OECD
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Screening Information Data Set
SIDS
for High Production Volume Chemicals

Organisation for Economic Co-operation and Development
OECD Initial Assessment

VOLUME 6
Part 1

Processed by UNEP Chemicals

June 2000

A Contribution to IPCS
International Programme on Chemical Safety

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

UNITED NATIONS

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New York and Geneva, 2000

This publication is a contribution to the Inter-Organization Programme for the Sound Management for Chemicals (IOMC).

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, FAO, WHO, UNIDO, and OECD (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safty. In January 1998, UNITAR formally joined the IOMC as a Participating Organization. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

UNEP CHEMICALS

June 2000

FOREWORD

Since 1988, the Member countries of the Organisation for Economic Co-operation and Development (OECD) have been working with one another and with their chemical industry to systematically investigate High Production Volume (HPV) existing chemicals. The objective of the work is to undertake an initial assessment of the risk posed by these chemicals to human health and the environment. The set of data elements needed for this exercise has been entitled the "Screening Information Data Set" or SIDS. Based on the SIDS and additional information when it is available, OECD member countries make a decision as to whether HPV chemicals should be considered as: (i) of low priority for further work, (ii) warranting special attention due to specific properties or effects, (iii) candidates for any further information gathering or testing, or (iv) candidates for further in-depth review with a view to possible risk reduction action.

The SIDS initial assessments for HPV chemicals prepared by OECD Member countries are discussed in a forum comprising experts from government and industry nominated by OECD Member countries as well as experts nominated by the International Programme on Chemical Safety (IPCS) for other countries. This process results in initial assessments that are widely acceptable. The SIDS project leads to assessments which are less comprehensive in nature than the IPCS risk assessment contained in the Environmental Health Criteria (EHC) documents but can be regarded as an important complement.

The OECD Council Decision-Recommendation on the Co-operative Investigation and Risk Reduction of Existing Chemicals [C(90)163/Final of 31 January 1991] requested the International Register of Potentially Toxic Chemicals (IRPTC) of the United Nations Environment Programme (UNEP) to make the information obtained from the co-operative investigation of existing chemicals available worldwide. Therefore UNEP Chemicals has produced from the SIDS initial assessment reports this document presented as OECD and UNEP chemicals contribution to IPCS.

The information is provided as an indication of the current state of knowledge of these chemicals based on the SIDS, but does not presume to be comprehensive. The co-operating organizations in IPCS (UNEP, ILO, WHO) and OECD disclaim all liability for direct or consequential damages resulting from the use of the SIDS Initial Assessment data.

Additional copies of this publication can be obtained from UNEP Chemicals in Geneva:

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Electronic version of this publication is accessible from OECD (http://www.oecd.org./ehs/) and UNEP Chemicals (http://irptc.unep.ch/irptc/) web pages or directly at the following address: http://irptc.unep.ch/irptc/sids/sidspub.html.

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INTRODUCTION

The OECD Screening Information Data Sets (SIDS) project is a cooperative effort of OECD countries designed to collect information on High Production Volume chemicals. One of the goals of the SIDS project is to locate the data needed for the initial assessment of these chemicals and to generate data which were lacking. This data often has been derived from unpublished studies or reports. Accordingly, the SIDS assessments are in many cases a unique source of information which has not been available before. The SIDS publications constitute a unique response of OECD and UNEP Chemicals to the recommendations of UNCED Agenda 21, to accelerate assessments of chemicals and enhance information exchange.

SIDS offer information and data on chemicals and their effects including such fields as:

-physico-chemical properties
-production data
-health effects
-analysis
-use
-effects on organisms and ecosystems
-environmental fate
-regulatory measures

UNEP/Chemicals, which among other objectives works to facilitate access to information needed for health and environmental risk assessment of chemicals, co-operates by integrating the SIDS dossiers produced by OECD countries into a single document for world wide distribution.

Whenever available, relevant data from UNEP Chemicals' "IRPTC Legal File" have been added to provide further information to the reader. SIDS publications are distributed free of charge to more than 1000 addresses around the world and are also available on direct request from UNEP Chemicals.

The present document represents the second series of OECD Initial Assessments that have been processed through UNEP chemicals. Starting with volume 4, the format used reflects the manner in which the data has been collected and submitted by the OECD sponsor countries.

Previous issues

SIDS Publication Vol. 1

- **(part 1)**: 2-butene; 1-octadecanol; neopentyl glycol; dipentaerythritol; pentaerythritol; copper phtalocyanine; 2,3,5,6-tetrachloropyridine; 2,3,4-trichloro-1-butene.
- **(part 2)**: isoctyl acrylate; 1,2-butanediol; nicotinic acid; aminotri(methylene phosphonic acid); t-butyl hydroperoxide; camphene.

SIDS Publication Vol. 2

- p-toluenesulfonamide; trimethylolpropane; m-nitroaniline; 2,6-di-tert-butylphenol; p-phenetidine; m-anisidine; 2,3-dichloronitrobenzene; dehydro-beta-linalool.

SIDS Publication Vol. 3

- **(part 1)**: urea; benzaldehyde; dimethyldioctadecylammonium chloride; diethylenetriamine; PBTC.
- **(part 2)**: cyclohexanone; hexamethylenediamine; 1,3-pentadiene
- **(part 3)**: dodecanedioic acid; sodium chloroacetate; texanol; chloroacetic acid.

SIDS Publication Vol. 4

- (**part 1**): acetone cyanohydrin; L-ascorbic acid; butanedioic acid, methylene; and 2,4-dinitrotoluene.
- (**part 2**): sodium dodecyl sulfate; triethanolamine; and N,N-dimethylamino-2-ethanol.

SIDS Publication Vol. 5

- (**part 1**): o-cresol; 1,4-dicyanobutane; 1-dodecanol; glutaraldehyde.
- (**part 2**): ethylene; maleic acid, dibutylester; methanesulfinic acid, aminoimino; triethylphosphate; vanillin.

ACETONE

CAS NO. 67-64-1

SIDS Initial Assessment Report (SIAR) for the 9th SIAM

Place: Paris, France Date: June 29-30, 1999
July 1, 1999

Chemical Name: Acetone

CAS No: 67-64-1

Sponsor Country: USA

National SIDS Contact Point in Sponsor Country:

Dr. Oscar Hernandez
Director, Risk Assessment Division
U.S. Environmental Protection Agency
Office of Pollution Prevention and Toxics (7403)
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HISTORY:

This high production volume (HPV) chemical was assigned to the USA in Phase 4 of the OECD HPV voluntary testing program. A SIDS Dossier was prepared by the Chemical Manufacturer's Association and submitted to the National SIDS Contact Point (USA) on March 14, 1997. The draft SIAR was reviewed on March 7, 1998 at SIAM 7 and the conclusions on the environment were accepted. Modifications to the health part were made in accordance with the comments received from the participants.

COMMENTS:

Deadline for Circulation:

Date of Circulation:

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

SHORT SUMMARY OF CONCLUSIONS OF INITIAL ASSESSMENT WHICH SUPPORTS THE RECOMMENDATIONS

Summary of hazard assessment

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/m^3 and in rats at 26,100 mg/m^3. 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.

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.

Summary of general exposure information

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.

IF FURTHER WORK IS RECOMMENDED – INDICATE ITS NATURE

None recommended

FULL SIDS SUMMARY

CAS NO: 67-64-1		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Freezing. Point			-94.6 °C
2.2	Boiling Point			56.1 °C at 760 mm Hg
2.3	Vapor Pressure			182 mm Hg at 20 °C 400 mm Hg at 39.5 °C
2.4	Partition Coefficient			-0.24 (Log Kow)
2.5	Water Solubility			100% at 20 °C
2.6	Flash Point			Cleveland open cup: -9 °C Tag closed cup: -17 °C
2.7	Flammability			Lower limit : 2.2% (v/v) at 25 °C Upper limit : 13.0% (v/v) at 25 °C
2.8	Autoignition Temperature			465 °C
2.9	Specific Gravity			0.791 at 20 °C
ENVIRONMENTAL FATE/BIODEGRADATION				
3.1.1	Photodegradation		 Calculated Calculated	Undergoes slow photolysis Water: $T_{1/2}$ >43 hr Air : $T_{1/2}$ = 80 hr
3.1.2	Stability in Water		SRC Program	Does not hydrolyze
3.1.3	Stability in Soil		SRC Program	Log K_{OC} = 0.30 (Calculated)
3.2	Monitoring Data			Water (µg/L): residential well water : 2 - 7 sea water : 5 - 53 ground water : 12 - 25 lake water : 1 - 50 storm water runoff : 0 - 100 cloud water : 0 - 17,300 industrial wastewater : 138 - 37,709 landfill leachate : 50 - 62,000 Air (µg/m^3): inside office building : 7.1 - 28.5 inside home : 9.5 - 81 urban street : 2.4 - 306 nonsmoking workplace : 4.7 - 415 inside aircraft cabin : 7.1 - 560 human breath : 230 - 11,285 smoking workplace : 9.5 - 21,085
3.3	Transport/Distribution		Fugacity Level 1 Calculated Measured	Distribution: Air :71.0% Water : 28.6% Soil : 0.0% Partition Coefficients: Octanol/Water : 0.58 Water/Air: 334

3.4	Type of Biodegradation			aerobic anaerobic
3.5	Biodegradation		OECD 301D	Freshwater: BOD_5 : 14% BOD_{15} : 74% BOD_{28} : 74% Seawater : BOD_5 : 38% BOD_{10} : 67% BOD_{15} : 69% BOD_{20} : 76%
3.6	Oxygen Demand			Theoretical (ThOD): 2.20 g O_2/g Chemical (COD) : 2.00 g O_2/g
3.7	Bioconcentration			Atlantic Cod BCF : 0.65
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish			LC_{50} (mg/L) : Fathead minnow : 15,000 Japanese medaka : 14,300 Mosquito fish : 13,000 Goldfish : >5000 Golden orfe : 9880 Bluegill sunfish : 8300 Rainbow trout : 7400 Brook trout : 6070
4.2	Acute Toxicity to Aquatic Invertebrates			LC_{50} (mg/L) : *Nitocra spinipes* : 16,700 *Daphnia magna* : 15,800 *Daphnia pulex* : 8800 *Daphnia cucullata*: 7635 *Artemia salina* : 2100
4.3	Toxicity to Aquatic Plants			NOEC (mg/L) : *Scenedesmus quadricauda* : 7500 *Selenastrum capricornutum* : 7000 *Chlorella pyrenoidosa* : 3400 *Scenedesmus pannonicus* : 4740 *Lemna gibba*: 5400 *Lemna minor*: 5400
4.4	Toxicity to Bacteria, Diatoms, and Protozoa			NOEC (mg/L) : *Escherichia coli* : 25,000 *Nitzschia linearis* : 11,610 *Skeletonema costatum* : 6000 *Chilomonas paramecium* : 3520 *Uronema parduczi* : 1710 *Pseudomonas putida* : 1700 *Microcystis aeruginosa* : 530 *Entosiphon sulcatum* : 28
4.5.2	Chronic Toxicity to Aquatic Invertebrates			NOEC (mg/L) : *Ceriodaphnia dubia* : 1866 *Daphnia magna* : 1660
4.6.1	Toxicity to Soil Dwelling Organisms		Predicted	NOEC (mg/L) : *Lumbricus terrestris* : >1000
4.6.2	Toxicity to Terrestrial Plants			NOEC (mg/L) : Ryegrass : >80 Radish : >80 Lettuce : >80 Corn : >80

