rats is unclear, although it is unlikely to be mediated by genotoxicity. The relevance of this effect for human health cannot be excluded, but further work to better characterize this effect is unnecessary in view of the existence of a NOAEL for chronic kidney toxicity. Nevertheless industry is voluntarily performing further investigation of this effect.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	85535-85-9
Chemical Name	Alkanes, C14-17, chloro-
Structural Formula	CxH(2x-y+2)Cly (Where x = 14-17 and y = 1-17)

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The main toxic effects for MCCPs are repeated exposure effects on the kidneys seen in adult animals and the internal haemorrhaging observed in lactating pups.

A NOAEL of 0.4 $mg.kg^{-1}.day^{-1}$ in rats can be identified for kidney effects from a 90-day study. Inner medullary tubular dilatation seen in the kidneys of female rats at 10 $mg.kg^{-1}.day^{-1}$ was, in terms of severity, slight increasing only marginally in severity and incidence at levels higher than this such that 8/10 females at 420 $mg.kg^{-1}.day^{-1}$ were affected; indicating a very shallow dose-response relationship. Although the effects seen at higher concentrations were mild in nature, their consequence for the functioning of the kidney, the underlying mechanism involved and its relevance to human health are unclear.

Exposure of rats to a C_{14-17} 52% chlorinated paraffin at approximately 400 $mg.kg^{-1}.day^{-1}$ in the diet produced internal haemorrhaging and deaths in the pups breast feeding from the treated dams. It is not known whether the internal haemorrhaging is mediated by the effects of MCCPs or their metabolites on the dams (thus in some way altering the quality of the milk received by offspring) or if the MCCPs and/or metabolites are transferred via the milk and cause direct effects in the neonates. This would appear to be a phenomenon specific for neonates as there is no indication of haematological effects in adult animals in conventional repeated-exposure studies. From the studies available, a NOAEL of 8 $mg.kg^{-1}.day^{-1}$ as a maternal dose can be identified for this effect. There is no knowledge on whether or not such effects are of relevance to human neonatal health.

Of the other toxicity endpoints, the acute studies indicate MCCPs are of very low toxicity via the oral, dermal, and inhalation routes. MCCPs are not skin, eye or respiratory tract irritants following single exposure although there is evidence for slight defatting of the skin as a result of repeated exposures. There are no concerns for sensitisation or mutagenicity using data from C10-13 Chloroalkanes. There are no concerns for carcinogenicity.

Environment

The ecotoxicity database for MCCPs is complicated because many tests have been conducted at concentrations well above the water solubility. 96-hour LC_{50}s for fish are significantly in excess of water solubility. No effects on mortality, growth or behaviour of Rainbow Trout (*Oncorhynchus mykiss*) were observed at 1 and 4.5 mg/l during a 60-day test. No effects occurred in eggs or larvae of Japanese medaka (*Oryzias latipes*) exposed for 20 days at 0.0029-3.4 mg/l. Several aquatic invertebrate species have been tested, but *Daphnia magna* is the only species to be

affected in both short-term tests (48-hour EC_{50} = 5.9 µg/l) and long-term tests (21-day NOEC = 10 µg/l based on mortality and reproductive effects) at concentrations below water solubility. Effects over 96 hours on the alga *Selenastrum capricornutum* occurred at concentrations above solubility, and the NOEC is an order of magnitude greater than that for *Daphnia*. The PNEC for the aquatic compartment is 0.2 µg/l, using an assessment factor of 50 on the *Daphnia* NOEC.

From the available toxicity data, it therefore appears that MCCPs are toxic to *Daphnia*, but no toxicity has been seen in long-term exposure to fish, other invertebrates or algae. Although it is possible that the effects seen with *Daphnia* were due to physical adsorption, at least in the acute toxicity tests, direct toxic effects of the MCCPs themselves cannot be ruled out.

Toxicity data for soil-dwelling organisms are not available. An extrapolation from aquatic toxicity data using the equilibrium partitioning method gives a provisional PNEC for the soil compartment of 2.1 mg/kg wet weight. This suggests tests may be required on the basis of a screening risk assessment. No significant effects were seen in a 5-day dietary study of mallard ducks (*Anas platyrhynchos*) and ring-necked pheasants (*Phasanius colchius*), other than a slight depression of food intake for mallards at the high dose level of 24,063 mg/kg food.

Exposure

C_{14-17} chloroalkanes – generally known as medium chain length chlorinated paraffins or MCCPs - are a complex mixture of components. Up to 160,000 tonnes are manufactured annually in Europe. They are used mainly as secondary plasticisers for polyvinyl chloride (PVC), with minor uses in metal working fluids, paints, adhesives and sealants, leather processing liquors and rubbers and other polymeric materials.

The substance is a viscous liquid of low volatility and low water solubility (~0.027 mg/l at 20^{o}C), with a log octanol-water partition coefficient (log K_{ow}) of 5.5-8 (depending on the degree of chlorination). The components do not hydrolyse in water, and from the available information can be considered not readily or inherently biodegradable (no data are available from standard tests).

The high log K_{ow} values imply a high potential for bioaccumulation, strong sorption to sewage sludge, soils and sediments and very low mobility in soil. Bioconcentration factors (BCFs) have been reported for a variety of aquatic organisms, but interpretation of the data is complicated by the very low water solubility. The best estimate of a fish BCF is 11,200 l/kg.

The main route of worker or consumer exposure is via skin contact (MCCPs are not sold directly to consumers, but exposure may occur via products containing them). Exposure to vapour is generally considered insignificant due to the low vapour pressures involved. The extent of absorption following skin contact is uncertain. The number of persons potentially exposed to MCCPs in the EU is not known but is expected to be of the order of many thousands.

NATURE OF FURTHER WORK RECOMMENDED

This substance is under discussion in the European Union Risk Assessment program under Regulation EEC/793/93.

1. Toxicity tests on soil organisms, on the basis of predicted high exposure to the soil compartment.

2. On the basis of a regional risk assessment in Europe, a long-term toxicity study with fish (early life stage), a bioconcentration study, toxicity tests on sediment organisms and a soil degradation study are being considered. Further information is also needed on releases to the environment from use in carbonless copy paper. These are post-SIDS requirements. Certain uses could be candidates for measures to reduce risks to the aquatic environment (e.g. some PVC production processes, formulation and use of certain metal cutting fluids, use in leather fat liquors, and use in carbonless copy paper during recycling). Although the current Daphnia data are considered adequate, industry has volunteered to perform some additional studies on this species.

3. Further information on the extent of dermal absorption is currently being considered. (Industry have provided information and this is being considered in the sponsor country)

4. It is recommended that further information should be obtained on the effects of prolonged (e.g. lifetime) exposure. It is proposed that a methodology should be developed to address this. At this stage it is thought that this may involve modeling, or alternatively, the conduct of a lifetime study in rodents.

5. It is recommended that information should be obtained on the relevance and significance of the mechanism to human health of the internal haemorrhaging seen in lactating pups.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-24-7
Chemical Name	Acetic anhydride
Structural Formula	$(CH_3CO)_2O$

CONCLUSIONS AND RECOMMENDATIONS

It is currently considered of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

In the hydrosphere, Acetic anhydride is rapidly hydrolyzed (half-life 4.4 min.) to acetic acid which is readily biodegradable. In the atmosphere, it is converted to Acetic acid which is subject to photooxidative degradation (half-life 22 days). Toxicity to aquatic organisms is moderate (18 to 3400 mg/l), but it persists only for a short time due to its rapid hydrolysis to acetate/acetic acid. It has virtually no potential for bioaccumulation (log Kow = -0.27). The PEC/PNEC ratio is much less than 1, indicating that acetic anhydride has a low potential for risk to the environment.

The critical effect for Acetic anhydride is irritancy at the site of contact. Because of its well-known corrosive and irritating effects on the eyes, skin and respiratory tract and low odor threshold, procedures, equipment (e.g. goggles, gloves, respirators), training and engineering controls (closed systems) have already been in place for many years to prevent exposure. Levels of acetic anhydride in facilities where it is produced and used in the manufacture of cellulose acetate esters are below 1 ppm 8 hr. time-weighted average (4.2 mg/m3). It is suggested that member country occupational exposure limits be revisited based on the additional results from a 90 day test, reported in the SIAR. Acetic anhydride is used exclusively as a chemical intermediate and there is no indication that its use is in general practice in the consumer industry.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	109-69-3
Chemical Name	1-Chlorobutane
Structural Formula	$CH_3CH_2CH_2CH_2$-Cl

CONCLUSIONS AND RECOMMENDATIONS

This chemical does not reveal any remarkable ecotoxicity and PEC/PNEC is lower than 1.

The chemical has some potential for mutagenicity but exposure is assumed to be low.

It is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

1-Chlorobutane is a stable liquid and its production volume was ca. 800 tonnes/year in 1990 - 1993 in Japan. This chemical is used as an intermediate for the synthesis of catalysts and other organic compounds in closed systems in Japan. The chemical is considered to be "not readily biodegradable". The bioaccumulation factor is 90 - 450.

PECs have been calculated based on several models considering its physico-chemical properties (e.g. molecular weight, water solubility, vapour pressure and partition coefficient). The worst estimated concentrations were 7.3×10^{-9} mg/l (air), 7.4×10^{-7} mg/l (water), 1.2×10^{-5} mg/kg (soil), 7.3×10^{-5} mg/kg (sediment).

For the environment, various NOEC and LC_{50} values were gained from test results; LC_{50} = 120 mg/l (acute fish); EC_{50} = 380 mg/l (acute daphnia); EC_{50} > 1,000 mg/l (acute algae); NOEC = 14 mg/l (long-term daphnia reproduction). Therefore, the chemical is considered to be slightly toxic to fish and daphnids. The lowest chronic toxicity result, 21 d-NOEC (reproduction) of *Daphnia magna* (14 mg/l), was adopted for the calculation of the PNEC, applying an assessment factor of 100. Thus the PNEC of 1-chorobutane is 0.14 mg/l. Since the PEC is lower than the PNEC, environmental risk is presumably low.

The chemical is produced in closed systems, and no data for consumer use are available. Based on the physico-chemical properties, the total exposed dose indirectly through the environment was estimated as 1.5×10^{-4} mg/man/day (i.e. 2.5×10^{-6} mg/kg/day). Also, the daily intake through drinking water is estimated as 2.5×10^{-8} mg/kg/day and through fish is calculated as 7.5×10^{-8} mg/kg/day. No data on occupational exposure are available. Neither monitoring data at work place nor data on consumer exposure have been reported.

The chemical showed no genotoxic effects in bacteria and no chromosomal aberration *in vitro*, while showing positive results in a mouse lymphoma assay.

In a 13-week repeated dose study, mortality and decrease of body weights were observed at the dose of 250 mg/kg/day or more, and these findings might be caused by its irritancy. At the highest dose (500 mg/kg/day), the effects to spleen (e.g. hematopoiesis) were also seen. In a preliminary reproductive/developmental toxicity screening test, the external examination of pups revealed depression of viability index and body weight gain at the highest dose (300 mg/kg/day). All gestation animals which delivered pups had lack of care behaviour in the 12 mg/kg/day group.

Salivation was observed in the lowest dose group (2.4 mg/kg/day). Therefore, the NOEL was less than 2.4 mg/kg/day for repeated dose toxicity and 60 mg/kg/day for F1 offspring.

The total exposed dose indirectly through the environment was estimated to be 1.5×10^{-4} mg/man/day (i.e. 2.5×10^{-6} mg/kg/day). Also, the daily intake through drinking water is estimated to be 2.5×10^{-8} mg/kg/day and through fish is calculated to be 7.5×10^{-8} mg/kg/day. For human health, margins of safety by indirect exposure from fish or drinking water are very large. Therefore, health risk is presumably low.

In conclusion, no further testing is needed at present considering its toxicity and exposure levels.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-76-2
Chemical Name	2-Butoxyethanol
Structural Formula	$CH_3CH_2CH_2CH_2\ OCH_2CH_2OH$

CONCLUSIONS AND RECOMMENDATIONS

2-Butoxyethanol is considered of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The main use is for 2-butoxyethanol is in paints and surface coatings, followed by cleaning products and inks. Other products which contain 2-BE include acrylic resin formulations, asphalt release agents, firefighting foam, leather protectors, oil spill dispersants and photographic strip solutions.

The principal health effects following acute exposure to 2-butoxyethanol are irritation of the eyes and respiratory tract. The critical effect identified in repeated dose animal studies is haematotoxicity. The lowest reliable NOAEL for haemolysis in the most sensitive species, the rat, is 24.6 ppm (22.5 mg/kg/day). The haematological effects are transient at lower doses and there are large species differences in the haematological response to 2-butoxyethanol exposure, with evidence to show that humans are less sensitive than rats. 2-Butoxyethanol is readily absorbed through the skin.

Taking into account the nature of the critical effect and the species difference, a comparison of estimated occupational exposures with the NOAEL for haemolytic effects indicates that the potential risk is generally low. However, for printing and cleaning, where there is prolonged exposure to high concentrations of 2-butoxyethanol, there are some concerns and adequate control measures are needed.

Due to low and intermittent exposure, the public health risk from the use of products containing 2-butoxyethanol is low. 2-Butoxyethanol is relatively non-volatile, miscible in water, readily biodegradable and non-bioaccumulative. There is no apparent risk to any of the environmental compartments.

NATURE OF FURTHER WORK RECOMMENDED

No further testing is recommended in the context of SIDS. An NTP 2-year inhalation study in rats and mice and an epidemiological study in France are currently being conducted. Given the potential for risk to human health in some situations, further work on the extent of dermal absorption would be useful.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	141-79-7
Chemical Name	Mesityl Oxide
Structural Formula	CH3 –CO-CH=C(CH3)2

Human Health

Mesityl oxide exhibits slight toxicity in acute mammalian studies. The acute oral toxicity has been examined in the rat, guinea pig, rabbit and mouse, and the median lethal dose in those species ranges from approximately 600 to 1100 mg/kg. The acute inhalation LC_{50} of mesityl oxide in the rat, mouse, and guinea pig has been estimated at from 4400 to 9000 mg/m^3. Mesityl oxide was irritating to the rabbit skin when tested under an occlusive patch.

A combined repeated dose and reproductive/developmental toxicity study by inhalation in rats gave a LOAEL of 124 mg/m^3 with no unusual findings. In this 49-day inhalation study conducted at levels up to 1212 mg/m^3, effects were transient and reversible and were attributed to the irritative property of the chemical. No neurotoxicity was observed. The NOEL for reproductive toxicity from this study was 412 mg/m^3 and no developmental toxicity was noted at any exposure concentration.

Ames/Salmonella reverse mutation and mouse micronucleus studies were negative.

Environment

Mesityl oxide has limited persistence in water, soil or air. The predicted soil absorption coefficient is low. It is readily biodegradable and has a low potential to bioconcentrate. Loss from water or soil will primarily be by volatilization to the air. Once airborne, mesityl oxide is reactive, with an overall OH rate constant of 79.48 x 10-12 cm3/molecule-sec and a predicted half-life of 1.615 hours.

Mesityl oxide has moderate acute toxicity toward aquatic invertebrate species and freshwater vertebrates as well as a variety of bacterial species. Acute toxicity data calculated using the US EPA QSAR computer program, ECOSAR, generally are in the range 50 to 500 mg/l for fresh- and saltwater organisms. Laboratory-derived data for several aquatic organisms including fish, invertebrates, algae, and bacteria were conducted in open systems. Acute toxicity values for aquatic species ranged from over 1000 mg/L for *Daphnia magna* to 71 mg/L for *Salmo gairdneri*, the rainbow trout. Mesityl oxide has low toxicity toward a variety of bacterial species and has been shown experimentally to be stimulatory to the germination of two species.

Effects on terrestrial plants range from inhibition of germination (lettuce) to a slight growth stimulating effect (bean plants). Mesityl oxide was slightly toxic to spider mites and caused an increase in alarm behavior in several species of ants.