4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species			NOEC (mg/kg) : Japanese quail : >40,000 ring-neck pheasant : >40,000
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	rat mouse rabbit		LD_{50} : 8400 mg/kg LD_{50} : 5250 mg/kg LD_{50} : 5300 mg/kg
5.1.2	Acute Inhal. Toxicity	rat		LC_{50} : 50,000 mg/m^3
5.1.3	Acute Dermal Toxicity	rabbit		LD_{50} : >15,700 mg/kg
5.2.1	Skin Irritation	rabbit		not irritating
5.2.2	Eye Irritation	rabbit	Draize	highly irritating
5.2.3	Respiratory Irritation	mouse	RD_{50}	weakly irritating
5.3	Sensitization	mouse	ear swelling	not sensitizing
5.4	Repeated Dose Toxicity	mice : male mice : female	OECD 408	NOEL : 1% (2258 mg/kg/day) 2% (5945 mg/kg/day)
		rat : male rat : female	OECD 408	NOEL : 1% (900 mg/kg/day) 5% (3100 mg/kg/day)
5.5	Genetic Toxicity In Vitro		OECD 471	bacterial test: reverse mutation : neg. At 10 mg yeast gene mutation : neg. at 5% forward mutation : neg. At 500 mM prophage induction : neg. at 10% non-bacterial test : chromosomal aberration : neg. at 5 mg/mL sister chromatid exchange : neg. at 5 mg/mL cell transformation : neg. at 0.5% alkaline elution : neg. at 1% mouse lymphoma : neg. At 30 mg/mL chromosomal malsegregation : pos. at 6.8%
5.6	Genetic Toxicity In Vivo	rat mouse hamster	OECD 474	embryo cell transformation assay : rat : negative at 0.1% mouse : negative at 0.01% micronucleus assay : negative at 865 mg/kg
5.7	Carcinogenicity	mouse		NOEL : 0.2 mL (dermal)
5.8	Toxicity to Reproduction	rat		NOEL : 0.5% (drinking water)
5.9	Developmental Toxicity/ Teratogenicity	rat mouse	OECD 414	NOEL : teratogenicity : >26,110 mg/m^3 developmental : 5220 mg/m^3
			OECD 414	NOEL : teratogenicity : >15,665 mg/m^3 developmental : 5220 mg/m^3
5.11	Experience with Human Exposure			see SIAR text

1. IDENTITY

Acetone is a clear colorless liquid that is highly flammable and infinitely soluble with water. Reagent grade acetone can contain up to 0.5% water as well as small amounts of other polar solvents. Acetone vapors have a characteristic sweet and fruity odor at low concentrations. The odor threshold for humans has been reported at values ranging from about 24 to 1615 mg/m^3, with 235 to 339 mg/m^3 being the range of odor recognition thresholds for most people and 95 mg/m^3 being the odor detection threshold for unadapted individuals (Devos *et al.*, 1990; Leonardos *et al.*, 1969).

Virtually every organ and tissue within the human body contains some acetone which is one of three biochemicals collectively referred to as ketone bodies. Acetone is produced within the body as a result of the breakdown and utilization of stored fats and lipids as a source of energy (Wieland, 1968). Consequently, conditions such as strenuous physical exercise and prolonged dieting, which lead to a break-down of fat within the body, may result in higher than average amounts of acetone in the bloodstream (Williamson and Whitelaw, 1978). Measurable amounts of acetone are continuously being excreted in the breath and urine of humans as a result of its high volatility and solubility in water (Wigaeus *et al.*, 1981).

2. GENERAL INFORMATION ON 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 (Bizzari, 1996). Production capacity in the United States constituted about 33% (1.3 million tonnes) of the global capacity, while the capacity in Western Europe and Asia (including Japan) was about 31% (1.2 million tonnes) and 19% (0.7 million tonnes), respectively. The average annual production of acetone is expected to rise at a global rate of 3.3% until the year 2000.

Major end uses of acetone can be divided into three separate categories. These include use as: i) a chemical feedstock, ii) a formulating solvent for commercial products, and iii) an industrial process solvent. The majority of worldwide production is used as a feed-stock to prepare methyl methacrylate/methacrylic acid and Bisphenol A (Bizzari, 1996). Several aldol chemicals, such as methyl isobutyl ketone, methyl isobutyl carbinol, isophorone, and diacetone alcohol, are also prepared directly from nascent acetone. Acetone has many favorable properties that make it useful as a formulating solvent for a variety of paints, inks, resins, varnishes, lacquers, surface coatings, paint removers, and automotive care products. As an industrial process solvent, acetone is used to manufacture cellulose acetate yarn, polyurethane foam, vitamin C, and smokeless gun powder. At least 75% of the acetone consumed in 1995 was used in captive processes for the preparation of downstream chemicals, while only about 12% was used as a formulating solvent for commercial products.

Large-scale commercial production of acetone is generally accomplished by one of two processes. The first, and by far the most common, is through the acid catalyzed hydro-lytic cleavage of cumene hydroperoxide (Bizzari, 1996). Acetone and phenol are formed as co-products in this reaction at a ratio of 0.61 to 1.00. The second process, catalytic dehydrogenation of isopropyl alcohol, accounted for about 6% of the US production in 1995. Other methods, such as biofermentation, propylene oxidation, and diisopropyl-benzene oxidation, are either experimental in nature or account for a very small percentage of worldwide production.

The release of acetone by chemical manufacturers' and end users accounts for a very small percentage (1%) of the estimated 40 million tonnes that are annually released to the environment (Table 1). Vegetative releases, forest fires, and other natural events account for nearly half (47%) of the estimated annual emissions of acetone, with another 50% resulting from the tropospheric photooxidation of propane and other alkanes and alkenes (Singh *et al.*, 1995). Since 1993, US industries have not been required to report their TRI (Toxic Release Inventory) emissions of acetone as required under SARA Title III, Section 313. In 1992, 2548 facilities reported a total environmental release of 60,904 tonnes of acetone with 60,904 tonnes emitted to the air, 454 tonnes to water, 254 tonnes to land, and 1446 tonnes injected underground (USEPA, 1994).

Table 1
Estimated average annual emissions of acetone from different sources

Acetone Source	Global Annual Emissions (tonnes x 10^{-6}) Average	Range
Primary Anthropogenic		
stationary sources	0.5	0.4 - 0.7
mobile sources	0.3	0.2 - 0.3
Primary Biogenic		
Vegetation	9	4 - 18
Secondary Anthropogenic		
propane oxidation	17	15 - 20
isobutane & isopropane oxidation	2	1 - 3
isobutene & isopropene oxidation	1	1 - 2
myrcene oxidation	0.2	0.2 - 0.3
Biomass Burning	10	8 - 12
Total	40	30 - 46

Acetone can be found as an ingredient in a variety of consumer products ranging from cosmetics to processed and unprocessed foods. Acetone has been rated as a GRAS (Generally Recognized as Safe) substance when present in beverages, baked goods, deserts, and preserves at concentrations ranging from 5 to 8 mg/L (Oser and Ford, 1973). It can also be detected in measurable amounts in onions, grapes, cauliflower, tomatoes, milk, cheese, beans, peas, and other natural foods. Milk from dairy cattle may contain very high levels of acetone, ranging as high as 225 mg/L for the milk from hyperketo-nemic cows (Andersson and Lundström, 1984). Acetone has also been identified, but not quantified, in air samples from numerous plants and microorganisms. In addition to its elimination in the expired air of all mammals, acetone is excreted as a metabolic end-product by some bacteria (*Clostridium butylicium*), molds, fungi (*Paecilaomyces variotii*), and algae (*Cryptomonas ovata palustris*) (George *et al.*, 1983; Sunnesson *et al.*, 1996; Collins and Kalnins, 1966).

Acetone is often detected as an end product of thermal combustion and biological decom-position. Except for tree foliage, the release of acetone from living vegetation has been poorly quantified (Khalil and Rasmussen, 1992). Emissions from poultry manure (530 g/kg), backyard waste incinerators (4.0 g/kg), pine wood combustion (2.8 g/kg), neoprene combustion (990 mg/kg), and wood burning stoves (145 mg/kg) have all been measured and reported (Smith *et al.*, 1977; Yocum *et al.*, 1956; Hartstein and Forshey, 1974; Lipari *et al.*, 1984).

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 *General Discussion*

A level I fugacity analysis revealed that acetone preferentially locates in the air compart-ment when released to the environment (Table 2). The fugacity analysis was based on the equilibrium established after the release of 100 moles (5.8 kg) of acetone into the envi-ronment (Mackay and Paterson, 1981). A substantial amount of acetone can also be found in water, which is consistent with the high water to air partition coefficient and its small, but detectable, presence in rain water, sea water, and lake water samples. Very little acetone is expected to reside in soil, biota, or suspended solids. This is entirely consistent with the physical and chemical properties of acetone and with measurements showing a low propensity for soil absorption and a high preference for moving through the soil and into the ground water (Steinberg and Kreamer, 1993).

Table 2
State-state distribution of acetone in the environment

Environmental Compartment	Mass Distribution (%)
Air	71.00
Water	28.58
Sediment	0.01
Soil	0.00
Biota	0.00
suspended solids	0.00

Acetone meets the OECD definition of readily biodegradable which requires that the biological oxygen demand (BOD) is at least 70% of the theoretical oxygen demand (THOD) within the 28-day test period (Table 3). Studies by the standard dilution method have shown greater than 75% of the acetone is biodegraded when using non-acclimated sewage seed from either a freshwater or a sea water sanitary waste treatment plant. These results compare favorably with the values from biodegradability tests performed according to OECD 301D guidelines. Using the OECD method, the BOD_5, BOD_{15}, and BOD_{28} for acetone were found to be 14%, 74%, and 74%, respectively (Waggy *et al.*, 1994). The BOD_5 of acetone has been measured by numerous investigators and produced values ranging from about 23% to 83% depending on the test and the type of sewage seed. The THOD of 2.20 g O_2/g of acetone has been found to be only slightly greater than the measured chemical oxygen demand (COD) value of 2.00 g O_2/g of acetone (Price *et al.*, 1974).

Studies with several different strains of anaerobic bacteria from municipal waste water treatment plants have shown that acetone is completely degraded to CO_2 following aceto-acetate formation through an initial carboxylation reaction and incorporated into the carbon cycle (Platen and Schink, 1989). Soil bacteria have also been shown to biode-grade acetone to CO_2 (Taylor *et al.*, 1980).

Table 3
The biological oxygen demand from acetone in water samples

Sample Type	Biological Oxygen Demand (g)				Author(s) (year)
	5 days	10 days	15 days	20 days	
freshwater	55	79	78	78	Lamb & Jenkins, 1952
freshwater	56	76	83	84	Price *et al.*, 1974
saltwater	38	67	69	76	Price *et al.*, 1974

Table 4
Comparison of the environmental fate and removal processes for acetone

Acetone Removal Process	Approximate Half-life (days)	Author(s) (year)
aqueous biodegradation	0.6	Rathbun *et al.*, 1993
volatilization river	6	Howard *et al.*, 1990
soil biodegradation	7	Sanders, 1995
total tropospheric removal	22	Meyrahn *et al.*, 1986
hydroxyl radical reaction	31	Meyrahn *et al.*, 1986
aqueous photolysis	40	Betterton, 1991
atmospheric photolysis	80	Meyrahn *et al.*, 1986
volatilization lake	100	Howard *et al.*, 1990

Two processes govern the photochemical removal of acetone from the troposphere: reaction with hydroxyl radicals and photolysis. The two processes occur at about equal rates in clear unpolluted skies yielding a total tropospheric lifetime of about 32 days (Meyrahn *et al.*, 1986). The reaction with hydroxyl radicals will predominate over photo-lysis in urban areas where hydroxyl radical concentrations are greater, and during cloudy winter-time conditions where photodecomposition is minimal. Rain out and other forms of wet deposition are considered to be minor tropospheric removal processes (Chatfield *et al.*, 1987). Calculated and measured rate constants have been used to estimate the elimination half-life ($t_{½}= 0.693/k_{calc}$) of acetone through various environmental processes (Table 4). These data show that acetone is rapidly biodegraded in water and that this is the dominant removal process in the environment. The slow removal of acetone from the troposphere indicates that it is relatively non-reactive and a minor contributor to urban ozone and peroxyacyl nitrate (PAN) concentrations (Derwent *et al.*, 1996).

3.1.2 *Predicted Environmental Concentration*

Measurable amounts of acetone can be found in both mobile and stationary emission sources (Table 5). The levels of acetone in the air from municipal landfills and cigarette smoke can be relatively high, but they are minor contributors to the total global mass. The direct release of acetone from vegetation is an important emission source that is often overlooked. In a qualitative evaluation, acetone was found to be emitted from all 22 of the forest plant species examined (Isidorov *et al.*, 1985).

Background levels of acetone in the atmosphere have been assessed from both ground level and airborne monitoring stations located throughout the world. The average acetone concentrations at rural ground level sites are generally lower than the values reported for urban areas (Table 6). The concentration of acetone in urban areas can show large unpre-dictable variations that are likely related to the amount of vehicle traffic and to the emis-sion of precursor alkanes and alkenes (Zweidinger *et al.*, 1988; Chatfield *et al.*, 1987). Airborne measurements of acetone in the upper troposphere and lower stratosphere reveal an average concentration of 190 to 285 ng/m^3 in these regions (Singh *et al.*, 1995).

Table 5
Mobile and stationary emissions of acetone

Emission Source	Airborne Concentration (mg/m^3)	Author(s) (year)
fuel or crude oil fire	0.02 - 0.16	Booher & Janke, 1997
automobile exhaust	0.09 - 4.50	Grimaldi *et al.*, 1996
factory fence line	1.9 - 9.7	Hoshika *et al.*, 1981
tree foliage	7.8 - 12.6	Khalil & Rasmussen, 1992
municipal landfill	15.7 - 77.1	Brosseau & Heitz, 1994
cigarette smoke	498 - 869	Euler *et al.*, 1996

Acetone has routinely been detected in the expired air of humans and in the air samples from many different occupied environments (Table 7). The levels in these samples can vary greatly, ranging from a few μg/m^3 to nearly 25 mg/m^3. Cigarette smoking, emissions from furnishings and construction materials, and excretion by the lung are perhaps the greatest contributors to indoor acetone levels. The acetone levels in indoor air are generally higher than those found outdoors (Jarke *et al.*, 1981).

Table 6
Background levels of acetone in urban and rural air samples

Location	Background Concentration (μg/m^3)	Range (μg/m^3)	Author(s) (year)
Smoky Mts, Tennessee	---	1.7 - 9.5	Arnts & Meeks, 1981
Copenhagen, Denmark	---	0.5 - 5.2	Granby *et al.*, 1997
Point Barrow, Alaska	2.4	0.7 - 6.9	Cavanagh *et al.*, 1969
Waldhof, Germany	3.8	---	Solberg *et al.*, 1996
Central Ontario	4.0	---	Shepson *et al.*, 1991
Eastern Georgia	4.3	0.0 - 15.9	Lee *et al.*, 1995
Los Angeles, California	3.8	0.2 - 15.2	Grosjean *et al.*, 1996
Ispra, Italy	4.7	---	Solberg *et al.*, 1996
Donan, France	4.7	---	Solberg *et al.*, 1996
Athens, Greece	---	1.7 - 18.3	Kalabokas *et al.*, 1997
Columbus, Ohio	5.0	0.0 - 21.8	Spicer *et al.*, 1996

Southern Germany	6.2	0.5 - 11.4	Slemr *et al.*, 1996
Western Colorado	---	2.4 - 8.3	Goldan *et al.*, 1995
Western Alabama	10.0	0.7 - 5.2	Goldan *et al.*, 1997
Sao Paulo, Brazil	---	0.5 - 7.4	Grosjean *et al.*, 1990
Rome, Italy	16.1	10.0 - 21.8	Possanzini *et al.*, 1996
Stockholm, Sweden	9.5	1.7 - 24.2	Jonsson *et al.*, 1985
Vancouver, Canada	19.2	8.3 - 30.9	Li *et al.*, 1997
Boston, Massachusetts	32.0	9.7 - 64.0	Kelly *et al.*, 1993
Houston, Texas	81.9	29.4 - 223.1	Kelly *et al.*, 1993

Table 7
Acetone concentration range in various airborne samples

Sample Type	Airborne Concentration ($\mu g/m^3$)	Author(s) (year)
inside office building	7.1 - 28.5	Daisey *et al.*, 1994
inside home	9.5 - 81	Lewis & Zweidinger, 1992
urban street	2.4 - 306	Jonsson *et al.*, 1985
nonsmoking workplace	4.7 - 415	Heavner *et al.*, 1996
inside aircraft cabin	7.1 - 560	Dechow *et al.*, 1997
human breath	230 - 11,285	Crofford *et al.*, 1977
smoking workplace	9.5 - 21,085	Heavner *et al.*, 1996

Fugitive stack emissions have been used to estimate fence line concentrations of acetone at three industrial sites. Airborne emissions reported under USEPA SARA Title III section 313 for the year 1989 or 1990 were used in conjunction with the USEPAs ISCST (Industrial Source Complex Short Term) dispersion model to calculate the highest 24-hr concentration and the highest average annual concentration of acetone at property sites beyond the fence line (Table 8). The highest average annual concentration at the three industrial sites ranged from 4.3 to 9.3 mg/m^3. Actual fence line measurements of acetone at five locations outside of the Eastman Chemical Company site in Kingsport, Tennessee showed that the average concentration ranged from 0.05 to 0.50 mg/m^3 which were notably lower than the predicted 24-hr average.

Table 8
Fugitive emissions of acetone and the resulting maximum predicted off-property concentrations

Company & Location	Fence Line Concentration (mg/m^3)	
	24-hr average	annual average
Eastman Chemical Co. Kingsport, TN	0.9	9.3
Hoechst-Celanese Corp. Narrows, WV	2.6	8.3
Hoechst-Celanese Corp. Rock Hill, SC	0.1	4.3

Acetone has been found in surface and ground water samples at concentrations that were highly dependent on the type of sample (Table 9). Ambient background levels of acetone are the result of both natural and commercial releases and are generally reflective of the physical processes affecting absorption from the air, movement through soil, and micro-bial biodegradation. A search of the open literature and the nearly 2000 entries in USEPAs STORET database revealed that acetone levels in natural water and industrial monitoring wells rarely exceeded 1 mg/L.

A USEPA-sponsored survey has determined the acetone concentrations in the discharge from 4000 industrial and publicly owned wastewater treatment plants (Table 10). The highest recorded individual concentration of 37.7 mg/L was found in the discharge from a paint and ink industry facility; whereas, the highest median concentration of 2.5 mg/L was associated with printing and publishing plants (Howard *et al.*, 1990). The highest reported aqueous acetone concentration was found in the wastewater from a specialty chemical manufacturing plant. Although wastewater acetone levels of about 200 mg/L were found in water samples from the primary influent at the wastewater treatment plant serving this manufacturing site, the levels in the receiving river water and sediment beyond the treatment plant were below the analytical detection limit (Jungclaus *et al.*, 1978). These results are in agreement with data showing that 94% of the acetone removed by a pilot-scaled wastewater facility occurs during secondary treatment (Bhattacharya *et al.*, 1996).

Table 9
Acetone concentration range in different water samples

Sample Type	Aqueous Concentration (μg/L)	Author(s) (year)
residential well water	2 - 7	Dewalle & Chain, 1981
sea water	5 - 53	Corwin, 1969
ground water	12 - 25	Sabel & Clark, 1984
lake water	1 - 50	Jungclaus *et al.*, 1978
storm water runoff	0 - 100	Line *et al.*, 1997
cloud water	0 - 17,300	Aneja, 1993
industrial wastewater	138 - 37,709	Howard *et al.*, 1990
landfill leachate	50 - 62,000	Brown & Donnelly, 1988

Predicted environmental concentrations (PECs) of acetone have been derived from the air and water monitoring data described above. The values listed in Table 11 have been taken from the published report that best provide a plausible worst case environmental concentration on both a global and regional scale. The $PEC_{(local)}$ and $PEC_{(global)}$ air concen-trations of 10,000 and 10 μg/m^3 were based on factory fence line concentrations (Table 5; Hoshika *et al.*, 1981) and ambient air concentrations for a remote region in the western US (Table 6; Golden *et al.*, 1995), respectively. The $PEC_{(local)}$ and $PEC_{(global)}$ water con-centrations of 2500 and 50 μg/L represent the highest median acetone concentration from an industrial wastewater treatment plant (Table 10; Howard *et al.*, 1990) and the highest reported natural water concentration of acetone from seawater (Table 9; Corwin, 1969).