Exposure

Estimated total U.S. production of mesityl oxide is 20,700 metric tons. However, a 1999 search of the SRI Chemical Economics Handbook (CEH) and of the journal, Chemical Marketing Reporter, for mesityl oxide & ketone production statistics and chemical production statistics in general indicated that mesityl oxide is no longer produced as an isolated product in the U.S. for sale. Mesityl oxide is a non-isolated or site-limited intermediate used in the manufacture of methyl isobutyl ketone (MIBK) and during manufacture one pound of mesityl oxide yields one pound of MIBK. Based on the previously mentioned 1999 search, the 1999 U.S. demand for MIBK was estimated to be 180,000,000 pounds and production capacity for U.S. facilities was 210,000,000 pounds. Therefore, similar amounts of mesityl oxide would be produced and consumed as an intermediate in MIBK manufacture.

Mesityl oxide is manufactured by the aldol condensation of acetone within a closed, continuous, process. Nearly all mesityl oxide formed is reacted further as an intermediate to the manufacture of MIBK. In some cases, the mesityl oxide is not isolated but is immediately converted to MIBK. In other cases, the mesityl oxide may be stored

temporarily on site for subsequent conversion to MIBK. Any mesityl oxide isolated might be purified by distillation; otherwise, only the final product (MIBK) is purified by distillation.

In cases where mesityl oxide is manufactured as a non-isolated intermediate and is formed only in low concentrations in a reaction mixture and reacted further, all in closed equipment, fugitive emissions are expected to be low. Economic considerations also motivate to minimize emissions in order to maintain process efficiency. Environmental concentrations are expected to be low due to mesityl oxide's use as an industrial intermediate and its rapid aquatic and atmospheric degradability. Use as a pesticide inert may cause seasonal short-term higher concentrations in areas of pesticide application.
Few workers are occupationally exposed to mesityl oxide. Potential exposures would occur only during sample collection and maintenance of equipment.

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

Human Health: The chemical possesses properties indicating low hazards for human health. Based on data provided by the sponsor country, appropriate risk management measures are being applied (engineering controls, occupational standards, drinking water standards, Material Safety Data Sheets, and other US regulations). Countries may desire to check their own risk management measures to find out whether there is need for additional measures. Therefore the chemical is of a low priority for further work.

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	629-11-8
Chemical Name	Hexamethylene glycol
Structural Formula	$HO-(CH_2)_6-OH$

CONCLUSIONS AND RECOMMENDATIONS

It is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The production volume of this chemical in Germany was 10,000-50,000t in 1991. The total production volume is used as an intermediate in chemical industry for the synthesis of polyesters and polyesterol-type polyurethanes, which are used for paints, laquers and varnishes.

The substance has no considerable potential for bio- and geoaccumulation. (log P_{ow} 0.0). It is readily biodegradable. In water, hydrolysis or photolysis are unlikely to occur.

The following aquatic effects concentrations are available: *Leuciscus idus:* 460-1000mg/l(LC_{50}, 96h:), *Daphnia magna* >500mg/l(EC_{50}, 24h&48h:), *Scenedesmus subspicatus*: 2200 mg/l (EC50, 72h). From these data a PNECaqua of 500μg/l was derived. No data are available on terrestrial organisms.

For production and processsing PECs of 0.19μg/l (site specific) and 29μg/l (generic) were estimated. With a PNECaqua of 500μg/l, the PEC/PNEC ratio is calculated as less than 1. Therefore no risk to the aquatic environment is to be expected. A significant exposure to the terrestrial compartment could not be identified.

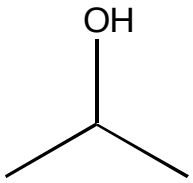
This chemical is not acutely toxic. It is considered as non-irritating to the skin and only slightly irritating to the eyes. No skin sensitising potential was revealed. 28 day repeated dose testing in rats revealed slight effect upon body weight in males or females at 1000mg/kg bw/day. The oral NOAEL was determined as 400 mg/kg bw/day. No indication of toxic effects on reproductive function or developmental toxicity were observed. Neither mutagenic nor clastogenic potential could be detected in *in vitro* tests with this chemical. No *in vivo* mutagenicity testing has been performed.

This chemical has very low toxic potential, and no local or organ-specific effects were detected. The toxic potency is also low under “worst-condition-assumptions” for workers, a risk can not be identified. There is no reason to assume consumer exposure.

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	67-63-0
Chemical Name	Isopropanol
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Isopropanol is currently considered of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Isopropanol is a high production volume chemical, which is used as an industrial solvent, a component of industrial and consumer products and as a disinfectant. There is considerable potential for both occupational and consumer exposure.

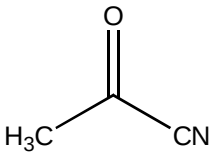
There are estimates of significant fugitive emissions. Biodegradation in aquatic and terrestrial habitats, a physical degradation in the troposphere occur rapidly, indicating that isopropanol will not persist in the environment.

The mammalian/human toxicological properties of isopropanol have been well characterized in multiple animal species and humans for a variety of exposure routes, exposure durations and toxicity endpoints. High quality studies have been conducted that evaluate acute toxicity, skin and eye irritation, skin sensitization, subchronic and chronic toxicity, reproductive toxicity, developmental and developmental neurotoxicity, acute and subchronic neurotoxicity, genotoxicity and cancer. In addition, studies are available that characterize the disposition of isopropanol in mammals.

The information obtained from this database allows for the characterization of toxicity hazard of isopropanol for both buman/mammalian and environmental effects. Taken together, these considerations support the conclusion that isopropanol is a low priority for further work.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-05-8
Chemical Name	Acetonitrile
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

This chemical is a candidate for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Acetonitrile is a volatile, colourless liquid with high water solubility. This chemical is used as a solvent in various extractions, the dissolution of cationic textile dyes, and is widely used in research and analytical laboratories.

Acetonitrile is considered readily biodegradable, and a log P_{ow} of -0.34 indicates low potential for bioaccumulation. PEC:PNEC for each scenario is less than one, indicating low concern over this chemical for the environment. Terrestrial organism data does not exist, but the calculated PEC_{soil} at regional and continental levels versus $PNEC_{aquatic\ organisms}$ is less than one, indicating low concern.

This chemical is readily absorbed from the gastrointestinal tract and through the skin and lungs, and all three routes of exposure lead to systemic effects. Acetonitrile is readily absorbed through the skin. This chemical is not of concern for consumers.

This chemical is widely distributed upon exposure and there are no indications that repeated dosing leads to accumulation in animal tissues. Exposure to this chemical produces symptoms characteristic of cyanide intoxication. Data from long and short-term studies showed that wide variations in both inter and intraspecies susceptibility exists. Acetonitrile is determined to be irritating to the eye but does not show corrosivity to the skin and eyes.

The results from one well-conducted subchronic inhalation study shows that mice are one of the most sensitive species; NOAEL is 100ppm. Acetonitrile did not induce gene mutations in bacteria, and showed weak clastogenic activity in mammalian cells. Weakly positive results have been reported for an *in vivo* mutagenicity test. In male rats, inhalatory exposure at 400ppm, a marginal increase in neoplasms was reported based upon an increased incidence of hepatocellular adenomas and carcinomas (when the data was combined). In the same study there was no evidence of carcinogenic activity in females. No fertility changes have been reported in animal studies, and acetonitrile is not considered to be toxic to fetuses at doses below those causing maternal toxicity.

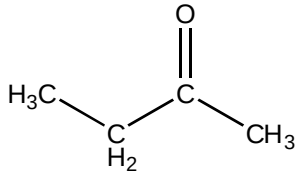
Acetonitrile has not been detected in consumer products, and calculated high margins of safety, indicate no concern to human safety following indirect exposure from the environment.

NATURE OF FURTHER WORK RECOMMENDED

There is a need for further information and/or testing:

- Sensitization: Need for testing for skin sensitization.
- Mutagenicity: Additional well-validated, *in vivo*, study in order to detect chromosome damage required.
- Workers: Work practices and the activities, information on the duration and frequency described.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-93-3
Chemical Name	Methyl Ethyl Ketone (MEK)
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Methyl Ethyl Ketone is currently considered of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

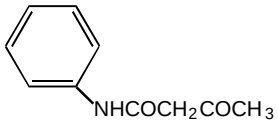
MEK is high production volume chemical (1940 million pounds annually in the world; 620 million pounds annually in US) which is primarily used in commercial and industrial settings and is rarely found in commercial products. The major use of MEK is as a solvent and chemical intermediate. As a solvent, MEK is used surface coatings, adhesives, inks, traffic making paints, cleaning fluids, and dewaxing agents. Manufacture of MEK takes place in an enclosed process and transport of the material occurs through enclosed systems or bulk carrier. This condition significantly limits exposure during manufacture and handling.

Based on physical and chemical properties, MEK is an unlikely environmental contaminant. It undergoes degradation in the atmosphere and in aqueous environments and has a low degree of toxicity to environmental species. MEK may contribute to the formation of photochemical smog.

MEK has been shown to be of a low order of toxicity following acute oral, dermal, and inhalation exposure. Contact with the eyes may produce irritation. MEK has not been shown to produce skin sensitization. No significant signs of toxicity were seen following repeated inhalation exposure of rats to MEK at high concentrations. MEK and its metabolic surrogate, 2-butanol, do not appear to present significant risk of adverse reproductive or developmental effects. MEK has not been shown to have any neurotoxic potential. MEK has been consistently negative in genotoxicity studies, both *in vitro* and *in vivo*. Human volunteers exposed to relatively high levels of MEK did not demonstrate any significant effects, other than minor irritation and sensory effects.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	102-01-2
Chemical Name	Acetoacetanilide
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is of low concern to aquatic organisms and is considered inherently biodegradable. The predicted environmental concentration is lower than the predicted no effect concentration. It is therefore currently considered of low potential risk and low priority for further work.

Health

The critical effect of this chemical is methemoglobinemia. This chemical is used as an intermediate and is produced in a closed system. Exposures at production sites are well controlled. It is therefore currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Acetoacetanilide (AAA) is a chemical intermediate used in the production of pigments. Approximately 10 000 metric tonnes are manufactured each year in a closed system. This substance is then isolated and transported under closed conditions to pigment manufacturing facilities. There is no known direct or consumer use. Non-aqueous wastes from manufacture are incinerated, and aqueous wastes are sent to a wastewater treatment facility for treatment.

Following environmental release AAA is expected to distribute in the aquatic environment, biodegradation is expected to be rapid. The predicted environmental concentration from the manufacture of AAA has been estimated to be 16 μg/L and 46 μg/L based on two different production sites. The predicted environmental concentration from pigment manufacture is estimated to be 8.6 μg/L.

The acute toxicity of AAA has been evaluated in a number of aquatic species including the fathead minnow, and several invertebrate species including *Daphnia*. In all cases the LC_{50} concentration was greater than 100 mg/L (the highest concentration tested) for the 96-hour exposure. The EC_{50} for algae of 318 mg/L was used to calculate a predicted no effect concentration of 0.32 mg/l using an assessment factor of 1000. Comparing the hypothetical $PEC_{initial}$ in water to the PNEC for algal toxicity, the ratio is less than one and therefore it may be concluded that AAA has a low potential risk to the environment.

Acetoacetanilide is manufactured in closed systems. Based on the results of air monitoring of bagging and drumming areas, airborne concentrations in the workplace which are at or below 0.3 mg/m^3 would be expected to result in an EHE of 0.04 mg/kg. There is no direct consumer exposure to AAA because the substance is used as an

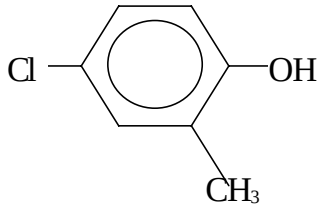
intermediate in other manufacturing processes. The EHE for indirect exposure is orders of magnitude lower.

Repeated oral exposure in rats to dose levels of > 30 mg/kg/day may result in methemoglobinemia. Daily doses of >100 mg/kg/day for 28 days result in reduced weight gains and feed consumption, possible cyanosis, methemoglobinemia, haemolytic anaemia, and extramedullary hematopoiesis in the spleen and liver. Animals allowed to recover for 14 days had hematologic parameters that were near normal with no evidence of anaemia or methemoglobinemia. The no-observable-effect level (NOEL) for 14 days of treatment was 102.4 mg/kg/day, but the NOEL for 28 days of treatment was 12 mg/kg/day with evidence that a dose level of 30 mg/kg for 6-8 weeks result in minimal methemoglobinemia (<5% MetHB) which is not clinically significant (NOAEL was 30 mg/kg/day). The NOEL for reproductive toxicity and developmental toxicity was 100 mg/kg. Mating and fertility were unaffected by treatment, and there were no microscopic lesions in the sex organs. There were no effects on gestation, implantation or viability, and no effects were observed in the pups.

Considering the effect on methemoglobinemia, the Estimated Dose of Low Concern (EDLC) is 0.3 mg/kg based on a NOAEL of 30 mg/kg from repeated dose studies and an Uncertainly Factor of 100. Based on the results of air monitoring of bagging and drumming areas, airborne concentrations in the workplace which are at or below 0.3 mg/m^3 would be expected to result in an EHE of 0.04 mg/kg. The EHE for indirect exposure is orders of magnitude lower. Using the occupational EHE, the ratio of EHE to the EDLC is less than 1, alternatively the margin of safety is 750, indicating that AAA is a chemical of low potential risk to man.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1570-64-5
Chemical Name	Phenol, 4-chloro-2-methyl
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is very toxic to aquatic organisms. The chemical is considered as readily biodegradable and has a low bioaccumulative potential. The predicted environmental concentrations are lower than the predicted no effect levels for all environmental compartments. It is currently considered of low potential risk and low priority for further work.

Health

This chemical is corrosive and toxic by inhalation. Workers exposure is considered to be low because the substance is produced in a closed system as an intermediate for the manufacturing of phenoxyherbicides. Consumer exposure is considered to be negligible. It is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The EU tonnage of (4-chloro-2-methylphenol) for the year 1989 has been estimated as a total of 15000 tons per annum based on the production volumes presented by the manufacturers and supported by the production and consumption figures of the herbicides MCPA (4-chloro-2-methylphenoxy acetic acid), MCPB (4-chloro-2-methylphenoxy butyric acid) and MCPP (mecoprop 2-4chloro-2-methylphenoxy-propionic acid). The main points of emissions are at manufacturing sites of the substance where PCOC is used as an intermediate for manufacturing of the phenoxyherbicides (i.e. PCOC processing and phenoxyherbicides formulation sites) and where these herbicides are used in agriculture (PCOC occurs as an impurity in the phenoxyherbicides). The environmental distribution of PCOC (using a Mackay fugacity level 1 calculation (Mackay & Paterson 1990) is expected to be 33% in air, 56% in water, 6% in soil and 5% in sediment.

The environmental exposure assessment is primarily based on monitoring data from the two main manufacturing sites in EU where all production and all processing of PCOC takes place, and where approximately 60% of the production volume in EU is formulated. A worst case environmental exposure scenario for a separate, but hypothetical, formulation site has also been considered. PEC local water is calculated as 0.0038 mg/l and 0.0014 mg/l for specific site and formulation, respectively. For the exposure assessment of PCOC in sewerage treatment plants (STP), the dissolved concentration of PCOC is assumed to be equal to the effluent concentration. The predicted environment concentrations for the sewerage treatment plant are: 0.004 mg/l [specific site], 0.0013 mg/l [formulation]. The predicted environmental concentration for soil is calculated as 0.00000088 - 0.000002 mg/kg.