3.2 Effects on the Environment

3.2.1 *Aquatic Effects*

As shown in Tables 12 and 13, acetone is minimally toxic to freshwater and marine or-ganisms exposed for 1 to 10 days. Acute NOEC for vertebrate and invertebrate organ-isms were greater than 3500 mg/L and the LC_{50} values were generally greater than 10,000 mg/L. The marine brine shrimp (*Artemia salina*) showed the greatest sensitivity to acetone with a 1-day LC_{50} value of 2100 mg/L.

When examined at a seawater concentration of 1.52%, acetone did not bioconcentrate in the tissues or organs of the Atlantic cod (*Gadus morhua*) (Rustung *et al.*, 1931). The 7-day EC_{50} values of greater than 10,000 mg/L and no observable effect levels of 5400 mg/L were similar for two species of aquatic duckweed, *Lemna gibba* and *Lemna minor* (Cowgill *et al.*, 1991). The 10-day LC_{50} values for acetone in the 3-brood test with *Daphnia magna* and *Ceriodaphnia dubia* were 4068 mg/L and 6693 mg/L, respectively (Cowgill and Millazo, 1991). The maximum acceptable concentration of acetone that did not affect the survival of *Daphnia magna* exposed for 28 days was approximately 2100 µL/L (1660 mg/L) (LeBlanc and Surprenant, 1983).

Table 10
Acetone concentrations in the discharge water from industrial and public wastewater treatment plants

Industrial Category	Number of Positive Occurrences	Median Acetone Concentration (µg/L)
nonferrous metal	2	6.6
textile mills	4	11.0
inorganic chemicals	8	13.8
porcelain/enameling	4	14.7
pesticide manufacturing	7	52.7
oil and gas extraction	5	59.2
pulp and paper	6	59.8
leather tanning	4	74.7
pharmaceuticals	6	75.4
mechanical products	6	84.4
photographic industries	1	94.9
publicly owned treatment works	40	96.8
organic chemicals	1	113.9
plastics and synthetics	10	164.1
petroleum refining	14	166.9
organics and plastics	24	374.4
explosives	23	388.0
auto and other laundries	2	437.5
electronics	12	441.2
rubber processing	1	604.4
transportation equipment	6	616.7
paint and ink	22	894.9
coal mining	1	2260.8
printing and publishing	7	2501.2

Table 11
Predicted environmental acetone concentrations

Area	Concentration Air (μg/m³)	Concentration Water (μg/L)
$PEC_{(local)}$	10,000	2500
$PEC_{(global)}$	10	50

3.2.2 *Terrestrial Effects*

The 5-day LC_{50} of acetone for Japanese quail (*Coturnix coturnix japonica*) and ring-neck pheasants (*Phasianus colchicus*) was greater than 40,000 mg/kg (Hill *et al.*, 1975). The EPAs ECOSAR program predicted a 14-day earthworm (*Lumbricus terrestris*) LC_{50} value of greater than 1000 mg/L (Meylan and Howard, 1998). Acetone vapors were shown to be relatively toxic to two types insects and their eggs. The time to 50% lethality (LT_{50}) was found to be 51.2 hr and 67.9 hr when the flour beetle (*Tribolium confusum*) and the flour moth (*Ephestia kuehniella*) were exposed to an airborne acetone concentration of 61.5 mg/m³ (Tunç *et al.*, 1997). The LT_{50} values for the eggs were 30-50% lower than for the adult. The direct application of acetone liquid to the body of the insects or surface of the eggs did not, however, cause any mortality.

The effects of acetone on the growth and germination of terrestrial plants and seeds has also been examined (Gorsuch *et al.*, 1990). A 168-hr exposure of ryegrass (*Lolium perenne*), radish (*Raphanus sativus*), and lettuce (*Lactuca sativa*) to acetone concen-trations as high as 80 mg/L did not cause any effects. The IC_{50} value obtained when tobacco pollen (*Nicotiana sylvestris*) was incubated with acetone for 18 hr was 20,500 mg/L (Kristen *et al.*, 1994). This value, however, conflicts with the 2-hr NOEC of 12 mg/L for the germination of another tobacco plant species, *Nicotiana tabacum* (Schubert *et al.*, 1995).

Table 12
Acute and chronic toxicity of acetone to aquatic invertebrates

Species	Duration (hr)	NOEC (mg/L)	LC_{50} (mg/L)	Author(s) (year)
Freshwater Organisms				
Water flea *Daphnia magna*	240	---	4068	Cowgill & Milazzo,
Water flea *Ceriodaphnia dubia*	240	1866	6693	Cowgill & Milazzo,
Water flea *Daphnia magna*	48	8500	15,800	Sloof *et al.*, 1983
Water flea *Daphnia pulex*	48	5800	8800	Canton & Adema,
Water flea *Daphnia cucullata*	48	---	7635	Canton & Adema,
Snail *Planorbella trivolvis*	96	≥ 100	---	Ewell *et al.*, 1986
Aquatic earthworm *Lumbriculus*	96	≥ 100	---	Ewell *et al.*, 1986
Sideswimmer *Gammarus fasciatus*	96	≥ 100	---	Ewell *et al.*, 1986

Pillbug *Caecidotea*	96	≥ 100	---	Ewell *et al.*, 1986
Flatworm *Dugesia*	96	≥ 100	---	Ewell *et al.*, 1986
Marine Organism				
Harpacticoids *Nitocra spinipes*	96	---	16,700	Lindén *et al.*, 1979
King crab *Lithodes antarcticus*	168	750	---	Lombardo *et al.*, 199
Grass shrimp *Palaemonetes pugio*	288	---	69,400	Rayburn & Fisher,
Brine shrimp *Artemia salina*	24	---	2100	Price *et al.*, 1974

Table 13
Acute toxicity of acetone to aquatic vertebrates

Species	Duration (hr)	NOEC (mg/L)	LC_{50} (mg/L)	Author(s) (year)
Freshwater Fish				
Fathead minnow *Pimephales*	48	12,000	15,000	Sloof *et al.*, 1983
Fathead minnow *Pimephales*	96	---	9100	Cardwell *et al.*, 1974
Japanese medaka *Oryzias latipes*	48	9500	14,300	Sloof *et al.*, 1983
Mosquito fish *Gambusia affinis*	96	10,000	13,000	Wallen *et al.*, 1957
Goldfish *Carassius auratus*	24	5000	---	Bridié *et al.*, 1979
Brook trout *Salvelinus fontinalis*	96	---	6070	Cardwell *et al.*, 1974
Golden Orfe *Leuciscus idus*	48	---	9880	Juhnke & Lüdemann,
Bluegill sunfish *Lepomis*	96	3700	8300	Cairns & Scheier,
Rainbow trout *Salmo gairdnerii*	48	5700	7400	Sloof *et al.*, 1983
Bleak *Alburnus alburnus*	96	---	11,000	Lindén *et al.*, 1979
Guppy *Poecilia reticulata*	48	6700	9600	Sloof *et al.*, 1983
Hydra *Hydra oligactis*	48	11,500	13,500	Sloof *et al.*, 1983
Pond snail *Lymnaea stagnalis*	48	3500	7000	Sloof *et al.*, 1983
Freshwater Amphibians				
Mexican axolotl *Ambystoma*	48	12,000	20,000	Sloof & Baerselman,
African clawed toad *Xenopus leavis*	48	20,000	24,000	Sloof & Baerselman,
Insects				
Mosquito *Aedes aegypti*	48	3500	15,000	Sloof *et al.*, 1983
Mosquito *Culex pipens*	48	8000	17,000	Sloof *et al.*, 1983

3.2.3 *Other Effects*

The ability of acetone to inhibit cell multiplication has been examined in a wide variety of microorganisms (Table 14). The results have generally indicated mild to minimal toxicity with NOECs greater than 1700 mg/L for exposures lasting from 6 hr to 4 days. Longer exposure periods of 7 to 8 days with bacteria produced mixed results; but overall the data indicate a low degree of toxicity for acetone. The only exception to these findings were the results obtained with the flagellated protozoa (*Entosiphon sulcatum*) which yielded a 3-day NOEC of 28 mg/L. This was likely a spurious value, however, and the result could not be verified from the tests with other species of protozoa.

The four species of green algae examined in the multiplication inhibition test were relatively insensitive to the effects of acetone treatment. The lowest NOEC of 3400 mg/L was obtained following the 48-hr treatment of *Chlorella pyrenoidosa*. The lowest NOEC for bacteria, in contrast, was found to be 530 mg/L following the 192-hr treatment of *Microcystis aeruginosa*. The IC_{50} values for acetone have also been measured and compared using commercial and natural bacterial test cultures. The IC_{50} value of 48,000 mg/L obtained using the Polytox™ test system was found to compare favorably with the IC_{50} of 48,619 mg/L for an activated sludge test culture (Nirmalakhandan *et al.*, 1994). The EC_{50} value for acetone in the Microtox™ test using the bacteria *Photobacterium phosphoreum* was found to be about 14,000 mg/L (Chen and Que Hee, 1995).

Table 14
Acetone toxicity thresholds in the cell multiplication inhibition test

Species	Duration (hr)	NOEC (mg/L)	Author(s) (year)
Flagellated protozoa *Entosiphon sulcatum*	72	28	Bringmann & Kühn,
Bacteria *Microcystis aeruginosa*	192	530	Bringmann & Kühn,
Bacteria *Pseudomonas putida*	16	1700	Bringmann & Kühn,
Ciliated protozoa *Uronema parduczi*	20	1710	Bringmann & Kühn,
Green algae *Chlorella pyrenoidosa*	48	3400	Sloof *et al.*, 1983
Flagellated protozoa *Chilomonas*	48	3520	Bringmann & Kühn,
Green algae *Scenedesmus*	48	4740	Sloof *et al.*, 1983
Marine diatom *Skeletonema costatum*	120	6000	Cowgill *et al.*, 1989
Green algae *Selenastrum*	96	7000	Sloof *et al.*, 1983
Green algae *Scenedesmus*	168	7500	Bringmann & Kühn,
Freshwater diatom *Nitzschia linearis*	120	11,610	Patrick *et al.*, 1968
Bacteria *Escherichia coli*	1.5	25,000	Reinhartz *et al.*, 1987

3.3 Initial Assessment for the Environment

Considering the availability of acute data for algae, crustaceans, and fish an assessment factor of 100 was used to calculate a predicted no effect concentration (PNEC) for acetone in an aqueous environment. Using the LC_{50} value of 2100 mg/L obtained with the marine brine shrimp (*Artemia salina*), the lowest PNEC value for acetone was calculated to be 21 mg/L.

The lowest PNEC was compared to the $PEC_{(local)}$ and $PEC_{(global)}$ values for water (Table 11) to calculate PEC/PNEC ratios. The $PEC_{(global)}$ of 50 µg/L produced a PEC/PNEC ratio of 0.002; whereas, the $PEC_{(local)}$ value of 2500 µg/L yielded a ratio of 0.12. These margins of exposure are each less than one; acetone was therefore judged to have low environmental risk potential.

4. HUMAN HEALTH

4.1 Human Exposure

Virtually every organ and tissue within the human body contains some acetone, which is one of three biochemicals collectively referred to as ketone bodies. Measurable amounts of acetone are continuously being excreted in the breath and urine of humans as a result of its high volatility and solubility in water (Brega *et al.*, 1991). The acetone found in the body is produced in the liver following the utilization of stored fats and lipids as a source of energy (Landau and Brunengraber, 1987). The ability of humans to naturally produce and dispose of acetone may to a large degree explain its relatively low toxicity following external exposure to moderate amounts of the vapor or liquid (Wigaeus *et al.*, 1981; Haggard *et al.*, 1944). The background levels of acetone in blood and urine can vary widely but tend to average 1 to 2 mg/L. The levels in expired alveolar air are, however, about 1000-fold lower at 1 µg/L (Morgott, 1993).

Exogenous exposures to acetone typically occur by the pulmonary route. The high blood- to-air partition coefficient suggests that a large percentage of inhaled acetone will be absorbed into the body; the occurrence, however, of a peculiar wash-in/wash-out effect effectively reduces the uptake to about 50% (Johanson, 1991). The miscibility of acetone in the fluid layers lining the lung appears to be responsible for the wash-in/wash-out phenomenon. Under normal conditions acetone is efficiently and effectively metabolized to a variety of products that are used as building blocks for the synthesis of glucose, amino acids, and other more complex biochemicals (Argilés, 1986). Sustained high blood levels of acetone can result in the induction of enzymes responsible for its own metabolism and the metabolism of other chemicals (Koop and Casazza, 1985; Forkert *et al.*, 1994). This compensatory response to high blood levels is responsible for the ability of acetone to potentiate the hepato- and nephrotoxicity of chemicals that undergo metabolic activation by microsomal enzymes to form toxic metabolites.

4.1.1 *Occupational Exposure*

High airborne concentrations of acetone have been found in a variety of occupational environments (Table 15). These levels reflect the high volatility and low intrinsic toxicity which combine to make acetone an attractive industrial process solvent. The predominant route of both occupational and consumer exposure to acetone is through vapor inhalation. Oral and dermal uptake can occur, but the body burden from these exposure routes is relatively small compared to respiratory absorption. Impermeable gloves should be worn together with a supplied air respirator when working with liquid acetone or when the vapor concentration exceeds the occupational exposure limit.

Table 15
Exposure to acetone in various occupations

Factory Type	8-Hour TWA Concentration (mg/m^3)	Author(s) (year)
automotive repair shop	12 - 77	Winder & Turner, 1993
print shop	6 - 235	Nasterlack *et al.*, 1994
electronics plant	2 - 648	Hallock *et al.*, 1993
fiberglass fabrication	40 - 1580	DeRosa *et al.*, 1996
varnish production	5 - 1448	Franco *et al.*, 1986
cellulose acetate factory	12 - 2876	Satoh *et al.*, 1996

The estimated human exposure (EHE) value for workplace employees has been set at 1780 mg/m^3 based on an examination of the data in Table 15. This exposure value for acetone also agrees well with the occupational exposure limits established in many countries and provides some assurance that it represents a plausible worst case concentration.

4.1.2 *Consumer Exposure*

Acetone can be found in wide variety of consumer and commercial products but only a few are known to contain high concentrations (Sack *et al.*, 1992). These include paints and paint-related products, such as paint thinners, finger nail polish removers, automotive waxes and tar removers (Table 16). Consumer exposures will most likely occur by the inhalation route and will be the greatest for those using adhesives, automotive products, and paint-related products that contain a high percentage of acetone.

Table 16
Average acetone concentration in various consumer product categories

Product Category	Number Products Assayed	Product Prevalence (%)	Average Concentration (%)
oils, greases & lubricants	71	5.3	0.2
cleaners for electronic equipment	111	16.1	0.3
household cleaners & polishers	463	10.8	0.3
miscellaneous products	76	17.2	7.4
fabric & leather treatments	91	14.6	12.9
adhesive-related products	69	24.3	18.8
automotive products	111	22.7	28.1
paint-related products	167	51.5	29.3

Using a USEPA modelling program entitled SCIES (Screening Consumers Inhalation Exposure Software), a 45-min exposure model was created for the application of a spray contact adhesive that contained 21% acetone. This scenario was selected because it depicts a realistic short duration exposure that involves the direct indoor air release of large amounts of acetone. Although consumer products such as nail polish removers can contain 70 to 80% acetone, the resulting air acetone concentrations are generally lower than those described in the following scenario because

of the small volumes of liquid typically applied. The spray contact adhesive scenario describes a plausible worst case consumer application where respirators may not be worn because of the short task duration and relatively low VOC content of the product.

SPRAY CONTACT ADHESIVE SCENARIO

Input Parameters

Use Rate	:	1 event/year
Mass of Product	:	225.0 g
Duration of Use	:	0.66 hr
Zone 1 Volume	:	40.0 m^3
Whole House Volume	:	292.0 m^3
House Air Exchange Rate	:	0.20 room air exchanges/hr
User Inhalation Rate	:	1.20 m^3/hr (during use)
User Inhalation Rate	:	1.10 m^3/hr (after use)
Molecular Weight	:	58.08 g/mole
Vapor Pressure	:	182 torr
Weight Fraction	:	0.210
Starting Time	:	9:00 AM

Output Summary

Evaporation Time	:	0.021 hr
Release Time	:	0.66 hr (duration of exposure)
Duration Following Use	:	8759.34 hr
Interval Between Uses	:	8760.00 hr

User Potential Dose Rate From Inhalation	:	1264.3 mg/yr
Non-User Potential Dose Rate From Inhalation	:	561.6 mg/yr

(mg/m^3)	Average (mg/m^3)	Peak
Concentration in Zone of Release :		
During period of use	556.03	907.19
During period after use	0.18	847.86
Concentration in Zone 2 :		
During period of use	10.90	27.75
During period after use	0.07	82.90

The modelling results shown above indicate average and peak exposures to acetone of 556 and 907 mg/m^3, respectively. The estimated short-term human exposure (EHE) value associated with the use of consumer products was therefore set at the peak exposure concentration of 900 mg/m^3 that was predicted in this scenario.

4.1.3 *Indirect Exposure*

Acetone levels in the body at any point in time are reflective of free fatty acid utilization and acetoacetate production by the liver. Consequently, many normal and abnormal physiological states can appreciably increase the body burden of acetone through the process of ketogenesis. Children and adolescents typically have higher acetone blood levels than adults due to their higher energy

expenditure. In fact, 2 to 5 day old infants have been found to have acetone blood levels ranging as high as 140 mg/L (Peden, 1964). Furthermore, vigorous exercise and the resulting utilization of fatty acids as a fuel source can lead to a condition commonly called post-exercise ketosis that results in a dramatic increase in blood ketone body concentrations. In addition to these normal physiological conditions, there are a number of clinical states that can result in human ketosis. In each of these conditions, the ketosis can be traced to the increased mobilization and utilization of free fatty acids by the liver. These conditions include pregnancy, fasting, prolonged vomiting, and alcoholism (Morgott, 1993).

Other clinical conditions, such as diabetic ketoacidosis and starvation, can lead to much larger increases in blood acetone levels (Table 17). In each of these situations, the elevations in blood acetone are typically accompanied by even larger increases in the remaining two ketone bodies, acetoacetate and β-hydroxybutyrate (Sulway *et al.*, 1971). Unlike acetone, however, these two ketone bodies disrupt normal acid-base balance and cause many of the acute symptoms of diabetes due to their ionization (Winek, 1976). Acetone, in contrast, is non-ionic and is produced together with carbonic acid during the breakdown of acetoacetate (Koorevaar and Van Stekelenburg, 1976). Because acetone has a normal physiological role in the body, the estimated short-term human exposure (EHE) value for endogenous acetone was set at 10 mg/L, which represents the upper limit for blood acetone in healthy individuals.

Table 17
Human plasma acetone concentrations expected under various exposure and health conditions

Physiological State or Condition	Plasma Concentration Range (mg/L)	(mg %)	(mM)
healthy	< 10	< 1.0	< 0.17
occupational exposure	< 100	< 10.0	< 1.72
diabetic ketoacidosis	100 - 700	10.0 - 70.0	1.72 - 12.04
toxic exposure	> 200	> 20.0	> 3.44

4.2 Effects on Human Health

About twenty separate instances of human acetone poisoning have been reported in the medical literature. Many of these case reports have involved patients seen in hospital emergency wards following either accidental or intentional ingestion of acetone. The case reports provide a clear picture of the signs, symptoms, and prognosis that accompany acute acetone intoxication. The most noticeable features of high exposures to acetone vapor are irritation to the eyes, nose, and throat. If the exposure is extremely large, as in cases of accidental ingestion of liquid acetone, fatigue, irritability, dizziness, and breathing irregularities may occur. When the poisoning is severe, these symptoms may precede the development of gastrointestinal disturbances and a temporary loss of consciousness. While many reports of severe acetone poisoning have been reported in the literature, no deaths have ever been recorded.

The following three methods have been used to study the sensory irritation potential of acetone for the eyes, nose, and throat: physiological techniques, psychophysical methods, and subjective ques-

tionnaires. It is important to understand the differences between sensory irritation and both sensitization and chemical irritation. Sensory irritation, known also as the "common chemical sense" or chemesthesis, occurs when a vapor or gas interacts with trigeminal nerve receptors in the ocular or nasal mucosa. Sensory irritation often occurs as a physical sensation that is described using a variety of terms including: pungency, piquancy, stinging, burning, and tickling. Sensitization, in contrast, is an allergic reaction that is manifested through a either a cell-mediated (dermal sensitization) or a humoral response (pulmonary sensitization) by the immune system. Chemical or primary irritation denotes an inflammatory reaction with localized redness and swelling. This type of irritation is found when a chemical solid or liquid makes direct contact with the skin or eyes. Sensory irritation is a generally milder effect than either sensitization or chemical irritation.