PCOC is very toxic to aquatic organisms. The acute toxicity to fish LC_{50} (96h) was observed to be 2.3-6.6mg/l. The EC_{50} (48h) to daphnids was 0.29-1.0 mg/l and the EC_{50} (96h) to algae was 8.2 mg/l and EC_{10} to algae (96h) was 0.89 mg/l. The NOEC (28 days) for fish was 0.5 mg/l for histopathological changes in kidneys and liver. NOEC (21 days) for Daphnia reproduction was 0.55 mg/l. The presence of an algae EC_{10}, a long term NOEC for fish and a Daphnia reproduction test suggest that use of an assessment factor of 10 may be appropriate. The predicted no effect concentration (PNEC) is 0.05 mg/l. The PNEC $STP_{microrgnaisms}$ is obtained by using the EC50 for inhibition of respiration of activated sludge microorganisms and an assessment factor of 100 (0.55 mg/l). Since no ecotoxicological data are available for soil organisms the equilibrium partitioning method has been applied ($PNEC_{soil}$ = 0.36 mg/kg).

A local risk for aquatic organisms is not anticipated as the predicted environment concentration is lower than the predicted no effect concentration (regardless of whether an assessment factor of 10 or 100 is employed). Similarly the risks for microorganisms in sewerage treatment plants and for soil organisms is not expected.

The most important sources of direct human exposure are assumed to be at production sites (with predicted exposures of up to 0.7 mg/kg/day) or in conjunction with the use of phenoxy herbicides where exposures of ca. 0.35 mg/kg/day is estimated. Indirect exposure is estimated as being several orders of magnitude lower than the above values at a regional level while consumer exposure to the substance as an impurity in lawn-treatment sprays may be as high as 0.07 mg PCOC /kg/event.

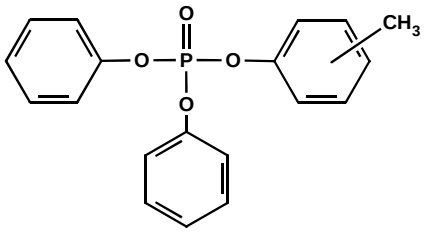
PCOC is corrosive and toxic by inhalation but is only moderately toxic in acute mammalian tests by other routes. The substance is not a skin sensitizer. In an OECD screening test 422, PCOC did not cause reproductive effects in rats. Tests for repeated dose toxicity suggest an NOAEL of 200 mg/kg and a LOAEL of 800/mg/kg (slight liver toxicity and decrease in haemoglobin concentration in the blood). PCOC was positive in an older mouse micronucleus test, but negative in a recent valid test performed according to the current OECD guideline. It did not give rise to genotoxicity in valid Ames tests. On the basis of current knowledge, the substance can not be considered a mutagen.

Repeat dose toxicity is not likely to present a major health problem. The margin of safety for workers based on a NOAEL of 200 mg/kg/day is 200/0.7 = 285. For the end-points irritation/corrosivity the concentration is below the level of concern.

For consumers exposure may be in the order of 0.07 mg/kg for each event corresponding to a daily dose of 9.6×10^{-4} mg/kg/day. With a NOAEL for repeat dose toxicity of 200 mg/kg/day the margin of safety is at least 20,000 for each single event.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	26444-49-5
Chemical Name	Diphenyl cresyl phosphate
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is toxic to aquatic organisms and considered not readily biodegradable. However the predicted environmental concentration is lower than the predicted no effect concentration. Therefore, it is considered of low potential risk and low priority for further work.

Health

The chemical is moderately toxic in a repeated dose toxicity study (i.e. liver, kidney, adrenal). This chemical is considered to be non-genotoxic. As margin of safety is very large, it is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Diphenyl cresyl phosphate is used as an additive for plasticizer and gasoline and as a flame retardant. The production volume in Japan was estimated to be 1,700 tonnes (1990 - 1993) and more than 1,000 tonnes/year with a highest production volume of 5,000 tonnes/year in Germany. The chemical is not produced but imported into Sweden, Denmark and Canada in volumes of 350 kg/year, 3 tonnes/year and 10 - 100 tonnes/year respectively. The chemical is also produced in the United States, however precise production data were not available. This chemical is used as the consumer product at 7 % in a filling foam for insulating air spaces.

The chemical is a stable liquid at pH 4, but is hydrolysed at pH 7 and 9. The half-life at pH 7 is about 47 days. This chemical is considered not readily biodegradable. Modelling of the potential environmental distribution of diphenyl cresyl phosphate (obtained from a Mackay generic level III fugacity model) showed this chemical would be distributed mainly to water and soil. The PEC_{local} was estimated based on Japanese and German production data to be 1.5×10^{-5} and 9×10^{-4} mg/l, respectively

The lowest acute toxicity data to fish, daphnids and algae were: 1.3 mg/l (96 h-LC_{50} of *Oryzias latipes*), 3.7 mg/l (24 h EC_{50} of *Daphnia magna*) and 0.55 mg/l (NOEC of *Selenastrum capricornutum*), respectively. The lowest chronic toxicity data to daphnid was 0.12 mg/l (21d-NOEC (reproduction) *Daphnia magna*). The lowest acute and chronic toxicity data for each trophic level were considered in calculating the predicted no effect concentration (PNEC). An assessment factor of 100 was used to both acute and chronic toxicity data to determine the PNEC. The PNEC was

calculated as 0.0012 mg/l. The chemical is strongly toxic to algae, and moderately toxic to fish and daphnids however the predicted environmental concentration is lower than the predicted no effect concentration. Therefore, the environmental risk is considered to be low.

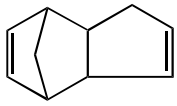
The chemical is produced in closed systems and therefore only limited occupational exposure is expected in filling it into drums. Inhalation is considered the main route of exposure. An average concentration of 0.3 mg/m^3 was measured at a Japanese production facility. This exposure level is equivalent to 0.005 mg/kg/day. As this chemical is not biodegradable and highly bioaccumulative, the exposure to the general population via the environment would be assumed through drinking water and fish. The concentration in drinking water is estimated to be equal to the calculated PEC (i.e. 9.0×10^{-4} mg/l) to provide a worst case calculation. The daily intake is calculated as 3×10^{-5} mg/kg/day (2 l/day, 60 kg b.w.). Using the maximum bioconcentration factor of 980, the concentration of this chemical in fish can be calculated as 8.82×10^{-4} mg/g-wet. As a daily intake of fish in Japan is estimated to be 90 g for 60 kg body weight person, the daily intake of this chemical will be 1.30×10^{-3} mg/kg/day.

Although the chemical showed no mutagenic effects in bacteria, a positive result was obtained in chromosomal aberration test *in vitro*. A recent negative micronucleus test confirmed that the chemical is not expected to be genotoxic. In a combined repeat dose and reproductive/developmental toxicity screening test, treatment at the mid dose (60 mg/kg/day), resulted in enlargement and cortical vacuolation of the adrenals in both sexes. In addition, an increase of food consumption and total cholesterol, a decrease of cholinesterase activities, and enlargement of the liver were found in male rats, and suppression of body weight gains, histopathological changes in the liver, kidneys and the thymus were found in female rats. For reproductive effects, only a fertility index and an implantation index decreased in the highest group (300 mg/kg/day). Therefore, NOEL for repeated dose toxicity was 12 mg/kg/day and NOEL for reproductive toxicity was 60 mg/kg/day.

For human health, a margin of safety was estimated to be 2400, based on occupational exposure. However, the frequency of exposure is very limited and the very few workers involved wear personal protective equipment. The human health risks for the public from indirect exposure via the environment and consumer use are also low.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	77-73-6
Chemical Name	Dicyclopentadiene
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is moderately toxic to aquatic organisms and is considered not readily biodegradable. The predicted environmental concentration is lower than the predicted no effect concentration. It is currently considered of low potential risk and low priority for further work.

Health

The chemical is moderately toxic in repeated doses toxicity study (i.e. liver, kidney, adrenal) and an irritant to the skin and eyes. Within the Sponsor country exposure is well controlled based on the only known use as an intermediate in a closed system for the manufacture of resins. Consumer exposure and estimated daily intake through in-direct exposure are also considered to be low. As margin of safety is very large, it is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Dicyclopentadiene is stable solid with a production volume of ca. 33,000 tonnes in 1993 in Japan. The chemical is used as an intermediate for production of resins in closed systems. This chemical is used as a consumer product at a concentration of 0.2% in Germany.

Dicyclopentadiene is considered not readily biodegradable. Direct photodegradation is expected and dicyclopentadiene has a high potential bioaccumulation. Modelling of the potential environmental distribution of dicyclopentadiene (obtained from a generic fugacity model (Mackay level III)) indicates that the chemical will be distributed mainly to water. Using production data from Japan and Germany the predicted environmental concentrations (PEC_{local}) of this chemical were estimated for the aquatic environment as 8.3×10^{-4} mg/l and 2.6×10^{-2} mg/l respectively.

The lowest acute toxicity data to algae, zooplankton and fish were: 27mg/l (72 h-EC_{50} of *Selenastrum*), 8mg/l (48 h EC_{50} D*aphnia magna*) and 4.3 mg/l (96 h LC_{50} of *Oryzias latipes),* respectively. The lowest chronic toxicity data to algae and zooplankton were; 18 mg/l (72 h-NOEC (growth) of *S. capricornutum)* and 3.2 mg/l (21d-NOEC (reproduction) *Daphnia magna).* The lowest acute and chronic toxicity data for each trophic level were considered in calculating the predicted no effect concentration (PNEC). An assessment factor of 100 was applied to both acute and chronic toxicity data to determine the PNEC, because chronic toxicity data for fish was absent. The PNEC was calculated as 0.032 mg/l. The chemical is moderately toxic to fish, daphnids and algae however the predicted environmental concentration is lower than the predicted no effect concentration and therefore, the environmental risk is considered to be low.

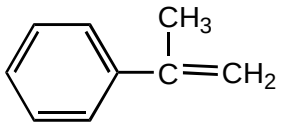
The main route of human exposure is inhalation with a limited numbers of workers potentially exposed during tank filling, sampling and analytical work. The concentration in the atmosphere was measured at two production sites as 12.9 mg/m^3 (range 2.7 - 90 mg/m^3) during sampling operations. Therefore, the worst case occupational Estimated Human Exposure (EHE_{inhal}) may be estimated as 0.94 mg/kg/day. Indirect exposure via the environment, the daily intakes through drinking water and fish are estimated as 8.7×10^{-4} mg/day and 1.5×10^{-2} mg/kg/day, respectively, based on PEC_{local} of 2.6×10^{-2} mg/l.

Dicyclopentadiene is considered as an irritant to skin and eyes. This chemical showed no genotoxic effects in bacteria and chromosomal aberration tests *in-vitro*. In a combined repeat dose and reproductive/developmental toxicity screening test, both male and female rats showed slight suppression of body weight, and two female rats died before the pregnancy. Histopathological examination showed single cell necrosis in the liver, and hyaline droplets and basophilic change in the tubular epithelium of the kidneys in male rats. This compound had no effects on reproductive parameters. The no-observable effect level (NOEL) was identified as 4 mg/kg/day for repeated dose toxicity and 100 mg/kg/day for reproductive toxicity.

For human health, the risk for workers is expected to be low because the frequency of exposure is very limited and personal protective equipment is worn. The risks to the consumer and the general population through indirect exposure are also assumed to be low because a margin of safety through drinking water or fish is calculated to be 5600 or 267. Therefore, it is currently considered of low potential risk and low priority for further work.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-83-9
Chemical Name	(1-Methylethenyl)benzene
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is moderately toxic to aquatic organisms and is considered as not readily biodegradable. The predicted environmental concentration is lower than the predicted no effect concentration. The chemical is therefore currently considered of low potential risk and low priority for further work.

Health

Within the Sponsor country exposure is well controlled because the only known use is as a closed system intermediate in the production of resins. The chemical is moderately toxic in a repeated dose toxicity study (i.e. kidney, liver, thymus). The chemical is also considered as an irritant to skin and eyes. Risks to human health from daily intake through occupational and indirect exposure are considered low. The chemical is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

(1-Methylethenyl)benzene is a stable liquid with a production volume of ca. 15,000 tonnes/year in 1993 in Japan. The chemical is produced in closed system and is used as intermediate for ABS resins and polyester resins. (1-Methylethenyl)benzene is considered as "not readily biodegradable" with a moderate bioaccumulation potential. It is expected to photodegrade.

Modelling of the potential environmental distribution of (1-metylethenyl)benzene (obtained from a generic fugacity model (Mackay level III)) showed the chemical is expected to distribute mainly to water and air. Using production data from Japan and Germany the predicted environmental concentration (PEC_{local}) of this chemical was estimated as 2.3×10^{-5} mg/l and 5.5×10^{-2} mg/l respectively for local exposure scenarios. In a 1977 Japanese environmental survey, the chemical was not detected from surface water and sediments.

(1-Methylethenyl)benzene is moderately toxic to fish, daphnids and algae The lowest acute and chronic toxicity data was considered to calculate the predicted no effect concentration. The lowest acute toxicity data was the 24 h-LC_{50} for *Oryzias latipes* (15 mg/l) and the lowest chronic toxicity was a 21d-NOEC (reproduction) for *Daphnia magna* (1.8 mg/l). An assessment factor of 100 was used to determine a predicted no effect concentration of 0.018 mg/l. The predicted no effect concentration is lower than the predicted environmental concentration and therefore the environmental risk is considered low.

(1-Methylethenyl)benzene is produced in closed systems and therefore only limited occupational exposure is

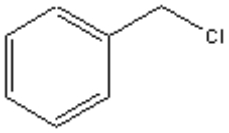
expected in sampling and bag or tank filling operations. Inhalation is considered the main route of exposure. Concentrations in the atmosphere were measured at two production facilities. An average concentration of 10.1 mg/m^3 was found in sampling operations (max 48.7 mg/m^3 - min 0.5 mg/m^3). The daily intake through inhalation is estimated to be 1.2 mg/kg/day as the worst case. Indirect exposure via the environment, PEC_{local} was estimated as 2.3×10^{-5} mg/l and daily intake through water is estimated to be 7.7×10^{-7} mg/day and through fish 4.8×10^{-6} mg/kg/day. This chemical is used on food contact material constituent, but there are no available data of a migration to food.

The chemical is considered as irritant to skin and eyes. The chemical showed no genotoxic effects in bacteria and chromosomal aberration tests *in vitro*. In a combined repeat dose and reproductive/developmental toxicity screening test, at the highest dose (1,000 mg/kg), histopathological examination demonstrated acidophilic change of hepatocytes and increase of fatty droplets in the fascicular zone of the adrenals in both sexes, increase of hyaline droplets and basophilic changes in the renal tubular epithelium and hyperplasia of the mucosal epithelium in the urinary bladder in male rats, vacuolation and infiltration of lymphocytes in the renal tubular epithelium and atrophy of the thymus in female rats. In the 200 mg/kg group, similar histopathological changes were found in the liver and kidneys of both sexes, and the thymus of female rats. The chemical had no effects on reproductive parameters. The, No-observable-effect-level (NOEL) was 40 mg/kg/day for repeated dose toxicity and 200 mg/kg/day for reproductive toxicity.

For human health, a margin of safety was estimated to be 33, based on occupational exposure calculation. However, the frequency of exposure is very limited and the very few workers involved wear personal protective equipment. Since the margin of safety in other cases is large such as 5.2×10^7 through drinking water and 8.3×10^6 through fish, the human health risks for the public from indirect exposure via the environment are low.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-44-7
Chemical Name	Benzyl chloride
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is hydrolyzed to benzyl alcohol in a temperature dependent manner in aquatic environment and benzyl alcohol is readily biodegradable. The chemical has high toxicity to aquatic organisms. However, toxicity of benzyl alcohol is low. Although PEC/PNEC ratio of the chemical is greater than 1 based on the local exposure scenario in the Sponsor country, PEC/PNEC ratio of benzyl alcohol is considered to be less than 1. Therefore, it is currently considered of low potential risk generally, but the environmental fate and degree of hydrolysis should be considered by each country.

Human Health

The chemical is toxic in a repeated dose study (i.e. stomach, heart, liver) and carcinogenic in rats (thyroid) and mice (liver, stomach, lung). Genotoxicity of the chemical seems weakly positive. The chemical is also considered as an irritant to skin, eyes and respiratory system. The chemical is considered as a possible carcinogen although there is no clear evidence in human. There is no available information on consumer use. As the chemical is rapidly hydrolyzed to benzyl alcohol in water phase, health risk via environment was assessed as benzyl alcohol exposure. As margin of safety for indirect exposure is more than 5×10^5, it is currently considered of low potential risk for the population via the environment. Depending on the current exposure situation further risk management in the workplace may be necessary or considered by countries.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Benzyl chloride is liquid at room temperature and the production volume is ca. 7,700 tonnes/year in 1993 in Japan. The chemical is used as intermediate for organic synthesis (benzyl alcohol, dyes and perfumes). No consumer use is reported. The chemical is classified as “readily biodegradable”. In a Japanese environmental survey, the chemical was not detected from surface water, sediments and biota in 1977 and 1990.

The potential environmental distribution of benzyl chloride obtained from a generic fugacity model (Mackey level III) showed the chemical will be distributed mainly to air and water. Predicted environmental concentration (PEC_{local}) of the chemical was estimated as 1.8×10^{-3} mg/l from Japanese local exposure scenario.

The main route of occupational exposure is inhalation with workers potentially exposed during drum and tank filling operation. The daily intake was estimated to be 0.096 mg/kg/day as the worst case, based on the average atmosphere concentration. As for indirect exposure via the environment, the assessment was conducted on assumption that all of benzyl chloride would be converted to benzyl alcohol and the environmental concentration would be the same of the predicted benzyl chloride concentration because benzyl chloride is rapidly hydrolysed to benzyl alcohol in water

phase. The daily intakes through drinking water and fish are estimated as 6.00 x 10^{-5} mg/kg/day and 1.35 x 10^{-4} mg/kg/day, respectively, based on the highest predicted environmental concentration of 1.80 x 10^{-3} mg/l.

As the lowest acute toxicity data to each of algae, zooplankton and fish, 96 h-EC_{50} of *Selenastrum capricornutum* (19.3 mg/l), 48 h-EC50 of *Daphnia magna* (3.2 mg/l) and 14 d-LC_{50} of *Poecilia reticulata* (0.39 mg/l) were selected. As the lowest chronic toxicity data to algae and zooplankton, 72 h-NOEC (growth) of *Selenastrum capricornutum* (10.0 mg/l) and 21d-NOEC (reproduction) of *Daphnia magna* (0.1 mg/l) were adopted. Therefore, the assessment factors of 100 were applied to both acute and chronic toxicity data to determine PNEC, according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects, because chronic toxicity data for fish was absent. Thus, PNEC of benzyl chloride is 0.001 mg/l. PEC/ PNEC ratio (1.8) of the chemical is greater than 1. However, the PEC/PNEC ratio of benzyl alcohol (0.015), which is a hydrolyzed product of the chemical, is expected to be less than 1. It is currently considered 'needs further work on environmental fate'.

Benzyl chloride is considered as an irritant to the skin, eye, respiratory system and some evidence of sensitization exists. Major toxicity of the chemical in subchronic study was the tissue damage in the heart and stomach, and a slight developmental change was observed on fetus. The no observed effect level was as 6.4 mg/kg/day for repeated dose toxicity and 50 mg/kg/day for developmental toxicity, respectively. As for benzyl alcohol, the no observed effect level was 100 mg/kg/day in a subchronic study and neoplastic changes were not observed in a two year carcinogenicity study.

For non-cancer endpoint, occupational risk is considered to be low because a margin of safety is calculated to be 66.7 as the worst case. There is no available information on consumer exposure. The margin of safety of benzyl alcohol for drinking water or fish was calculated as 1.67 x 10^6 or 7.41 x 10^5, based on no observed effect level of 100 mg/kg/day. As the margin of safety for benzyl alcohol via indirect exposure is sufficient, it is currently considered of low potential human risk.

In carcinogenicity study, thyroid C-cell adenoma/carcinoma in female rats and hemangioma/hemangiosarcoma, forestomach carcinoma/papilloma in male mice and forestomach carcinoma/papilloma, lung alveolar-bronchiolar adenoma/carcinoma in female mice were observed in a dose-dependent manner. Hepatocellular carcinoma/adenoma was observed in only male mice in none dose-dependent manner. *In vitro* genotoxicity study showed negative or weakly positive and *in vivo* micronucleus test presented the negative result. Therefore the possibility of occupational cancer risk could not be excluded.

NATURE OF FURTHER WORK RECOMMENDED

Depending on the current exposure situation further risk management in the workplace may be necessary or considered by countries.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-13-1
Chemical Name	Acrylonitrile
Structural Formula	CH_2=CH-CN

CONCLUSIONS AND RECOMMENDATIONS

Environment

Acrylonitrile is toxic for aquatic organisms and is not readily biodegradable. Ready biodegradability can however be assumed in the industrial setting where dedicated industrial biotreatment plants and acclimated microorganisms are used. A number of PEC/PNEC ratios for emissions to the aquatic environment were above 1. There is some concern about coastal sites which do not have waste water treatment plants and which release effluent directly into marine estuaries or the open sea. More information on the dilution at point of outflow has been requested.

Human Health

Acrylonitrile is acutely toxic to humans by inhalation, in contact with skin and if swallowed. It is also a severe eye irritant and may cause sensitization by skin contact. Repeat dose toxicity studies in animals have shown treatment-related changes in the gastrointestinal tract, central nervous system and adrenal gland. There are occasional reports of liver and kidney damage. It is a rodent carcinogen, tumours being observed in the brain, Zymbal gland, gastrointestinal tract and mammary gland. Detailed, recent epidemiological studies do not however provide evidence of human carcinogenicity. Acrylonitrile is an *in vitro* mutagen, indicating that the mechanism of carcinogenicity may be genotoxic. This is not however supported by the results of *in vivo* mutagenicity studies. It is concluded that there is a need for active management of the identified risk and further consideration of the risk management measures currently being applied in relation to workers, consumers and the population exposed via the environment.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

World production of acrylonitrile in 1985 exceeded 3,000,000 tonnes per annum. Estimated world capacity in 1991 was 4,200,000 tonnes per annum, while world demand in 1993 was 3,846,000 tonnes. Current production volume in the EU is in excess of 1,250,000 tonnes per annum, US production is approximately 1,500,000 tones per annum, Japan produces approximately 600,000 tonnes per annum, and the rest of the world accounts for the balance. In 1996, approximately 53% of the total EU production of acrylonitrile was used in production of fibres, 20% in production of ABS and SAN resins and 27% for other uses.

Acrylonitrile does not occur naturally in the terrestrial environment, although it has been detected in interstellar space. Anthropogenic acrylonitrile can potentially be released to the environment during (1) synthesis of the monomer, (2) polymer production, (3) end product usage. Release of acrylonitrile may also occur as a result of (4) combustion of hydrocarbon fuels and (5) cigarette smoking. The major compartments of release are water and air. There is rapid photodegradation of acrylonitrile, while in the aquatic environment acrylonitrile, while not readily biodegradable based on available information, degrades rapidly in wastewater treatment plants following acclimation, and also degrades, although at a slower rate, if released directly into the marine or freshwater environment. PECs for the aquatic environment for production of acrylonitrile and further processing to polymers, acrylamide and adiponitrile have been calculated using the approach outlined in the EU TGD: PEClocal, water (production) = 0.003 - 0.03 mg/L; PEClocal, water (processing site) = 0.003 - 1.18 mg/L.

The data set for acrylonitrile includes a wide range of information on short and long term toxicity in fish, Daphnia and other aquatic invertebrates. Acrylonitrile is moderately toxic to fish, with 96-hour LC_{50} for fresh water fish generally lying in the range of 10 - 20 mg/l (nominal). A recent short term study in the saltwater species *Cyprinodon variegatus*, carried out in full compliance with current protocols, reported a 96-hour LC50 of 8.6 mg/l. The lowest 48 hour EC50 for Daphnia was 7.6 mg/l. The fish early life stage toxicity test in *Pimephales promelas*, using flow-through conditions, provided a LOEC/NOEC of 0.34 mg/l, while a 30 day flow through test in mature fish of the same species provided a long-term LC50 of 2.6 mg/l. If the value of 0.34 mg/l is taken as a LOEC, a NOEC may be derived by application of safety factor of 2, giving a NOEC of 0.17 mg/l. Applying an assessment factor of 10 to the NOEC derived from the fish early life stage toxicity test gives a PNEC of 17 µg/l. For micro-organisms, the lowest EC50 for specific bacterial populations were in the range 1 - 10 mg/l. The conservative value of 1 mg/l has been assumed for NOEC in newly exposed populations and applying a factor of 10 to this derives a PNEC of 100 µg/l.

For the majority of the 43 sites involved in the production and further processing of acrylonitrile in the European Union, the derived PEC/PNEC ratios for the aquatic environment including sediment, for soil and for the atmospheric compartment for these sites are below 1. In the case of 4 sites the PEC:PNEC ratios for the aquatic environment lie between 1.3 and 3.8, however a default dilution factor of 10 was used in the assessment of these sites. Given the dilution factors applying at other sites where information has been provided, it is concluded that these sites present little risk to the local environment. Three sites located in coastal positions have PEC:PNEC ratios of greater than 1, do not have waste water treatment plants and the levels of acrylonitrile in effluent are relatively high compared with the majority of other sites. It is concluded that such sites, releasing directly to the marine environment with little or no pre-treatment of effluent, are of some concern and further information on dilution at the point of outflow is needed.

It is considered that there is no potential for dermal exposure to acrylonitrile during production under normal working conditions, as closed systems are used. Methods for sampling and taking measurements are devised in such a way that exposure via this route should not occur. For processing, again the risk or potential for dermal exposure to acrylonitrile is low to negligible to low based on confirmed good occupational hygiene practice, and given that the systems used in processing are partially closed. In addition local exhaust ventilation and the strictly monitored use of personal protective equipment is applied. However for the purposes of this report and in particular with regard to the area of risk characterisation a very worst case scenario for dermal deposition is assumed i.e. between 0.0 and 0.1 mg/cm2/ day.

For consumers, the available data suggest that exposure via either the oral or dermal route of exposure is very low, based on the level of residual acrylonitrile monomer present in consumer products and the amount of this monomer that can be released to give exposure to the consumer.

It can also be concluded that people living close to or in the surroundings of acrylonitrile production or processing plants are exposed to low to negligible levels of acrylonitrile in the air.

Acrylonitrile is acutely toxic to humans, causing irritation of the eyes and nose, weakness, laboured breathing, dizziness, impaired judgement, cyanosis, nausea, and convulsions following accidental exposure to high levels. Neuropathological effects have been reported at high doses. The main toxic effects seen in animals include respiratory changes, cyanosis, convulsions and death. Reported LD50s in a number of species range from 24 - 186 mg/kg, it is also acutely toxic via inhalation and via dermal exposure and is a skin irritant. Acrylonitrile is already classified in accordance with EU criteria for all these end-points. Additional data presented in this risk assessment additional supports classification in the EU system as a respiratory irritant (R37), a severe eye irritant (R41) (Risk of serious damage to eyes) and as a skin sensitiser (R43).

In animals repeated exposure to acrylonitrile results in damage to the gastrointestinal tract, central nervous system and adrenal gland. There are occasional reports of liver and kidney damage. The respiratory tract is also affected following inhalation exposure, based on histopathological changes in the nasal turbinates of rats in the Quast et al.,(1980) two year study. A LO(A)EL of 20 ppm was established in the study, treatment-related nasal changes being evident at this exposure level, and this was used as a starting point in the risk assessment in relation to inhalation

exposure. A No Adverse Effect Level (NAEL) of 4 ppm for the inhalation route was been derived from the LO(A)EL of 20 ppm, by application of a safety factor of 5. In relation to oral administration of acrylonitrile, the N(A)OEL is estimated to be 3 ppm (0.25 mg/kg/day) in drinking water, based on the information from the Biodynamics study (1980) study in rats which showed systemic toxicity, probably attributable to metabolic release of cyanide.

The results of a range of mutagenicity and genotoxicity tests indicate that acrylonitrile interacts only weakly with DNA and that the DNA-active compound is the metabolite epoxide cyanoethylene oxide, CEO. The negative results obtained in *in vivo* genotoxicity tests with acrylonitrile may be due to metabolism of CEO by glutathione and by (in man) epoxide hydrolase to produce non-DNA-reactive species. This metabolic detoxification of the epoxide may not occur *in vitro*.

Acrylonitrile is classified in the EU as carcinogenic (Category 2. R45), based on the results of studies in the rat following either oral (drinking water or gavage) administration or via inhalation. The common target organs identified were the central nervous system (brain and spinal cord), zymbal gland, gastrointestinal tract (tongue, non-glandular stomach and small intestine) and mammary gland. A linear dose:response relationship for the incidence of astrocytomas was observed in both in the inhalation and the drinking water studies. On the basis of the animal carcinogenicity and positive *in vitro* mutagenicity data acrylonitrile is considered to be a genotoxic carcinogen, although a non-genotoxic mechanism of carcinogenicity has also been suggested. Recent detailed epidemiological studies do not however provide evidence of human carcinogenicity, and IARC in 1998 re-categorised acrylonitrile from category 2a to category 2b, based mainly on the new epidemiological evidence.

In relation to reproductive toxicity, at 65 mg/kg via the oral route embryotoxicity and foetotoxicity occurred in the presence of maternal toxicity, but there was also evidence of an effect on foetal development. Given the maternal toxicity, the developmental effects seen may not indicate a true teratogenic hazard. Inhalation of 80 ppm acrylonitrile also caused developmental effects, while foetotoxicity was observed at exposure levels as low as 25 ppm, a exposure level which was again maternally toxic. Although acrylonitrile has been reported to damage the testes of rats, no effects on fertility were seen in a 3-generation fertility study.

It is concluded that the carcinogenicity of acrylonitrile remains of concern, given its carcinogenicity in rodents and positive *in vitro* mutagenicity data. It is considered however that the legislative requirements and the consequent controls which operate in the industry are sufficient in imposing pressures to drive down exposures to significantly below the OEL of 2 ppm, as supported from recent measured data from industry.

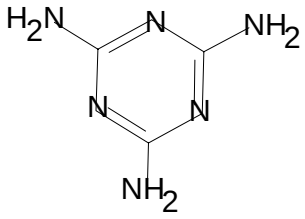
Consumer exposure and indirect exposure via the environment are theoretically possible, but considered to be very low. However, due to its carcinogenicity, there is a need for further consideration of risk management measures.

NATURE OF FURTHER WORK RECOMMENDED

Information on dilution at the point of outflow for specific coastal sites.

There is a need for active management of the identified risk which arises as a concern regarding carcinogenicity, and a need for further consideration of risk management measures currently being applied in relation to workers, consumers and the population exposed via the environment.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-78-1
Chemical Name	Melamine, 1,3,5-Triazine-2,4,6-triamine
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment:

The toxicity of the chemical to aquatic organisms is low. PEC/PNEC ratios are below 1 when based on realistic worst case conditions and on monitored concentrations.

Therefore, melamine is currently considered of low potential risk and low priority for further work.

Health:

The toxicity of melamine is low. Repeated exposure resulted in urinary bladder stones and other lesions of the urinary tract. Bladder tumours occured only in male rats after prolonged irritation of the epithelium by the bladder stones. Melamine is not genotoxic. The exposure of workers and consumers is low.

Therefore, melamine is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASON FOR THE CONCLUSIONS AND RECOMMENDATIONS

Melamine is produced in large amounts on few sites. Its main use is as an intermediate in the synthesis of melamine resins.

Environment:

The outstanding physical-chemical property concerning the risk assessment is a low n-octanol/water partition coefficient. Melamine is not readily biodegradable but adapted waste- water treatment plants can degrade it effectively. Water is the most relevant compartment in the environmental fate of the substance.

The ecotoxicity is low, data are available from different species and different trophic levels.

The environmental exposure estimations were based on some monitored concentrations and on the EUSES model. No relevant risk was detected for the environment. Most of the estimated risk characterisation ratios (PEC/PNEC) were lower than 1. Those few modelled risk characterisation ratios being slightly above 1 could be revised (and lowered to < 1) by assuming realistic worst case conditions.