The studies listed in Table 18 were conducted both in the workplace using acetone-exposed employees and in the laboratory using naive volunteers exposed to acetone in an inhalation chamber. The studies using objective physiological and psychophysical tech-niques showed acetone to be an extremely weak sensory irritant. Subjective symptom questionnaires, in contrast, indicated that acetone was a sensory irritant at much lower vapor concentrations. Recent research indicates that the irritancy responses observed using subjective symptom questionnaires are likely caused by the odor of acetone (Dalton *et al.*, 1997). Investigators have shown that both acetone and phenyl ethyl alcohol, a known non-irritant with a strong odor, produced subjective irritancy responses in humans following a 20-min inhalation exposure at 1900 mg/m^3. Objective psychophysical methods, in contrast, showed little if any irritancy effect in humans exposed under the same conditions.

The scientific literature contains eight different studies that have measured either the neurobehavioral performance or neurophysiological response of humans exposed to acetone. Many of the early neurotoxicity studies with acetone were not amenable to reliable statistical analysis because of the variability in the data and the inability to reproduce the results. A close inspection of these early investigations also reveals many problems with design, conduct, or interpretation that hinder their use.

Among more recent studies with acetone, NOAELs ranging from vapor concentrations of 600 mg/m^3 to greater than 2375 mg/m^3 have been reported. The wide range in effect levels are likely due to statistical errors caused by large numbers of independent variables, analytical problems, and the failure to use multiple concentrations to evaluate dose-response characteristics. Neurobehavioral studies with acetone-exposed employees have recently shown that 8-hr exposures up to 2375 mg/m^3 were not associated with any dose-related changes in reaction time, vigilance, or digit span scores (Satoh *et al.*, 1996). When the test subjects were divided into three age groups, a statistically significant decrease in simple reaction time and digit span scores was observed in one of the groups 30 to 44 years of age, but not in the older or younger age groups.

Table 18
Reported cases of human sensory irritation from acetone vapors

Test Method	Type of Subjects	No Effect Level (mg/m^3)	Author(s) (year)
Subjective			
questionnaire	naive	475	Nelson *et al.*, 1943
questionnaire	workers	< 595	Satoh *et al.*, 1996
questionnaire	naive	595	Matsushita *et al.*, 1969

questionnaire	naive	1185	DiVincenzo *et al.*, 1973
questionnaire	workers	1900	Raleigh & McGee,
questionnaire	both	2375	Seeber *et al.*, 1992
questionnaire	naive	2850	Stewart *et al.*, 1975
questionnaire	workers	3560	Oglesby *et al.*, 1949
Objective			
acoustic	naive	7120	Roberts *et al.*, 1996
spirometry	naive	18,985	Douglas, 1974)
psychophysics	naive	> 23,730	Cometto-Muñiz *et al.*,
psychophysics	naive	> 23,730	Cometto-Muñiz *et al.*,
laterialization	workers	> 35,600	Wysocki *et al.*, 1997
laterialization	naive	> 83,070	Wysocki *et al.*, 1997

4.2.1 *Acute Toxicity*

The acute effects of a single exposure to acetone vapor have been examined in mice, rats, guinea pigs, and cats. The adverse effects observed in laboratory animals are generally similar to the signs of central nervous system depression seen in cases of human intoxication. Vapor concentrations in excess of 24,000 mg/m^3 are generally required to elicit any sign of acute acetone intoxication in laboratory animals. Animal studies have demonstrated that the acute narcotic effects of acetone are strongly dependent upon both the length and magnitude of the exposure (Flury and Wirth, 1934; Haggard *et al.*, 1944; Kagen, 1924; Specht *et al.*, 1939). Regardless of the species examined, the narcotic effects of acetone tend to proceed through several distinct phases that can be described as follows: drowsiness, lack of coordination, loss of autonomic reflexes, narcosis, respira-tory failure, and death.

The hallmark of animal studies with acetone is the extremely high vapor concentrations or long exposure duration needed to produce an adverse effect. An 8-hr inhalation LC_{50} value of 50,100 mg/m^3 was reported for female rats (Pozzani *et al.*, 1959). Single-dose oral lethality studies have also been performed in rats, mice, and rabbits. The oral LD_{50} was found to be 10.7 mL/kg (8.5 g/kg) in rats, 90.4 mmol/kg (5.25 g/kg) in mice, and greater than 5.3 g/kg in rabbits (Smyth *et al.*, 1962; Tanii *et al.*, 1986; Krasavage *et al.*, 1982). An examination of the oral LD_{50} values for male and female rats from different age groups reveals that acetone is more acutely toxic for newborn rats than for adults (Table 19). The LD_{50} values for rats aged 14 days and older were not, however, substantially different (Kimura *et al.*, 1971).

Table 19
Acute lethality of acetone to Sprague-Dawley rats from different age groups

Age Group	Weight Range (g)	LD_{50} (g/kg)	95% Confidence Limits (g/kg)
newborn (24-48 hr)	5 - 8	2.8	2.1 - 4.8
immature (14 day)	16 - 50	7.1	4.9 - 10.1
young adult	80 - 160	11.5	8.6 - 15.3
old adult	300 - 470	10.7	9.8 - 11.8

The ability of acetone to dehydrate and delipidate unprotected skin is well known from industrial and laboratory experience. Laboratory animal studies have confirmed this ob-servation and also shown a low potential for systemic toxicity following exposure by the dermal route. The 24-hr dermal LD_{50} was found to be greater than 20 mL/kg (15.7 g/kg) in rabbits (Smyth *et al.*, 1969).

4.2.2 *Irritation/Sensitization*

Acetone did not cause contact hypersensitization in the mouse ear swelling test or the guinea pig maximization test (Descotes, 1988; Nakamura *et al.*, 1994). The sensory irritation potential for acetone vapors was determined by measuring the concentration-related decline in the respiration rate of mice. The RD_{50} values for acetone were found to be 183,970 mg/m^3 and 55,725 mg/m^3 in two separate studies (Kane *et al.*, 1980; De Ceaurriz *et al.*, 1981).

Studies conducted in rabbits have generally shown that acetone can be a severe eye irritant when applied undiluted and left in contact with the cornea. Dilute aqueous solutions, however, are minimally irritating. Corneal thickness measurements three days after the treatment of rabbits with 0.1 mL of undiluted acetone produced severe eye irritation (Morgan *et al.*, 1987). An acetone concentration of 3.9 M (225 g/L) was found to cause a 50% increase in ocular edema after a 1-hr exposure. Acetone treatment for up to several minutes was shown to destroy the corneal epithelium, but not the corneal stroma. All injury to the corneal epithelium was reversible within 4 to 6 days. Acetone was not found to be a corrosive eye irritant (Märtins *et al.*, 1992).

4.2.3 *Repeated Dose Toxicity*

The subchronic toxicity of acetone has been examined in rats following oral gavage and drinking water consumption. In the gavage study, acetone was administered in water to male and female rats for 90 consecutive days at dose levels of 100, 500, and 2500 mg/kg (Mayhew and Morrow, 1988). The rats showed an increase in several hematological parameters and an increase in the serum activity of three enzymes. Increases in the absolute liver and kidney weight were observed for female rats at the two highest dose levels. Increases in organ-to-body weight ratios were also observed, but only at the highest dose level tested. Male rats administered 2500 mg/kg showed an increase in organ-to-body weight ratios for the liver and kidney, but the absolute weights of the organs were unaffected. No liver pathology was observed, however some histopatho-logical abnormalities were observed in the renal tubular cells of male and female rats treated at the high dose.

In a more relevant study, acetone was administered in the drinking water of mice and rats for either 14 days or 13 weeks. The drinking water concentrations and calculated average daily doses of acetone are presented in Table 20 (Dietz *et al.*, 1991). No mouse or rat mortality was observed in either the 14-day or the 13-week study. Overt clinical signs of toxicity were only observed in the rats treated at the 10% level in the 14-day study. Acetone-induced increases in relative kidney weight were observed in the male and female rats treated for 13 weeks. The kidney weight changes were reportedly associated with a nephropathy that occurred spontaneously in untreated control rats. The increases in the relative liver weight of male and female rats were not associated with histopatho-logic changes and may have been caused by microsomal enzyme induction. Hematologic effects consistent with macrocytic anemia were noted in male rats along with hyperpig-mentation in the spleen. The most notable findings in mice were increased liver and decreased spleen weights, which were confined exclusively to female mice administered a 5% concentration of acetone (Dietz, 1991). The authors concluded that the no-observed-effect-level was 1% for male rats and male mice, 2% for female mice, and 5% for female rats.

Table 20
Time-weighted-average dose for male and female Fisher 344 rats and B6C3/F_1 mice exposed to acetone in their drinking water

Water Concentration (%)	14-Day Average Dose (mg/kg/day)				13-Week Average Dose (mg/kg/day)			
	Rats		Mice		Rats		Mice	
	male	female	male	female	male	female	male	female
0.125	-	-	-	-	-	-	380	-
0.25	-	-	-	-	200	200	611	892
0.5	714	751	965	1569	400	600	1353	2007
1.0	1616	1485	1579	3023	900	1200	2258	4156
2.0	2559	2328	3896	5481	1700	1600	4858	5945
5.0	4312	4350	6348	8804	3400	3100	-	11,298
10.0	6942	8560	10,314	12,725	-	-	-	-

4.2.4 *Reproduction/Devlopmental Toxicity*

Acetone showed minimal reproductive and developmental effects in animals exposed either by inhalation or via drinking water. No reproductive performance changes or testicular histopathological effects were noted in male rats treated with 0.5% acetone in their drinking water for 6 weeks (Larsen *et al.*, 1991). In another study, however, an acetone drinking water concentration of 5% caused a mild decrease in testicular weight, a moderate increase in the incidence of abnormal sperm, and depressed sperm motility after 13 weeks of treatment (Dietz *et al.*, 1991). These findings indicate that high concentrations of acetone can have a mild effect on rat spermatogenesis.

The potential for acetone vapors to cause developmental effects was examined in virgin and pregnant rats and mice (Mast *et al.*, 1988). Mated rats were exposed by inhalation to 1045, 5220, or 26110 mg/m^3 of acetone on days 6 through 19 of gestation. Mice were ex-posed at concentrations of 1045, 5220, or 15665 mg/m^3 of acetone on days 6 through 17 of gestation. No effects were seen in the mean liver or kidney weights of pregnant dams, the organ-to-body weight ratios, the number of implantations, the mean percentage of live pups per litter, the mean percentage of resorptions per litter, or the fetal sex ratio. No treatment-related effects were seen in maternal or virgin body weight, or the maternal uterine weight of the treated mice. A treatment-related increase was observed in the liver-to-body weight ratios for pregnant dams. A statistically significant reduction in fetal weight, and a slight, but statistically significant increase in the incidence of late resorptions was also seen in mice exposed to 15,665 mg/m^3 of acetone. The incidence of fetal malformations in mice was not altered by gestational exposure to acetone at any exposure concentration. The no-observed-effect level for developmental toxicity was found to be 5220 mg/m^3 for both rats and mice. Acetone did not produce any teratogenic effects at any of the exposure concentrations tested. The no-observed-effect level for teratogenicity was, therefore, greater than or equal to 15,665 mg/m^3 for mice and 26,110 mg/m^3 for rats.