Health:

The toxicity to mammals is also low. Studies ranging from skin irritation to carcinogenicity are available. Melamine is not genotoxic but it causes carcinomas of the urinary bladder at high doses in male rats only. Formation of bladder stones occurred and these calculi are necessary for the induction of tumours. Carcinomas are induced by continuous irritation of the bladder epithelium by the calculi, so that melamine acts only indirectly as a non-genotoxic carcinogen. A threshold concept can be used. Melamine is not irritating to skin and eye, not sensitising and not teratogenic.

No relevant risk was detected for humans. The estimated margin of safety for workers is at least 210, that for consumers at least 6000.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-83-8
Chemical Name	Diisobutylketone
Structural Formula	$(CH_3)_2$-CH-CH_2-CO-CH_2-CH-$(CH_3)_2$

CONCLUSIONS AND RECOMMENDATIONS

Environment

Based on structure activity relationship the chemical is not expected to exhibit ecotoxicity of concern. The derived PEC/PNEC ratio is less than 1. Based on the known use pattern and estimated exposure the chemical is currently considered of low potential risk and low priority for further work.

Human Health

The chemical is a respiratory irritant but otherwise considered as having low toxicity. Exposure is considered to be low in the Sponsor country. Therefore, it is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The EU consumption volume of diisobutylketone (DIBK) is ca.5500-6500 t/a. It is mostly used as an solvent in leather finishing products and in paints and lacquerers.

DIBK is "readily biodegradable" and has a low potential for accumulation (logPow = 2.56). Aquatic PECs of up to 16.2 µg/l were estimated for the different uses. Only short-term test results are available with aquatic species from three trophic levels and the PNEC for the aquatic compartment is estimated to be 23 µg/l.

For the environment, based on the known properties and exposure pattern, it can be concluded that there presently is no risk for the environment.

The consumer exposure is considered to be low as only very few of the DIBK-containing products are accessible to the consumer. Mean occupational exposure during formulation and use of DIBK-containing products is estimated to be about 16-39 mg/m^3

DIBK is not corrosive or sensitizing. Respiratory irritation was observed in humans at concentrations above 50 ppm. The NOAEL for repeated dose following inhalation exposure is in the region of 534 ppm. For reproductive toxicity, no increased risks to offspring were observed in the absence of parental effects. The NOAEL for parental toxicity was determined as 300 mg/kg bw/d and for reproductive effects 1000 mg/kg bw/d. Bacterial mutagenicity tests are negative, as well as a *Saccharomyces cerevisiae* mitotic gene conversion assay. DIBK does not induce chromosome aberrations in rat liver cells *in vitro*.

Satisfactory margins of safety could be derived for the exposure of workers and therefore it can be concluded that there is currently no need for further information and/or testing of for risk reduction measures beyond those which are being applied.

NATURE OF FURTHER WORK RECOMMENDED

None.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	112-24-3
Chemical Name	Triethylene tetramine
Structural Formula	H_2N-CH_2-CH_2-NH-CH_2-CH_2-NH-CH_2-CH_2-NH_2

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is toxic to algae, but PEC/PNEC ratios are lower than 1. It is currently considered of low potential risk and low priority for further work.

Human Health

The chemical is genotoxic *in vitro*, a severe irritant to skin and eyes and a skin sensitiser, but exposure is low and well-controlled. Therefore, it is currently considered of low potential risk and low priority for further work. However due to its hazard character appropriate classification and labelling are recommended.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The production volume of triethylenetetramine (TETA) in 1990 is 1200-1500 t/a in Germany, ca. 6000 t/a in the Netherlands, >11000 t/a in the USA and ca. 1800 t/a in Japan. TETA is mostly used as intermediate in chemical synthesis. Ca. 160 t/a are directly used as curing agent for epoxy resins in Germany. For Sweden, a similar use pattern was described. TETA is stable in neutral solution and is classified as "non biodegradable". The most sensitive environmental species to TETA is the alga *Scenedesmus subspicatus* (72h-EC10 = 0.67 mg/l). A PNEC of 13.4 µg/l is determined.

TETA has a moderate acute toxicity: LD50 (oral, rat) > 2000 mg/kg bw, LD50 (dermal, rabbit) = 550-805 mg/kg bw. The NOAEL for repeated dose toxicity is 600 ppm (92 (male), 99 (female) mg/kg bw) for mice (oral, 90 days). In *in vitro* tests the substance showed genetic toxicity whereas in *in vivo* test negative results were found. There are no animal data on reproductive toxicity available. From experience with humans TETA reveals no effects on reproduction. TETA is a severe irritant to skin and eyes. TETA induces skin sensitisation in guinea pigs, mice and man.

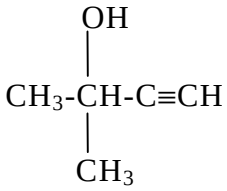
The highest aquatic local PEC during processing as an intermediate was estimated to be 4.5 µg/l.

The estimated human exposure at the workplace is estimated at < 0.143 resp. < 0.0143 mg/kg bw. Data on consumer exposure are not available.

NATURE OF FURTHER WORK RECOMMENDED

Appropriate classification and labelling are recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	115-19-5
Chemical Name	2-Methylbut-3-yn-2-ol
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment: The chemical does reveal low ecotoxicity.PEC/PNEC ratios are less than 1. Therefore, it is currently considered of low potential risk and low priority for further work.

Health: The chemical is harmful after acute oral exposure and of low toxicity after dermal and inhalative exposure. In some cases skin and eye irritation were reported in workers. The chemical is a mild irritant after prolonged skin exposure. However, exposure for workers, consumers and populations via the environment is low in the Sponsor country. Therefore, it is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The production volume of 2-Methylbut-3-yn-2-ol in Germany was 1,000 - 5,000 t/a in 1991 In Germany, 80% (of maximum 5,000 t/a) of the 2-methylbut-3-yn-2-ol is used in chemical industry as an intermediate for scents, cosmetics, vitamins and plant-protective agents. The remaining 20% were used as stabilizer for 1,1,1-trichloroethane in a concentration range of 3-7% (v/v). 1,1,1-trichloroethane was industrially used for cleaning and degreasing of metal surfaces, electronic structural parts, polymers and films. As 1,1,1-trichloroethane is no longer used, the corresponding use of 2-methylbut-3-yn-2-ol has also been stopped.

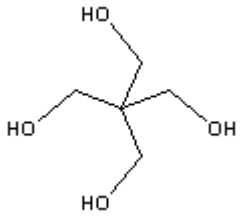
In Switzerland, 5,000-10,000 tonnes were produced in 1991 by one manufacturer as an intermediate only.

2-Methylbut-3-yn-2-ol is not readily biodegradable but is inherently removable from water. Based on its physico-chemical properties the hydrosphere is the preferred compartment. Local PECs were calculated for production and processing. The highest PEC_{local} of 34 µg/l was calculated for the Swiss production site using default parameters. Short-term tests with fish, daphnids and algae are available. The most sensitive species was the marine invertebrate *Chaetogammarus marinus*. With an assessment factor of 1000 a $PNEC_{aqua}$ of 359 µg/l was derived.

Taking into account the systemic toxicity of 2-Methylbut-3-yn-2-ol, there is no reason for concern; the substance is of low potential risk and low priority for further work. The most sensitive NOAEL is derived from a 4 week oral gavage study in rats with a NOAEL of 50 mg/kg b.w. Taking an EHE of 1.35 mg/kg/d for workers into account, there is a MOS of 37. Via the environment a daily uptake of 0.001 mg/kg b.w. was calculated giving a MOS of 50,000.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	115-77-5
Chemical Name	Pentaerythritol
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

Although the chemical is not readily biodegradable, toxicity to aquatic organisms is very low. PEC/PNEC ratio is less than 1 based on the local exposure scenario in the Sponsor country. Therefore, it is currently considered of low potential risk and low priority for further work.

Human Health

The chemical caused only soft faeces and diarrhoea in a repeated dose study. The chemical is not considered as an irritant to skin and eyes. Within the Sponsor country exposure is well controlled in a closed system. Estimated daily intake via indirect exposures is considered to be low. As margin of safety for indirect exposure is more than 500,000, it is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Pentaerythritol is a stable solid and the production volume was ca. 25,000 tonnes/year in 1996 and 1997 in Japan. The chemical is used as intermediate for Alkyd resin, Rosin ester, Explosive and Lubricants. No consumer use is reported. The chemical is classified as 'Biodegradable'. The bioconcentration factor ranged from 0.3 – 2.1.

The potential environmental distribution of pentaerythritol obtained from a generic fugacity model (Mackey level III) showed the chemical will be distributed mainly to water and soil. Predicted environmental concentration (PEC_{local}) of the chemical was estimated as 4.3×10^{-3} mg/l and 5.1×10^{-5} mg/l from Japanese local exposure scenario.

The main route of occupational exposure is inhalation with limited workers during bag filling operation. The average concentration in the atmosphere was measured at production sites as 8.5 mg/m^3 (range 0.35-20.3 mg/m^3) and the daily intake as the worst case was estimated as 1.2 mg/kg/day. There is no available information on the consumer use. For indirect exposure via the environment, the daily intakes through drinking water and fish are estimated as 1.43×10^{-4} mg/day and 1.35×10^{-5} mg/kg/day, respectively, based on PEC_{local} of 4.30×10^{-3} mg/l.

Predicted No Effect Concentration (PNEC) of the chemical was determined using a *Daphnia magna* 48 h immobility data (600 mg/l). The assessment factor of 1000 used to an acute toxicity data to determine PNEC, according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects, because only one acute toxicity data is available among algae, cladocera and fishes. Thus, PNEC of the chemical is determined as 0.6 mg/l, tentatively.

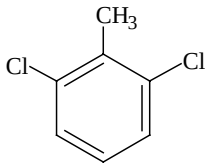
Thus, PEC / PNEC is 0.0072. Effects of the chemical on aquatic ecosystems are of low concern at present.

Pentaerythritol was not mutagenic in bacterial and chromosomal aberration tests *in vitro*. The chemical is not considered as an irritant to the skin and the eyes, nor as a sensitizer. In a combined repeat dose and reproductive/developmental toxicity screening test, both male and female rats showed only soft faeces and diarrhoea. The chemical did not show any toxicity to parents and offsprings. The no observed effect levels were 100 mg/kg/day for repeated dose toxicity and 1000 mg/kg/day for reproductive/developmental toxicity.

For human health, the risk for workers is expected to be low because the margin of safety is 83.3 as the worst case. The risks for consumer and the general population through indirect exposure are also assumed to be low because a margin of safety through drinking water or fish is calculated to be 6.98×10^5 or 7.38×10^6. Therefore, it is currently considered of low potential risk and low priority for further work.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	118-69-4
Chemical Name	2,6-Dichlorotoluene
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is not readily biodegradable and has relatively high bioconcentration potential. Although toxicity of the chemical seems relatively high to Daphnia, PEC/PNEC ratio is less than 1 based on the local exposure scenario in the Sponsor country. It is currently considered of low potential risk and low priority for further work.

Human Health

The chemical is moderately toxic in a repeated dose study (i.e. liver, kidney, thymus) and reproductive/developmental toxicity study (maternal toxicity). Occupational exposure is expected to be low as it is produced in closed system in Sponsor country. No consumer use is reported. Estimated daily intake through indirect exposure is also considered to be low. As the margin of safety is more than 200, it is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

2,6-Dichlorotoluene is stable liquid and the production volume is ca. 80 tonnes/year in 1996 in Japan. The chemical is used as intermediate for pesticide and pharmaceuticals. No consumer use is reported. The chemical is classified as “not readily biodegradable”. Bioconcentration factor is 246 – 828.

The potential environmental distribution of 2,6-dichlorotoluene obtained from a generic fugacity model (Mackey level III) showed the chemical would be distributed mainly to air and water. Predicted environmental concentration (PEC_{local}) of the chemical was estimated as 7.3×10^{-6} mg/l from Japanese local exposure scenario. In Japanese environmental survey, the chemical was not detected from surface water and sediments in 1982.

The main route of human exposure is inhalation with a limited numbers of workers potentially exposed during sampling operation. As there is no available data of the atmosphere concentration, the daily intake is calculated as 0.12 mg/kg/day as the worst case, based on the predicted high concentration and the possibility of exposure period. There is no available information on consumer use. Indirect exposure via the environment, the daily intakes through drinking water and fish were estimated as 2.43×10^{-7} mg/kg/day and 9.07×10^{-6} mg/kg/day, respectively, based on PEC_{local} of 7.30×10^{-6} mg/l.

As the lowest acute and chronic toxicity data, 48 h EC50 (1.8 mg/l) value and 21 d NOEC (0.32 mg/l) of *Daphnia*

magna were adopted, respectively. The assessment factors of 100 were used to both acute and chronic toxicity data to determine PNEC, because chronic toxicity data for fish was absent. Thus, PNEC of the chemical is 0.0032 mg/l. PEC/PNEC ratio is about 0.0023 and the bioconcentration factor of the chemical is moderate. Therefore, effects of the chemical on aquatic ecosystems are at low concern at present.

2,6-Dichlorotoluene had no genotoxic effects in bacteria and chromosomal aberration test *in vitro*. In a combined repeat dose and reproductive/developmental toxicity screening test, both male and female rats showed histopathological changes in liver, kidney and thymus, and maternal toxicity was observed. The no observed effect levels were obtained as 30 mg/kg/day for repeated dose toxicity and 100 mg/kg/day for reproductive toxicity.

For human health, the risk for workers is expected to be low because the margin of safety is 250. The risks for consumer and the general population through indirect exposure are also assumed to be low because the margin of safety through drinking water or fish is calculated to be 1.23×10^8 or 3.31×10^6. Therefore, it is currently considered of low potential risk and low priority for further work.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	126-99-8
Chemical Name	Chloroprene
Structural Formula	$H_2C=CH-C(Cl)=CH_2$

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is not readily biodegradable and has a low bio- or geoaccumulation potential. PEC/PNEC ratios are calculated as less than one. The chemical is currently considered of low potential risk and low priority for further work.

Human Health

The chemical is considered as a carcinogen. In the Sponsor country, control measures are in place to avoid significant human 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.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The production volume of Chloroprene is ca. 52,000 t/a in Germany, 36,000 t/a in France, 35,000 t/a in Northern Ireland, 163,000 t/a in the USA and 87,000 t/a in Japan. It is used as intermediate, for the production of polychloroprene. Chloroprene is "not readily biodegradable" and has a low bio- or geoaccumulation potential. The most sensitive environmental species to chloroprene is *Daphnia magna* (21d-NOEC = 3.2 mg/l). The derived PNEC is 32 µg/l.

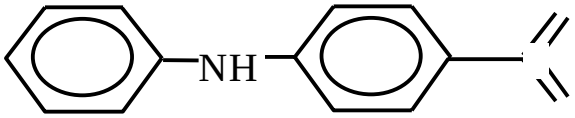
In a recent 90-day inhalation study the NOAEL was determined to be 32 ppm for rats and mice. For the hamster the NOAEL for repeated dose (2-year-study) was 10 ppm. For reproductive toxicity no damaging effects were recorded in rats in a study in which two successive generations of rats were exposed up to a concentration of 100 ppm, although other poorly documented tests describe an influence on the male fertility of rats at smaller concentrations. No effect on reproductive parameters was noted for rats and mice in the recent 90-day-study after inhalation up to 80 ppm. No teratogenic effect was observed with rabbits up to 175 ppm. In the recent 2-year inhalation study chloroprene was found to be carcinogenic in rats and mice. The data on short-term mutagenicity are conflicting; however, in the recent micronucleus test with mice of the 90-day inhalation study no induction of micronucleated erythrozytes could be detected.

The aquatic PEC was estimated to be 0.25 µg/l. No data on consumer or workplace exposure is available yet.

NATURE OF FURTHER WORK RECOMMENDED

The chemical is considered as a carcinogen. In the Sponsor country, control measures are in place to avoid significant human 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.	836-30-6
Chemical Name	Benzenamine, 4-nitro-N-phenyl
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

This chemical is not biodegradable, but bioaccumulative and toxic to aquatic species. However, PEC/PNEC is less than 1. It is currently considered of low potential risk and low priority for further work.

Health

This chemical may cause methemoglobinaemia, but exposure is low. It is currently considered of low potential risk and low priority for further work

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The substance is manufactured at a limited number of sites world-wide. It is manufactured solely for use as a chemical intermediate for industrial uses and thus is essentially fully consumed in chemical reductive alkylation reaction downstream of manufacture. There is no consumer exposure.

The substance is not acutely toxic neither orally nor by inhalation. Subchronic studies showed a decrease in the body weight gain, histopathological effects on kidney, liver and spleen, slight anaemia and increased methaemoglobinaemia. Neither adverse reproductive nor genotoxic effects have been detected.

The substance is not a skin or eye irritant and there is no evidence of it producing skin sensitisation.

In humans, due to its nitroaromatic structure, 4-NDPA is considered to have the potential to cause methaemoglobin formation.

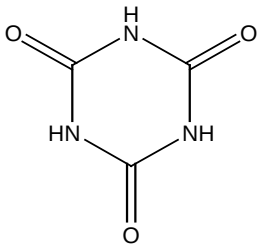
4-NDPA is acutely toxic to aquatic invertebrates. It is not readily biodegradable and its partition coefficient shows a potential for bioaccumulation. The substance is persistent and only slowly photodegradable.

Sources of environmental release arise during manufacturing, in very low quantities. For the representative facilities, the liquid effluents are treated on site previous to effluent discharge into the aquatic environment. Solid process wastes, consisting of distillation residues from production sites, are incinerated.

In conclusion, 4-NDPA is tested persistent in the environment and no environmental residues from production activity have been detected. It is currently considered of low potential risk and low priority for further work but because of its high aquatic toxicity, there may be a risk from production sites.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-80-5
Chemical Name	Isocyanuric acid
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Isocyanuric acid is lowly toxic in acute toxicity studies. This chemical is considered to be slightly irritating to eyes, but not to the skin. Several subchronic oral toxicity studies demonstrated renal damages, such as dilatation of the renal tubules, necrosis or hyperplasia of the tubular epithelium, increased basophilic tubules, neutrophilic infiltration, mineralization and fibrosis. These changes were probably caused by crystal of this chemical in renal tubules. The mechanism of this renal toxicity is supported by the toxicokinetics studies in animals and humans, showing that this chemical is quickly absorbed and excreted to urine within a few hours as an unchanged form. NOAEL is considered to be 150 mg/kg/day. In a developmental toxicity study, reduction of fetal body weights and crown/rump lengths was observed and NOAEL was 200 mg/kg/day**,** but this most likely reflects toxicty to the dams. No reproductive toxicity was observed (NOAEL: 600 mg/kg/day). A variety of *in vitro* and *in vivo* genotoxicity studies show this chemical is not genotoxic. Two years studies of rats and mice indicate this chemical has no carcinogenic potential.

Environment

Isocyanuric acid is not readily biodegradable (OECD 301C: 0% after 14-day) and stable in water. Bioconcentration factor to fish is low (<0.5, in Carp for 6 weeks).

Toxicity of this chemical to aquatic organisms seems to be low because all toxicity data are higher than 32 mg/l (NOEC for reproduction of *Daphnia magna*). 48-EC_{50} for immobilisation of *Daphnia magna* was 1000 mg/l. For testing in fish, Medaka (*Oryzias latipes*), both 96-h LC_{50} and 14-day LC_{50} were more than 100 mg/l. For algal test (*Selenastrum capricornutum*), 72-h EC_{50} and 72-h NOEC were 620.0 mg/l and 62.5 mg/l, respectively. No data are available for effects on terrestrial organisms.

Exposure

The production volume is ca. 20,000 tons/year in Japan in 1995. This chemical is used as an intermediate of chemical products in a closed system at industries. A generic fugacity model (Mackey level III) shows that this chemical will be distributed mainly (99.9%) in water phase after it is discharged into water.

As for consumer exposure, this chemical is used in the form of chlorides for disinfection of water. In Japan, trichloroisocyanurate is mainly used in swimming pool, and the average concentration of isocyanuric acid is estimated as 50 to 100 μg/ml.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	111-77-3
Chemical Name	2-(2-Methoxyethoxy)ethanol
Structural Formula	CH_3-O-CH_2-CH_2-O-CH_2-OH

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

DEGME has a low acute oral and dermal toxicity. Based on the available skin and eye irritation studies, DEGME is not classified as an irritant to the skin and eye. Classification as sensitizing agent is not indicated. With respect to repeated dose toxicity, the available data set for oral toxicity revealed an overall NOAEL of 900 mg/kg b.w. In the available inhalation study, no effects were observed in rats at the highest administered dose of 1060 mg/m^3 for 6 hour/day, 5 days/week for 90 days.

In a dermal study with guinea pigs, DEGME related effects were seen at all dose groups. Decreased spleen weight was observed at doses of ≥ 200 mg/kg b.w. and slight histopathological changes in the liver, and elevated urinary calcium levels were seen at ≥ 40 mg/kg b.w. day. A marginal effect level of 40 mg/kg b.w. is established, however the relevance of this finding for human health is not known.

DEGME is considered to be non- mutagenic. Data on carcinogenicity are not available. In fertility studies with mice and rats, DEGME caused no effects in mice and rats at 4000 mg/kg b.w. in drinking water or ≈ 610 mg/kg b.w. by gavage, respectively. However, in the 6 week repeated dose study with rats, the testes weight was decreased and testicular atrophy and altered sperm production was observed at 3600 mg/kg b.w.. In oral developmental studies no embryotoxic or teratogenic effects were observed at a dose of 200 mg/kg b.w./day. At high doses (≥ 1800 mg/kg b.w.) visceral malformations, especially of the cardiovascular system, were observed. In the available dermal developmental study a NOAEL of 50 mg/kg b.w./day is established.

Environment

2-(2-Methoxyethoxy)ethanol (DEGME) seems to be readily degradable (failing the 10-day window criteria), and is expected to have a low bioaccumulation potential in the environment.

For the *Daphnia magna* test, 48-h EC_{50} was 1192 mg/l. For testing in fish, 96-h LC_{50}s were 5700 mg/l for *Pimephales promelas*, 7500 mg/l for *Lepomis macrochirus* and >1000 mg/l for *Oncorhynchus mykiss*. For the algae test, EC_{50} values were > 1000 mg/l (96-hour) and > 500 mg/l (72-hour). DEGME caused no acute adverse effects to microorganisms (0.5-h EC_{50} > 1995 mg/l for activated sludge, 17-h EC_{50} > 10,000 mg/l for *Pseudomonas putida*). $PNEC_{aqua}$ of 12 mg/l was calculated according to the result of the *Daphnia magna* acute toxicity with an assessment factor of 100.

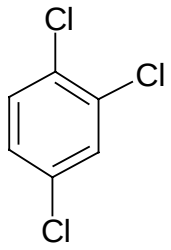
Exposure

The annual production of DEGME in the European Union in the period 1990-1993 was about 20,000 tonnes. The substance is used as an anti-icing agent in jet fuel and also as (co)solvent with applications in paints or floor polish. Consumer use may occur via exposure to a.o. paints, paint stripper, cleaning agents and detergents. Dermal and inhalatory exposure are the main routes of exposure for workers and consumers. Releases into the environment may occur during its production and other life cycle steps.

NATURE OF FURTHER WORK RECOMMENDED

There is a need for further information and consideration of exposure and risk assessment for human health. A detailed risk assessment has been agreed in the European Union Risk Assessment Programme under Regulation EEC/793/93. The EU risk assessment concluded that there is a need for specific measures to limit the risks to consumers (from paint or paint strippers containing this substance) and to workers from dermal exposure.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	120-82-1
Chemical Name	1,2,4-Trichlorobenzene
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The substance shows acute oral toxicity at levels between 750 and 1100 mg/kg. The substance shows some eye irritation, however not to a degree to warrant classification. Whilst some skin irritation is seen after acute exposure, irritation is mainly the result of repeated application rather than of acute exposure. Evidence for lung irritation is largely anecdotal. The substance appears to have weak skin sensitising properties, however not to a degree to warrant classification.

There are several assays to assess the repeated dose and chronic toxicity. The oral NOAEL is taken as 6 mg/kg bw/day based on a 2-year carcinogenicity study in rats. The target organs appear to be the liver, the kidneys and adrenals. The NOAEL is probably close to the level at which effects on liver enzymes and relative organ weights can be seen. A NOAEC of 3 ppm (23 mg/m^3) has been used. The equivalent oral dose has been calculated as 3.2 mg/kg bw/day. Whilst slightly lower than the oral value, this is not considered to be unreasonable, as the effects seen are very similar to those seen at comparable oral doses. For dermal application the systemic LOAEL is 450 mg/kg bw/day and the NOAEL is 150 mg/kg bw/day based on a four week rabbit study. These levels are substantially higher than comparable figures for the oral or the inhalational route. For local effects on the skin, only a LOAEL of 30 mg/kg bw/day could be determined.

The database for genotoxicity is complicated; available data, both from in vitro and in vivo test, are conflicting, but taking the quality of the data into account, on balance, 1,2,4-TCB is not considered to express genotoxic effects in vivo. 1,2,4-TCB produced hepatocellular carcinomas in B6C3F1 mice (feeding study) with a NOAEL of 21-16 mg/kgbw/day. The use of the mouse strain B6C3F1 in the carcinogenicity study is complicated by the fact that this strain of mice is known to produce a high incidence of hepatocellular carcinomas when exposed to substances which have a toxic effect on the liver. Since the primary possible concern- for a carcinogenic effect is associated with the potential of the substance to cause changes in the liver, a NOAEL that is based on an absence of effects on the liver, i.e. the NOAEL for repeat dose toxicity, is considered to be adequate for the purposes of this risk assessment. There was no significant difference in mononuclear leukaemia and pituitary gland Tumors in a 2 year carcinogenecity study but a slight increase in the incidence of Zymbal's glands tumours in the F344 rat. The incidence reported is however not sufficiently high to lead to the conclusion that this study shows a positive carcinogenic effect.

There are several studies available on the toxicity of TCB on reproduction, including developmental toxicity and fertility. All studies however suffer from deficiencies in the test design relative to the current OECD Guidelines.

The data on the effects of 1,2,4-TCB is inadequate to properly establish a LOAEL on reproductive toxicity. A NOAEL for effects on the foetus based on a conservative evaluation of a two generation study can however be established as 33 mg/kg bw/day for males and 53 mg/kg bw/day for females, which is at a level of 5 to 10 times the NOAEL chosen for repeated dose toxicity. It is considered unlikely that results of additional reproductive toxicity studies would lead to a lower NOAEL for reproduction.

The NOAEL and NOAEC used in the risk characterisation for repeat dose toxicity covers all chronic effects of the substance including systemic toxicity, carcinogenicity and reproductive toxicity. The residual concerns for carcinogenicity are thus also reflected in the evaluation of the margin of safety (MOS) where relevant.

Environment

1,2,4- Trichlorobenzene (1,2,4-TCB) is stable to hydrolysis and photodegradation in water. Atmospheric photodegradation is measured to have a half-life of 30 days. 1,2,4-TCB is not ready biodegradable, however, 1,2,4-TCB was concluded to be biodegradable to some extent depending on adaptation. 1,2,4-TCB was concluded to be inherently biodegradable and based on this, the half-life in surface water is estimated to be 150 days and the half-life in soil and sediments 300 days. 1,2,4-TCB has a high adsorption capacity with an average K_{oc} of 1400 and the mobility in soil is expected to be low. 1,2,4-TCB has a log K_{ow} of 4.02 and a "realistic worst case" bioconcentration factor BCF for fish of 2000 was established based on several experimental test data.

1,2,4-TCB 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 0.7 for Golden ide to 6.3 mg/l for Zebra fish. The acute toxicity for *Daphnia magna* ranged from 1.2 mg/l to 3.39 mg/l with an average value of 2.1 mg/l. Other crustaceans ranged from 0.45 mg/l for *Mysidopsis bahia* to 3.02 mg/l for crayfish. For algae, the acute toxic EC_{50} was 1.4 mg/l and NOEC 0.37 mg/l. The long-term toxicity NOEC for fish ranged from 0.04 mg/l for *Brachydanio rerio* to 0.5 mg/l for *Pimephales promelas*. The chronic NOEC for *Daphnia magna* ranged from 0.06 mg/l to 0.36 mg/l. For the terrestrial compartment, the earthworm acute EC_{50} ranged from 127 to 251 mg/kg soil, for plants from 48 to 240 mg/kg and for soil micro-organisms, EC_{50} in a respiration test was 50 mg/kg.

An assessment factor of 10 was used to calculate a predicted no effect concentration (PNEC) for 1,2,4-TCB in the aqutic environment since long-term data was present for fish, Daphnia and algae: $PNEC_{aqua}$ 0.004 mg/l. For the terrestrial environment, an assessment factor of 1000 was used: $PNEC_{soil}$ 0.05 mg/kg. For non compartment specific effects relevant to the food chain, an assessment factor of 10 was applied to the $NOAEL_{oral}$ for rats of 100 ppm diet (2 year study): $PNEC_{oral}$ 10 ppm diet.

Exposure

The production volume of main manufacturers in EU of 1,2,4-TCB was 7000 tonnes, the import was 2000 tonnes and the export 7600 in 1994/1995. 1,2,4-TCB is manufactured and used in the chemical industry as an intermediate in closed systems for the manufacture of herbicides and higher chlorinated benzenes. Furthermore, 1,2,4-TCB is used as process solvent, as a dye carrier, in metal working fluids, dielectric fluids and heat transfer medium. Former uses include use of the substance in degreasing agents, septic tanks, drain cleaners, wood preservatives and insecticide. Besides direct exposure from production and use of 1,2,4-TCB, indirect exposure may take place from forming of trichlorobenzenes during the combustion of organic material when chlorine is present (e.g. during incineration of waste, PVC, etc.). 1,2,4-TCB is also formed during industrial cracking or environmental degradation of hexachlorocyclohexanes and other higher chlorinated benzenes.

1,2,4-TCB may be released into the environment during production, use and disposal and has been detected in most environmental compartments. The atmospheric compartment is estimated to be the primary recipient (based on the relatively high vapour pressure) in some of the use areas (e.g. solvent), in other areas, the aquatic compartment is the

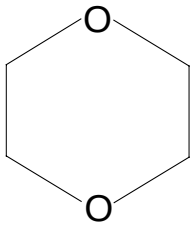
primary recipient (e.g. intermediate in industrial processes, dye carrier). However, release of 1,2,4-TCB from the accumulated volume in electrical equipment still in use or from disposal of such equipment, as well as the formation of trichlorobenzenes during combustion of waste and PVC has only been roughly estimated or discussed.

NATURE OF FURTHER WORK RECOMMENDED

Further investigation of existing slides of Zymbal gland tumours are needed to provide an improved basis for risk assessment.

In the context of the EU risk assessment programme, risk reduction measures are being considered that would ensure a reduction in levels of 1,2,4 TCB in the environment caused by emission from open downstream use of the substance (e.g. dye carrier)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-91-1
Chemical Name	1,4-Dioxane
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,4-Dioxane has been shown to cause eye and respiratory irritation in humans at relatively high (>50 ppm) exposure levels. Fatalities, characterised by severe liver and kidney damage, have also been reported in workers from repeated exposure to very high levels. Limited evidence exists for increased liver cancer and reproductive outcome from occupational exposure to 1,4-dioxane.