4.2.5 *Neurotoxicity*

Mild neurobehavioral changes have been observed in rats repeatedly exposed to high vapor concentrations of acetone. Female rats were exposed 4 hr/day for 2 weeks at acetone concentrations of 7120, 14240, 28480, and 37975 mg/m^3 were examined for their response to avoidance and escape stimuli before and after each exposure (Goldberg *et al.*, 1964). Repeated daily exposures to

14,240 mg/m^3 of acetone produced an inhibition of avoidance behavior but did not produce any signs of motor imbalance. Acetone concentrations of 28,480 and 37,975 mg/m^3 produced ataxia in several animals after a single exposure, however, a rapid tolerance developed and ataxia was not seen on subsequent days. In a recent schedule controlled operant performance study, acetone did not cause any permanent effects in rats exposed to the vapor for 13 weeks at 2375, 4750, and 9495 mg/m^3 (Christoph and Stadler, 1997).

4.2.6 *Carcinogenicity*

Information on the carcinogenicity of acetone is available from dermal studies performed in mice. In each of these studies, acetone was used as the vehicle to evaluate the effects of a test chemical. The test design therefore included untreated and vehicle-treated study groups. The carcinogenicity of acetone was evaluated in a group of 29 female ICR/Ha Swiss mice treated topically with 0.1 mL of acetone or 0.1 mL of an acetone-water mixture (9:1) three times per week for up to 424 days (Van Duuren *et al.*, 1978). Histopathological analysis of all major organs revealed a total of 14 lung tumors, one liver tumor, one forestomach tumor, and no skin tumors in the acetone and acetone/water treatment groups. Lung papillary tumors were seen in 37% of the untreated mice and 24% of the acetone or acetone-water treated mice. The incidence of forestomach tumors in acetone or acetone-water treated mice was comparable to untreated mice. Except for one undifferentiated malignant liver tumor, which was not cited as a remarkable finding, the incidence of systemic tumors in the acetone and acetone-water treated mice was not different from the background incidence in untreated mice. In another study, the application of 0.2 mL of acetone to the shaved dorsal skin of male and female CF1 mice once per week for two years had no effect on the survival of the 300 animals tested (Zakova *et al.*, 1985). Dermal inflammatory reactions (focal acanthosis, dermal fibrosis) were seen in 6% of the animals and a fibrosarcoma was seen in one male mouse. An historical analysis of the organ pathology observed in two previous dermal carcinogenicity studies showed no evidence of a treatment-related increase in tumors or organ lesions from acetone (Ward *et al.*, 1986). Sixty female SENCAR mice received 0.2 mL of acetone once or twice per week for up to 92 weeks. The major organs and tissues from all of the animals were examined both macroscopically and microscopically following necropsy. Fifty percent of the animals survived past 96 weeks of age with 15 of the mice dying due to neoplastic lesions and 27 due to non-neoplastic lesions.

4.2.7 *Genotoxicity*

Acetone has been repeatedly tested in a variety of prokaryotic and eukaryotic test systems without causing genotoxic effects. Studies in the *Salmonella* assay have shown acetone to be non-mutagenic and to be an acceptable vehicle for dissolving and delivering water- insoluble chemicals to the tester strains (Anderson and MacGregor, 1980). EPA-spon-sored studies have shown acetone to be negative in *Salmonella* strains TA97, TA98, TA100, and TA1535 at levels up to 1 mg/plate (NTP, 1987). Subsequent studies then found that acetone was negative in strains TA92, TA94, TA98, TA100, TA1535, and TA1537 at a concentration of 10 mg/plate (Ishidate *et al.*, 1984). Acetone was not geno-toxic to *Schizosaccharomyces pombe* either with or without metabolic activation (Abbondandolo *et al.*, 1980). Acetone induced aneuploidy, but not mitotic recombination or point mutations, in *Saccharomyces cerevisiae* when tested at concentrations greater than 40 mg/mL using a cold-interruption procedure (Zimmermann *et al.*, 1985). These effects were not observed, however, when *Saccharomyces cerevisiae* was tested according to the standard overnight incubation procedure (Albertini, 1991).

Acetone did not produce genotoxic effects in an embryo cell transformation assay per-formed in rats and mice, and was also negative in a micronucleus assay using hamsters (Rhim *et al.*, 1974;

Basler, 1986). Acetone did not cause chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells treated at concentrations up to 5 mg/mL (Loveday *et al.*, 1990). Acetone concentrations ranging from 10.5 to 20.9 mM (0.6 to 1.2 mg/mL) also did not cause chromosomal aberrations or sister chromatid exchanges in cultured human lymphocytes (Norppa, 1981). Acetone did not cause point mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells treated at a level of 10 mg/mL (Amacher *et al.*, 1980).

4.2.8 *Epidemiology*

An epidemiological evaluation of mortality and clinical laboratory data for 948 employees in a fiber production plant exposed to 8-hr average acetone concentrations of 900, 1830, and 2540 mg/m^3 over 23 years produced no unusual findings (Table 21). The liver enzymes, clinical chemistry values, and hematological parameters were all within normal range (Ott *et al.*, 1983a,b,c). Standard mortality ratios for death from all causes, cardio-vascular disease, and malignant neoplasms were below expectations by 55%, 61%, and 43%, respectively.

Table 21
Observed and expected mortality rates for men and women occupationally exposed to acetone

Cause of Death	Male Mortality Ratio		Female Mortality Ratio	
	observed	expected	observed	expected
all causes	24	53.8	3	6.7
malignant neoplasm	5	10.0	2	2.3
cardiovascular disease	15	40.4	2	2.8

Four health surveillance studies have been conducted on acetone-exposed employees from cellulose acetate facilities located worldwide. The studies did not reveal any evidence of systemic toxicity or dose-related adverse heath effects based on the results obtained from a wide variety of biochemical and hematological tests (Table 22).

Table 22
Occupational health surveys with acetone exposed workers

Factory Location	Number Examined	Employed (years)	Exposure (mg/m^3)	Clinical Measurements	Author (year)
United States	800	Unknown	425 - 5100	hematology & urinalysis	Oglesby *et al.*, 1949
United States	948	< 23	900 - 2540	ematology, urinalysis, & mortality	Ott *et al.*, 1983
Italy	60	> 5	305 - 2490	ematology, urinalysis, & clinical chemistry	Grampella *et al.*, 1987
Japan	110	15	48 - 2415	Hematology, immunology, & clinical chemistry	Satoh *et al.*, 1996

4.3 Initial Assessment for Human Health

The inhalation EHE values for occupational and consumer groups have been set at 1780 and 900 mg/m^3, respectively. The most critical effect of acetone inhalation for both industrial and consumer contact is central nervous system depression. This endpoint was selected over the more commonly reported sensory irritation effects based on the findings from a recently completed comprehensive review of the odor and irritancy potential of acetone (Arts *et al.*, 1998). The authors of this review concluded that subjective reports of acetone's irritancy were unreliable and likely related to its distinctive odor. Furthermore, the authors determined that the true irritancy threshold for acetone vapors was very high, ranging somewhere between 23,730 and 94,930 mg/m^3. Clinical case studies, controlled human volunteer studies, animal research, and occupational field evaluations all indicate that the NOAEL for the CNS-related effects of acetone is about 2375 mg/m^3. Acetone is therefore considered to have a low potential for neurological risk to humans.

In a subchronic drinking water study, renal toxicity and increased liver and decreased spleen weights were observed. The reported NOAEL's were 900mg/kg/d and 3,100 mg/kg/d for male and female rats, and 2,258 mg/kg/d and 5,945 mg/kg/d for male and female mice. Worst-case EHE's on a body weight basis for occupational and consumer exposures are 254 mg/kg/d and 16 mg/kg/d, respectively. Developmental toxicity and teratogenicity of acetone were measured in rats and mice. For developmental endpoints the NOAEL in rats and mice is 5,220 mg/m^3, while no teratogenic effects were observed at the highest doses tested of 26,111 mg/ m^3 in rats and 15,665 mg/m^3 in mice. Acetone is therefore considered to have a low potential for renal damage and developmental effects in humans.

The unconsciousness, respiratory distress, and vomiting associated with cases of accidental or intentional exposure to acetone appear to occur when the blood levels are in excess of 1000 mg/L. Likewise, the drowsiness observed in patients with uncontrolled diabetes mellitus has been associated with acetone blood levels in excess of 150 mg/L. By com-parison, an 8-hr occupational exposure to 1780 mg/m^3 of acetone is expected to result in an acetone blood level of about 60 mg/L. This shows that the blood levels associated with occupational exposures to acetone are below those causing central nervous system depression.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

An examination of all available information on the biological activity of acetone indicates that the vapors are mildly toxic after both direct contact or systemic absorption. The primary effect of acute high-level exposure appears to be central nervous system depres-sion. Comparative studies with other solvents have shown that the irritative properties of acetone vapor are extremely mild and are often confused with its odor. Although many cases of accidental or intentional human acetone poisoning have occurred, no instances of death or permanent injury have been recorded. Appreciable quantities of acetone are continually being produced and eliminated in the body as a result of energy needs. Normal background levels in the blood can, therefore, dramatically fluctuate depending upon age, eating habits, and level of physical fitness.

The data indicate that acetone does not appear to pose a neurotoxic, carcinogenic, or reproductive health hazard at the concentrations reported to be found in the environment. Information obtained from occupationally exposed individuals, animal feeding studies, and *in vitro* screening assays support this conclusion. The kidney appeared to be the most sensitive target tissue in the animal studies. Acetone has also been tested in a wide variety of aquatic and terrestrial organisms and

produced minimal to mild effects in every instance. The mild effects have allowed acetone to be used as a carrier solvent for dissolving and testing less soluble chemicals. The preceding analysis shows that acetone has a low potential for harming both human health and the environment.

5.2 Recommendations

Acetone has a low priority for further work. The health and environmental effects of acetone have both been well studied.