A NOAEL (inhalation) of 111 ppm (105 mg/kg/day) 1,4-dioxane was determined from a single chronic rat inhalation study (no LOAEL determined). The NOAEL (oral) in rats (the most sensitive species) is 10 mg/kg/day derived from a two year drinking water study. The lowest dose (LOAEL), associated with histopathological effects in the liver was 16 mg/kg/day. 1,4-Dioxane has been shown to cause multiple site tumors in more than one animal species (oral route only), with liver tumors being the only tumor type seen in all species tested. The mechanism(s) for tumourigenicity in animals, although not fully characterised, appears to be epigenetic in nature and as such, a threshold for effect is considered likely.

Although a study on reproduction/fertility effects was not available, the requirements for assessing this endpoint were deemed satisfied, on account of the availability of data on effects on reproductive organs from well conducted repeat dose animal bioassays and a developmental study. Limited evidence of effects on fertility and development were seen in these studies.

Environment

1,4-Dioxane is not expected to bioconcentrate in fish, but is expected to biodegrade slowly in soil or water. This chemical is considered unlikely to provide any contribution to global warming or ozone depletion, due to the small quantities released, its low partitioning to air and its relatively short half-life in the atmosphere.

According to results available in the literature, this chemical can be classified as practically non-toxic to aquatic micro-organisms, plants, invertebrates and fish. For the algae test, 8-day EC_{50} was 5600 mg/l. Acute toxicity to invertebrates ranges from an EC_{50} of 163 mg/l for *Ceriodaphnia dubia* to an EC_{50} of 5500 mg/l for *Daphnia magna*.

A 7-day NOEC was 625 mg/l for *Ceriodaphnia dubia*. Acute toxicity to fish ranges from an LD_{50} of 6155 mg/l for Channel catfish to an LD_{50} of >10,000 for bluegill sunfish, a NOEC for fathead minnow was > 145 mg/l. The lowest value of long-term test results was the NOEC (8 days) of 575 mg/l for Cyanobacteria. $PNEC_{water}$ of 57.5 mg/l was calculated based on this result with an assessment factor of 10.

Exposure

Worldwide production figures were reported to be 10,000 - 20,000 tons in 1991, which declined to 8,000 - 10,000 tons in 1994 due mainly to the decreasing use of chlorinated hydrocarbons and increasing recovery of 1,4-dioxane in the pharmaceutical industry.

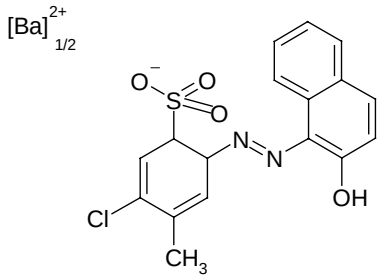
Occupational exposure to 1,4-dioxane in Australia may occur from its use in laboratory applications, lens manufacture and film processing and from manufacture/processing of ethoxylated chemicals. In the EU, occupational exposure may occur from the use in laboratory applications, production of magnetic tapes, manufacture of medicines, use as solvent in the production of other substances and the use of products containing the substance such as cleaning agents, paints, lacquers and varnishes.

Data collected by sponsor countries indicate that exposures to the general public, mainly from products containing 1,4-dioxane as an impurity, are much lower (orders of magnitude) than occupational exposures.

NATURE OF FURTHER WORK RECOMMENDED

In the context of the EU Existing Substances Regulation 793/93 a detailed risk assessment has been carried out which has identified a concern for human health risks specifically due to worker exposure. Member countries are encouraged to consider exposure levels in their own countries to determine if a detailed risk assessment is needed.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	5160-02-1
Chemical Name	barium bis[2-chloro-5-[(hydroxy-1-naphthyl)azo]toluene-4-sulphonate]
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

After single oral administration pigment red 53:1 can be designated to be of low toxicity. It does not irritate the skin and eyes and is not a sensitizer. Repeated administration of high concentrations causes changes in haematological parameters as well as having an effect on spleen, liver and kidneys. A NOEL of 25 mg/kg bw was derived from a 2 year feeding study with rats. Pigment red 53:1 proved to be non-genotoxic in various in-vitro and in-vivo studies. Several long-term toxicity and carcinogenicity studies in mice and rats revealed no carcinogenicity. However, in one study high dosed male Fisher rats developed fibrosarkomas of the spleen. Since pigment red 53:1 is not genotoxic, the carcinogenic findings are considered to be a consequence of tissue damage. Studies of reproduction toxicity gave no indication of impairment of fertility. With regards to occupational exposure, no workplace measurements are available. However, based on the following theoretical worst case scenario (total dust 1mg/m^3; volume inhaled 0.8 m^3 per hour; 70% respirable; 70% sytemically available; 8 hour shift), the systemic burden of a worker would hypothetically result in 0.065 mg/kg body weight per day. In relation to the NOELs for repeated exposure of rats and mice (see 4.2b) safety margins of 385 up to 1385 are calculated. Based hereupon, no significant health risk is seen for workers.

Based on all available data pigment red 53:1 is considered to be of low potential risk for human health.

Environment

The highest PEC_{local} of 41.5 µg/l was calculated resulting from paper recycling using a realistic worst case scenario. On the other hand a pigment red concentration of 3.4 µg/l was measured in one waste water sample from a German de-inking plant, resulting in a PEC_{local} of 0.11 µg/l. As the water solubility of pigment red is about a factor of 50 to 10 000 higher than the estimated PECs for the scenario paper recycling it can be concluded that pigment red represents with high probability a low potential risk to the aquatic environment.

Exposure

The production volume of pigment red 53:1 in 1991 was 1500 t in Germany. About 2/3 of this amount were exported. Additionally, 250 t were imported in the same year.

Pigment red 53:1 is used particularly for short-life printed matter, for colouring plastics, PVC, polyurethane foam, natural rubber stocks and in paints. Releases into the environment may mainly occur during production, formulation and paper recycling. Pigment red 53:1 is classified as "non biodegradable". In short-term tests with fish and daphnia no effect was found in concentrations up to the water solubility of 2 mg/l. As no acute effects were found no PNECaqua was derived.

NATURE OF FURTHER WORK RECOMMENDED

No further work is necessary.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	67-64-1
Chemical Name	Acetone
Structural Formula	CH_3-CO-CH_3

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The acute toxicity is low. Acetone is not a skin irritant or sensitiser but is a defatting agent to the skin. Acetone is an eye irritant. The subchronic toxicity of acetone has been examined in mice and rats that were administered acetone in the drinking water and again in rats treated by oral gavage. Acetone-induced increases in relative kidney weight changes were observed in male and female rats used in the oral 13-week study. Acetone treatment caused increases in the relative liver weight in male and female rats that were not associated with histopathologic effects and the effects may have been associated with microsomal enzyme induction. Hematologic effects consistent with macrocytic anemia were also noted in male rats along with hyperpigmentation in the spleen. The most notable findings in the mice were increased liver and decreased spleen weights. Overall, the no-observed-effect-levels in the drinking water study were 1% for male rats (900 mg/kg/d) and male mice (2258 mg/kg/d), 2% for female mice (5945 mg/kg/d), and 5% for female rats (3100 mg/kg/d). For developmental effects, a statistically significant reduction in foetal weight, and a slight, but statistically significant increase in the percent incidence of later resorptions were seen in mice at 15,665 mg/m3 and in rats at 26,100 mg/m3. The no-observable-effect level for developmental toxicity was determined to be 5220 mg/m^3 for both rats and mice. Teratogenic effects were not observed in rats and mice tested at 26,110 and 15,665 mg/m^3, respectively. Lifetime dermal carcinogenicity studies in mice treated with up to 0.2 mL of acetone did not reveal any increase in organ tumor incidence relative to untreated control animals.

The scientific literature contains eight different studies that have measured either the neuro-behavioural performance or neurophysiological response of humans exposed to acetone. Effect levels ranging from about 600 to greater than 2375 mg/m^3 have been reported. Neurobehavioral studies with acetone-exposed employees have recently shown that 8-hr exposures in excess of 2375 mg/m^3 were not associated with any dose-related changes in response time, vigilance, or digit span scores. Clinical case studies, controlled human volunteer studies, animal research, and occupational field evaluations all indicate that the NOAEL for this effect is 2375 mg/m^3 or greater.

Environment

Acetone has been tested in a wide variety of aquatic and terrestrial species. Acute toxicity to fish ranges from an LC_{50} of 6,070 mg/L for Brook trout to 15,000 mg/l for Fathead minnow. The lowest LC_{50} for aquatic invertebrates is 2,100 mg/L, ranging to 16,700 mg/L. The NOEC's for toxicity to aquatic plants range from 5,400-7,500 mg/L. The chronic NOEC for Daphnia is 1,660 mg/L. Tests using Ring-neck pheasant and Japanese quail produced no adverse effects at 40,000 mg/kg. In summary, ecotoxicity testing shows that acetone exhibits a low order of toxicity.

An assessment factor of 100 was used to calculate a predicted no effect concentration (PNEC) for acetone in an

aqueous environment, because acute toxicity data were available for algae, crustaceans, and fish. The lowest PNEC value for these species was calculated to be 21 mg/L when using the LC_{50} value of 2100 mg/L for marine brine shrimp.

Exposure

Worldwide production capacity of acetone was 3.8 million tonnes in 1995 with the actual volume produced being somewhat less at 3.7 million tonnes. Production capacity in the United States constituted about 33% (1.3 million tonnes) of the global capacity, while Western Europe and Asia (including Japan) were about 31% (1.2 million tonnes) and 19% (0.7 million tonnes), respectively. Major end uses of acetone can be divided into three separate categories as: i) a chemical feedstock, ii) a formulating solvent for commercial products, and iii) an industrial process solvent. Acetone can be found in wide variety of consumer and commercial products but only a few are known to contain high concentrations. These include paints and paint-related products, such as paint thinners, finger nail polish removers, automotive waxes and tar removers.

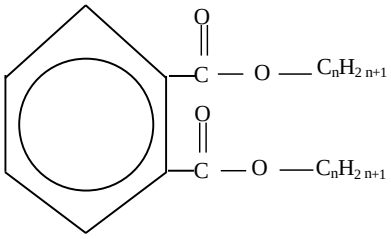
PECs have been derived based on the results from air and water monitoring data. The PEC_{local} (2500 µg/L [water], 10,000 µg/m^3 [air]) and PEC_{global} (50 µg/L [water], 10 µg/m^3 [air]) values are intended to represent plausible worst case environment concentrations on a global and regional scale.

High concentrations of acetone can be detected in a variety of occupational environments (up to 2876 mg/m^3 at cellulose acetate factory). The predominant route of both occupational and consumer exposure is through vapor inhalation. The estimated human exposure (EHE) value for workplace employees is 1780 mg/m^3. Using a USEPA modelling programme entitled SCIES (Screening Consumers Inhalation Exposure Software), a scenario intended to represent a likely indoor consumer use of a product (45 min application of a spray contact adhesive that contained 21% acetone) predicted a short-term exposure (EHE) value of 900 mg/m^3 for the consumer use of the product.

NATURE OF FURTHER WORK RECOMMENDED

None recommended.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	68515-48-0 and 28553-12-0
Chemical Name	1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich, and di-«isononyl» phthalate
Structural Formula	 n= 8 to 10

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In rat, DINP is significantly absorbed from the gastrointestinal tract (at least 50 %), rapidly eliminated and not accumulated in tissues. Only metabolites are recovered in urine (monoester, oxidative monoester, phthalic acid). Dermal absorption is very limited (<4 % in 7 d). DINP has a low oral, dermal and inhalation acute toxicity. DINP is not an irritant for skin and eyes. A low sensitizing potential can be anticipated.

The NOAEL of 36 mg/kg is derived from a two year study with Fischer rats, based on kidney (increased kidney weights in both sexes) and liver effects (histopathological and biochemical findings). DINP is not genotoxic *in vitro/vivo*. In few cases it induces cell transformation. In carcinogenicity studies, DINP induces significant excess of liver neoplasia from 1,500 ppm (~335 mg/kg/d) in female mice, leading to a NOAEL of 112 mg/kg/d. DINP acts as a peroxisomal proliferator. Hepatic effects produced in rats do not occur in Cynomolgus Monkeys treated up to 14 days (500 mg/kg/d), neither in marmoset monkeys treated for 13 weeks, up to 2,500 mg/kg/d. In rodents, as this was demonstrated for DEHP, it can be assumed that PPARα is involved in hepatic tumour promotion; although the risk to human is low, the potential human carcinogenicity is not completely disregarded for this aspect. Regarding mononuclear cell leukemia, a clear increase incidence is observed as well as a shortening of their onsets in Fisher rats; although this type of natural rat leukemia occurs in very high incidence in this strain of rat, it cannot be totally ignored. So, a NOAEL of 88 mg/kg/d is assumed.

With respect to reprotoxicity, from the available studies in rat, no overt effect is observed in reproductive organs as well as no change in reproductive indices. In mice a NOAEL of 276 mg/kg/d is identified based on decrease in testicular weight (742 mg/kg d in a 104 week study) accompanied with abnormal /immature sperm forms in a 13 week study at 5,770 mg/kg d. At this dose, uterus/ovary atrophy are also observed.

NOAEL For developmental effects derived from a two-generation study in rat a decrease in live birth and survival indices is noted at a high dose range level (966-2246 mg/kg) leading to a NOAEL of 1% (622mg/kg/d, lowest value of the dose range level). For slight bodyweight offspring decrease as well as for parental toxicity (slight liver changes) a LOAEL of 159 mg/kg/d (lowest value of the dose range level is 159-395 mg/kg/d of maternal intake during the post partum period for the females) is set up. In developmental studies the NOAEL for conceptus in rat is 500 mg/kg/d based on significant increase of skeletal and visceral variations at the 1,000 mg/kg/d high dose concurrently with slight signs of maternal toxicity.

In regard with oestrogenic activity, except one *in vitro* study in which DINP shows the ability to stimulate cell proliferation (ZR 75 cell proliferation), all available *in vitro/in vivo* assays are negative.

Environment

Di-isononylphthalate (DINP) is readily biodegradable. The substance has a high potential for accumulation in soil (estimated Koc = 286000), but a low bio-accumulation potential (estimated BCF for fish <14).

Due to its very low solubility, no acute toxicity in fish, invertebrates or algae could be observed. No long-term toxicity could be observed in algae or invertebrates at the limit of solubility. No valid long-term fish studies are available, but a read-across from tests performed with other long-chain phthalates (> C6) indicates that no effects are to be expected for DINP at the limit of water solubility or above. No effects were observed in acute toxicity studies with sediment organisms. No effects were observed in studies with terrestrial organisms.

Exposure

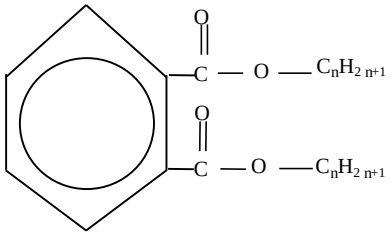
The consumption of diisononylphthalate in the EU is estimated to be 121000 t/a. It is mostly used as a plasticizer in PVC (> 90 %), minor uses are as a plasticizer in other polymers, in paints, inks, adhesives, glues and sealing compounds.

NATURE OF FURTHER WORK RECOMMENDED

Based on the use pattern of diisononyl phthalate a detailed risk assessment is recommended considering:

- clarification of bioaccumulation potential; and
- investigation of toxicity towards sediment dwellers based on data from other long-chain phthalates.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	68515-49-1 and 26761-40-0
Chemical Name	1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich, and di-«isodecyl»phthalate
Structural Formula	 n= 9 to 11

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

DIDP is significantly absorbed from the gastro- intestinal tract (at least 50%) rapidly eliminated and not accumulated in tissues. Only metabolites are recovered in urine or bile (monoester, oxidative monoester, phthalic acid). By inhalation route, a large amount of DIDP is eliminated from the body, only a small fraction of DIDP or metabolites is retained in the body. Dermal absorption is very limited.

DIDP has a low acute oral, dermal and inhalation toxicity. DIDP is not a dermal or an ocular irritant, and is neither a respiratory irritant under normal conditions. A low sensitizing potential can be anticipated.

In relation to chronic toxicity, a NOAEL of 15 mg/kg/day is identified in a 13-week oral study in dog for liver effects (i.e. swollen and vacuolated hepatocytes) but with some uncertainties remain concerning the reliability of this study. In rat, a NOAEL of 60 mg/kg/d is derived from a 90 day study in rats based on slight liver changes in females at the higher dose.

DIDP is not genotoxic *in vitro/vivo*. It induces cell transformation in one assay. No chronic/carcinogen studies are available. Nevertheless, by analogy with DINP and based on the same pattern in response to peroxisome proliferation, a NOAEL of 112 mg/kg/d is assumed for liver neoplasia derived from a mice well-conducted 2-year study with DINP. In rodents as it was demonstrated for other phthalates, it can be assumed that hepatic tumours are related with peroxisome proliferation; although the risk to humans is low, the potential human carcinogenicity cannot be completely disregarded.

With respect to reprotoxicity, testicular effects in rats are limited to slight increase in testicular weights but without histological findings and no change in reproductive indices is documented. For developmental effects derived from a two-generation study in rat a decrease in Live Birth Survival Index is observed leading to a LOAEL of 0.2 % (103 mg/kg/day, lowest value of the dose range level) with concurrent hepatic effects related to peroxisomal proliferation

in parents. For slight bodyweight offspring decrease in the two-generation study a NOAEL of 263 mg/kg/d (lowest value of the dose range level) is set up. In developmental studies the NOAEL for conceptus in rat is 500 mg/kg/d based on significant increase of skeletal and visceral variations at the 1,000 mg/kg/d high dose concurrently with slight signs of maternal toxicity

No estrogenic activity *in vitro/vivo* was observed in available test results.

Environment

DIDP is readily biodegradable (failing the 10-day window). The substance has a high potential for accumulation in soil (K_{oc} = 286000), but a low bioaccumulation potential (BCF for fish: < 14.4).

Due to its very low solubility, no acute toxicity in fish, invertebrates or algae could be observed. No long-term toxicity could be observed in algae or invertebrates at the limit of solubility. No long-term fish studies are available, but a read-across from tests performed with other long-chain phthalates (> C6) indicates that no effects are to be expected for DIDP at water solubility or above. No effects were observed in toxicity studies with soil or sediment organisms.

Exposure

The consumption of diisodecylphthalate in the EU is estimated to be 200000 t/a. It is mostly used as a plasticizer in PVC (> 90 %), minor uses are as a plasticizer in other polymers, in paints, inks, sealing compounds and ceramics.

NATURE OF FURTHER WORK RECOMMENDED

Based on the use pattern of diisodecylphthalate phthalate, a detailed risk assessment would be necessary.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7722-84-1
Chemical Name	Hydrogen Peroxide
Structural Formula	H-O-O-H

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Hydrogen peroxide is an endogenous metabolite in the aerobic cell. The likely adverse effects by exogenous hydrogen peroxide concern local toxicity, although absorption at very high rates may also cause oxygen embolism with potentially serious consequences. Based on human case reports, the hazard of embolism may arise at fairly low doses (15-150 mg/kg bw) when hydrogen peroxide is introduced into body cavities such as in surgery or after oral intake.

Concerning single exposures, notable effect end points are acute toxicity (by the oral route: LOAEL approximately 100 mg/kg bw) and, for hydrogen peroxide vapours, irritant effects in the eyes and airways (LOAEL 3.5-10 mg/m^3), irritant effects on the skin (LOAEL 20 mg/m^3), for hydrogen peroxide water solutions, eye irritation (mild irritation at the concentration of 6 %, moderate irritation at 8%, severe irritation and corrosion at ≥ 10 %) and skin irritation/corrosivity (slight irritation at 10 %, moderate irritation at 35 %, corrosion at ≥ 50 %). The potential of hydrogen peroxide to cause skin sensitization was judged to be extremely low.

Concerning repeated exposures, oral administration (drinking water) in mice gave NOAELs of 26 mg/kg bw/day in males and 37 mg/kg bw/day in females based on a dose-related reduction of food and water consumption and local effect (duodenal mucosal hyperplasia). There is suggestive evidence from animal studies causing some concern that levels of about 10 mg/m^3 may be associated with local changes in the lungs, reminiscent of oxygen toxicity, as well as local effects in the skin.

Hydrogen peroxide is a mutagen and genotoxicant in a variety of *in vitro* test systems, but negative results from DNA repair and micronucleus studies, and from a study of *in vivo* genotoxicity and mutagenicity in the mouse skin after repeated applications, are not in support of a significant genotoxicity/mutagenicity *in vivo*. A local carcinogenic effect was observed in the duodenum of a catalase-deficient mouse strain administered 0.4 % H_2O_2 in drinking water. Although an underlying genotoxic mechanism cannot be excluded, the weight of evidence at this time does not suggest that the carcinogenic properties of hydrogen peroxide should be regarded as practically significant.

Regarding reproductive toxicity, a 90-day drinking water study with mice did not indicate effects in reproductive organs, and there is a gap in the basic data requirement for developmental effects. However, it was presumed that because of the rapid degradation of the substance on absorption and due to local effects, studies would be unlikely to reveal any specific developmental effects.

Environment

Hydrogen peroxide is a naturally occurring substance (typical background concentrations < 1 - 30 µg/l). Almost all cells with the exception of anaerobic bacteria produce it in their metabolism. H_2O_2 is rapidly degraded in the environment (biotic and abiotic). Its half-life times are estimated to be < 1-5 days in surface water and sediment, one day in air and from minutes to a few hours in soil. Hydrogen peroxide does not bioaccumulate (log K_{ow} < -1). Hydrogen peroxide adsorbs poorly to sediment particles and is rapidly degraded, thus accumulation in the sediment is also not expected.

Despite the H_2O_2 decomposing mechanisms in all aerobic cells, hydrogen peroxide is toxic to aquatic organisms, Exposure of aquatic environment may have harmful effects on biota. Algae are the most sensitive organisms (EC_{50} = 1.6-5 mg/l, NOEC = 0.1 mg/l). Acute toxicity to invertebrates varies from 2 to 17.7 mg/l, and to fish from 16.4 to 37.4 mg/l. Chronic toxicity to invertebrates is studied on zebra mussels (NOEC was 2 mg/l). No data for long term tests on fish is available.

PNEC to aquatic organisms according to the EU Technical Guidance Document would be 2 µg /l using the algal NOEC of 0.1 mg /l and an assessment factor of 50. Hydrogen peroxide is a naturally occurring substance (typical background concentrations <1 – 30 µg /l), Concentrations close to 30 µg /l are rare – occurring during summer afternoons in surface waters with high DOC level. On the basis of a field study, it is evident that even natural levels of H_2O_2 may be harmful to some organisms causing "natural risks". Calculated PNEC of 2 µg /l seems to over estimate the toxicity and therefore PNEC = 10 µg /l is recommended.

Exposure

The estimated use of hydrogen peroxide was 670 000 t/a for 1995 in the EU. This chemical is used for bleaching of pulp and textiles, chemicals manufacture, environmental applications and various other purposes including consumer products.

Hydrogen peroxide is used in large volumes for the production of other chemicals, for bleaching of pulp, paper and textiles, for disinfection in the food processing industry, for etching in the electronics industry, for cleaning of metal plates and for water treatment and other environmental applications. Significant exposures to the vapours of hydrogen peroxide at or above occupational exposure limit levels may occur in the loading of tankers**,** in some applications of disinfection and in etching of circuit boards. In small-scale open uses involving manual handling, splashes of the more concentrated substance to the skin were noted to cause white spots.

Concerning consumer products, available household bleaches may contain up to 20 % hydrogen peroxide causing an obvious hazard of injury in case of a splash to the eye. Consumers may be exposed to hydrogen peroxide during bleaching and dyeing of the hair, and through the use of tooth bleaches or mouth washes. Presently, some applications and products may contain high enough concentrations of hydrogen peroxide to cause symptoms of irritation. Contact lenses contain low residues of hydrogen peroxide when the substance is used for disinfection.

NATURE OF FURTHER WORK RECOMMENDED

Site specific data on the production plants in Europe and PECs calculated using generic scenarios according to EU Technical Guidance Document indicates possible local risks to aquatic environment, especially if no biological waste water treatment system exists. Exposure data from industry will clarify this issue.

The hazards of repeated inhalation exposures to hydrogen peroxide are poorly defined, and they should be further explored (as a possible post SIDS activity) to enable the assessment of risks to workers. An experimental study performed with an appropriate animal model may be needed to resolve the problem.

In the context of the EU Existing Substances Regulation 793/93 a detailed risk assessment is being carried out.

OECD Member countries outside of the EU are invited to note this information and investigate the necessity for risk assessment in their own countries.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-67-1
Chemical Name	2,2'-Azobis(2-methylpropionitrile)
Structural Formula	$(H_3C)_2C(CN)\ N{=}{=}NC(CN)(CH_3)_2$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

2,2'-Azobis(2-methylpropionitrile) is considered not to be irritating to skin and eyes, or a skin sensitizer. In an OECD combined repeat dose and reproductive/developmental toxicity study in rats at 2, 10 and 50 mg/kg/day, this chemical was toxic to the liver as well as the kidneys. Increases in eosinophilic bodies and basophilic changes of the renal tubular epithelial cells in the kidneys were observed only in treated male rats. This male rat specific renal toxicity might be caused by accumulation of α_{2u}-macroglobulin as one of the possible mechanisms. Centrilobular hypertrophy of hepatocytes with the related changes in hepatotoxic blood parameters was detected at the middle and high doses in both sexes. NOAEL for repeated dose toxicity was considered to be 2 mg/kg/day, based on hepatic toxicity. As there was only a reduction in viability and body weight of offsprings after birth at the high dose, most likely due to maternal toxicity, NOAEL for reproductive toxicity was considered to be 50 mg/kg/day. This chemical may not be genotoxic, based on negative results of bacterial mutation testing and chromosomal aberration *in vitro* testing.

Environment

2,2'-Azobis(2-methylpropionitrile) is not readily biodegradable (OECD 301C: 0% after 28-day), and it is stable in water ($T_{1/2}$ = 304 days at pH 7).

72-h EC_{50} of algae, *Selenastrum capricornutum* is more than 9.4 mg/l, and 72h NOEC is 4.2 mg/l. For the *Daphnia magna* test, 48-h EC_{50} for immobilisation is more than 10 mg/l, and 21-day EC_{50} and 21-day NOEC for reproduction are 7.5 mg/l and 2.2 mg/l, respectively. For testing in fish, Medaka (*Oryzias latipes*), 96-h and 14-day LC_{50} values are both more than 10 mg/l. No data are available for effects on terrestrial organisms.

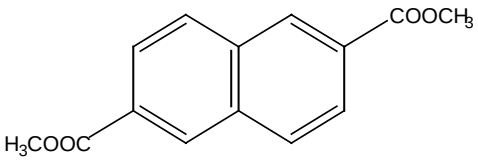
Exposure

The production volume of 2,2'-Azobis(2-methylpropionitrile) is 1,100 tons/year in 1993 in Japan. This chemical is used in closed systems as an initiator of polymerisation in polymer industry, and not included in consumer products, therefore no consumer exposure is expected.

This chemical is released into the environments from the production and process sites, and as an example its amount is reported to be 1 kg/year by a processor who treats 12 tonnes/year. A generic fugacity model (Mackey level III) shows that most (98.6%) of this chemical will distribute in water phase after it is discharged into water.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	840-65-3
Chemical Name	Dimethyl 2,6-naphthalenedicarboxylate
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Oral LD_{50} of this chemical for rats is more than 2,000 mg/kg. There are no available data for irritation and sensitisation. In an OECD combined repeat dose and reproductive/developmental toxicity study in rats at 30, 100, 300 and 1000 mg/kg/day, no toxic effects were observed. Therefore, NOAEL was considered to be 1000 mg/kg/day for both repeated dose toxicity and reproductive toxicity. This chemical is not genotoxic, based on negative results in bacterial mutation test and chromosomal aberration test *in vitro*.

Environment

Dimethyl 2,6-naphthalenedicarboxylate is stable in water ($T_{1/2}$ = 263 days at pH 7 at 25°C). This chemical is not readily biodegradable (OECD 301 C: 7% after 28-day) and moderately bioaccumulative (BCF in Carp = 6.1~63).

No toxicity was observed up to the maximum dispersible concentration with a dispersant (THF/HCO-30). For testings in algae, *Selenastrum capricornutum* (72-h EC_{50}, 72-h NOEC), in fish, Medaka (96-h LC_{50}, 14-day LC_{50} of *Oryzias latipes*), and in daphnid, *Daphnia magna* (24-h EC_{50} for immobilisation), all results were more than 0.1 mg/l, which is the highest concentration that this chemical can be dispersed. For the daphnid reproduction test, 24-h EC_{50} was 0.02 mg/l, which was also the maximum dispersible concentration using a different dispersant (TMF/HCO-50).

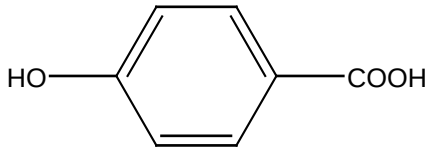
Exposure

The production volume is ca. 250 tonnes/year in 1996 in Japan. All of this produced in Japan is used as monomer unit of polyester, and no consumer use is reported.

A generic fugacity model (Mackey level III) shows that this chemical will distribute mainly into the water phase (87.9%) when it is discharged into water.

NATURE OF FURTHER WORK RECOMMENDED

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	99-96-7
Chemical Name	4-Hydroxybenzoic acid
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Oral LD_{50} of 4-hydroxy benzoic acid for rats is more than 2,000 mg/kg. This chemical is considered to be slightly irritating to skin and moderate to eyes, and a mild skin sensitizer. In an OECD combined repeat dose and reproductive/developmental toxicity study in rats at 40, 200 and 1,000 mg/kg/day, this chemical induced rale and rhinorrhea, indicative of imitation to respiratory tract irritation, and small fluctuation of blood chemistry with no changes of histopathological findings and organ weights. These changes of blood chemistry are considered not to be adverse. Therefore, no sign of toxic effects in repeated dose toxicity testing were detected at the highest dose of 1,000 mg/kg/day. Reproductive toxicity was not observed up to the highest test dose of 1000 mg/kg/day, suggesting no reason for concern. This chemical is not genotoxic, based on negative results of bacterial mutation test and chromosomal aberration test *in vitro*. In vaginal cornification and uterotrophic assay of mice, this chemical showed estrogenic response.

Environment

4-Hydroxybenzoic acid is readily biodegradable (OECD 301C: 100 % after 28-day), and low bioaccumulative based on Log P_{ow} value (1.37 at 25 °C).

Toxicity of this chemical seems to be relatively low to aquatic organisms because all toxicity data to test organisms belonging to three trophic levels were higher than 32 mg/l. For the algal test (*Selenastrum capricornutum*), 72-h EC_{50}, 72-h NOEC and 96-h EC_{50} are 68.5 mg/l, 32.0 mg/l and 42.8 mg/l, respectively. For testing in daphnids, *Daphnia magna*, both 48-h EC_{50} for immobilisation and 21-day EC_{50} for reproduction were more than 100 mg/l. LC_{50}s of *Oryzias latipes* were >100 mg/l (48 hours), 92.8 mg/l (72 hours) and 92.8 mg/l (72 hours), 14-day LC_{50} was 66.5 mg/l. No data are available for effects on terrestrial organisms.

Exposure

It is produced ca. 10,000 tons/year by one company in Japan, and 142 tons (ca. 1.4 %) is wasted through a waste-water treatment plant with a removal rate of 97 % together with 4.4×10^9 L/year effluent into sea. This chemical is used as intermediate for pesticide, antiseptics and pharmaceuticals. No consumer use is reported.

A generic fugacity model (Mackey level III) shows that most (99.5%) of this chemical will be distributed in water phase after discharged into water.

NATURE OF FURTHER WORK RECOMMENDED