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H E D S E T

Data Sheet

CAS-No.:	67-64-1
EINECS-No.:	200-662-2
IUPAC-Name:	Acetone

1.03 Submitter Identification

Company	Environmental Protection Agency
Street	401 M Street, SW
Date	02/20/97
Postal Code	20460
Town	Washington, DC
Country	United States
Phone	202-260-3749
Telefax	202-260-8168
Telex	N/A

1.04 OECD and Company Information

Type	lead organization
Name	Environmental Protection Agency
Partner	Chemical Manufacturers Association
Date	02/20/97
Street	401 M Street, SW
Postal Code	20460
Town	Washington DC
Country	United States
Phone	202-260-3749
Telefax	202-260-8168
Telex	N/A
Other Manufacturer	no

1.1 Substance Information

Molecular Formula:	C3H6O
Molecular Weight:	58.08
Smiles Code:	CC(=O)C
Substance Type	organic
Physical Status	liquid
Purity	99.5-99.8% (w/w)

1.2 Synonyms

Remark	2-Propanone
	Beta-Ketopropane
	Acetone

Dimethyl Ketone
Methyl Ketone
Propanone
Ketone Propane
Ketone, Dimethyl

1.3 Impurities

Remark	Water, not more than 0.5 wt % (ASTM D1364); acidity (as free acetic acid), not more than 0.002 wt %, equivalent to 0.019 mg of KOH per gram of sample (ASTM D1613); water miscibility, no turbidity or cloudiness at 1:10 dilution with water (ASTM D1722); alkalinity (as ammonia), not more than 0.001 wt % (ASTM D1614); and permangamate time, color of added $KMnO_4$ must be retained at least 30 min at 25 C in the dark (ASTM D1363).
Remark	Other impurities that have been identified include: benzene (0-50 ppm), acetaldehyde (0-70 ppm), methanol (0-500 ppm), diacetone alcohol (0-300 ppm), mesityl oxide (0-10 ppm), formaldehyde (0-1 ppm), isopropanol (0-100 ppm).
Reference	Kirk-Othmer. 1991. Encyclopedia of Chemical Technology, Fourth Edition. Volume 1. John Wiley & Sons. New York.
	Gerlich, O. (1995). Euclid data sheet: Acetone. Existing Substance Dossier. Phenolchemie GmbH. Gladbeck, Germany.

1.5 Quantity

Quantity Produced or Imported	>1,000,000 tons (1993)
Produced 12 mo After Regulation	yes
Imported 12 mo After Regulation	yes
Remark	11 Producers in United States, global production.
Information Source	Chemical Manufacturers Association

1.6.1 Labelling

Labelling	As in Directive 67/548/EEC
Specific Limits	no
Symbols F	Nota
R Phrases	11
S Phrases	9-16-23-33
Text	Keep container in a well-ventilated place--Keep away from sources of ignition--No smoking--Do not breathe vapors--Take precautionary measures against static discharges. Separate the phrases with '-' and the text for S-phrases with '--'.

1.6.2 Classification

Classification	as in Directive 67/548/EEC
Class of Danger	highly flammable
R Phrases	11

1.7 Use Pattern

Type	industrial
Category	chemical industry: used in synthesis
Remark	bisphenol-A, isophorone, methyl isobutyl ketone, other chemical intermediates

Type	industrial
Category	basic industry: basic chemicals
Remark	major use as solvent for fats, oils, waxes, resins, plastics, lacquers, paints, inks, varnishes, rubber cements

Type	industrial
Category	chemical industry: used in synthesis
Remark	methyl methacrylate, methacrylic acid and higher methacrylates (33%)

Type	industrial
Category	process solvent: used in manufacturing
Remark	smokeless gunpowder, cellulose acetate yarn, vitamin intermediates

Type	industrial
Category	other
Remark	antiseptic solution, cleaning and drying agent, pharmaceutical aid

1.8 Occupational Exposure Limit Values

Type of Limit	8-h TWA PEL (OSHA)
Value	2400 mg/m^3 (1000 ppm)
Country	United States
Reference	Code of Federal Regulations 41:50-204.50, 1994.

Type of Limit	8-h TWA
Value	1185 mg/m^3 (500 ppm)
Country	Australia
Remark	Short-Term Exposure Limit 2400 mg/m^3 (1000 ppm)

Type of Limit	8-h MAK (DE)
Value	1200 mg/m^3 (500 ppm)
Country	Austria, Germany, Switzerland (DFG-MAK/DFG-Peak)
Remark	Short-Term Exposure Limit 6000 mg/m^3 (2500 ppm)

Type of Limit	8-h TWA TLV
Value	1780 mg/m^3 (750 ppm)

Country	Belgium, Luxembourg: ARAB-TWA/ARAB-STEL Ireland, Italy: ACGIH-TWA/ACGIH-STEL Portugal, Spain: ACGIH-TWA/ACGIH-STEL
Remark	Short-Term Exposure Limit 2400 mg/m^3 (1000 ppm)
Type of Limit	8-h TWA OEL
Value	800 mg/m^3 (330 ppm)
Country	Czechoslovakia
Remark	Short-Term Exposure Limit 4000 mg/m^3 (1660 ppm)
Type of Limit	8-h TWA (AGSM)
Value	600 mg/m^3 (250 ppm)
Country	Denmark
Type of Limit	8-h TWA
Value	200 mg/m^3 (84 ppm)
Country	China
Type of Limit	8-h TWA OEL
Value	1200 mg/m^3 (500 ppm)
Country	Finland
Remark	Short Term Exposure Limit 1500 mg/m^3 (625 ppm)
Type of Limit	8-h TWA OEL
Value	1800 mg/m^3 (750 ppm)
Country	France
Type of Limit	8-h TWA OEL
Value	600 mg/m^3 (250 ppm)
Country	Hungary
Remark	Short Term Exposure Limit 1200 mg/m^3 (500 ppm)
Type of Limit	8-h TWA OEL
Value	1780 mg/m^3 (750 ppm)
Country	India
Remark	Short Term Exposure Limit 2375 mg/m^3 (1000 ppm)
Type of Limit	MAC (Japan)
Value	470 mg/m^3 (200 ppm)
Country	Japan
Type of Limit	MAC (NL) 8-h TWA
Value	1780 mg/m^3 (750 ppm)
Country	The Netherlands
Type of Limit	8-h TWA OEL
Value	2400 mg/m^3 (1000 ppm)
Country	The Philippines
Type of Limit	8-h TWA OEL
Value	200 mg/m^3 (84 ppm)

Country	Poland
Type of Limit	8-h TWA
Value	200 mg/m^3 (84 ppm)
Country	Russia
Remark	Short Term Exposure Limit 200 mg/m^3 (84 ppm)
Type of Limit	8-h TWA OEL
Value	600 mg/m^3 (250 ppm)
Country	Sweden
Remark	Short Term Exposure Limit 1200 mg/m^3 (500 ppm)
Type of Limit	8-h TWA OEL
Value	2400 mg/m^3 (1000 ppm)
Country	Turkey
Type of Limit	8-h TWA (EH40)
Value	1780 mg/m^3 (750 ppm)
Country	United Kingdom
Remark	Short Term Exposure Limit 3560 mg/m^3 (1500 ppm)
Type of Limit	8-h TLV TWA (ACGIH)
Value	1780 mg/m^3 (750 ppm)
Country	United States
Remark	Short-Term Exposure Limit 2375 mg/m^3 (1000 ppm)
Remark	Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than four times per day.

1.9 Source of Exposure

Remark	Acetone is a product of the photooxidation of some alkane and alkene compounds that are found in urban air and is also a by-product resulting from oxidation of humic substances. In addition, natural sources of acetone include by-products from forest fires, volcanoes, and metabolism of insects and higher animals.
Remark	Acetone is a normal constituent of human blood and is a component of human breath (of metabolic origin).
Remark	Acetone may be released to the environment as stack emissions, fugitive emissions, and in waste water in its production and use in the manufacture of methacrylates, as a solvent, and as a chemical intermediate in the manufacture of methyl isobutyl ketone and other chemicals.
Remark	Acetone has also been identified in wastewater from industrial and municipal treatment plants.

Remark	Acetone does not appear to be persistent in the environment due to its biodegradability, despite its widespread presence in the environment.

2. Physico-chemical Data

2.1 Melting Point

Value	-94.6 °C
GLP	no data
Reference	Handbook of Chemistry and Physics (1986). R.C. Weast (ed.), 67th Ed., p. C51. CRC Press Inc. Boca Raton, FL.

2.2 Boiling Point

Value	56.1 °C at 760 mm Hg
GLP	no data
Reference	Handbook of Chemistry and Physics (1986). R.C. Weast (ed.), 67th Ed., p. C51. CRC Press Inc. Boca Raton, FL.

2.3 Density

Value	0.791 g/mL at 20 °C
GLP	no data
Reference	Handbook of Chemistry and Physics (1986). R.C. Weast (ed.), 67th Ed., p. C51. CRC Press Inc. Boca Raton, FL.

2.4 Vapour Pressure

Value	182 mm Hg at 20 °C
GLP	no data
Reference	Kirk-Othmer Encyclopedia of Chemical Technology (1991). 4th Ed. Volume 1. John Wiley & Sons, New York, NY.

Value	230 mm Hg at 25 °C
Method	other (calculated)
GLP	no data
Reference	NOMO5 Program. Syracuse Research Corp.,Syracuse, NY.

2.5 Partition Coefficient

Value	-0.24
Type	Log P_{ow}
GLP	no
Reference	Hansch, C. and Leo, A. (1979). Substituent Constants for Correlation Analysis in Chemistry and Biology, p. 179. John Wiley & Sons, New York, NY.

2.6 Water Solubility

Description	miscible
GLP	no data
Remark	Miscible with water, alcohol, dimethylformamide, ether.
Reference	The Merck Index (1983). M. Windholz (ed.), 10th Ed., p. 57. Merck & Co., Rahway, NJ.

2.7 Flash Point

Value	-17 °C
Type	closed cup
GLP	no data
Reference	Fire Hazard Properties of Flammable Liquids, Gases, and Volatile Solids (1991). National Fire Protection Association, NFPA 325M, 10th Ed. Quincy, MA.

2.8 Auto Flammability

Value	465 °C (autoignition temperature)
GLP	no data
Reference	Fire Hazard Properties of Flammable Liquids, Gases, and Volatile Solids (1991). National Fire Protection Association, NFPA 325M, 10th Ed. Quincy, MA.

2.9 Flammability

Result	highly flammable
GLP	no data
Reference	Fire Hazard Properties of Flammable Liquids, Gases, and Volatile Solids (1991). National Fire Protection Association, NFPA 325M, 10th Ed. Quincy, MA.

2.10 Explosive Properties

Result	not explosive
GLP	no data
Reference	Fire Hazard Properties of Flammable Liquids, Gases, and Volatile Solids (1991). National Fire Protection Association, NFPA 325M, 10th Ed. Quincy, MA.

3. Environmental Fate and Pathways

3.1 Stability

3.1.1 Photodegradation

Type	air
Light Source	xenon lamp
Light Spect.	250-330 nm
Rel. Intens.	Based on intensity of sunlight
Spectrum	lambda (max) >295 nm epsilon (max) 295 nm

Concentration	200 mg/L
GLP	no data
Test substance	no data
Result	Quantum yield varied with wavelength from 1.59 to 0.27 for CO_2 production. Direct photolysis half-life was 32 days. The half-life reported is the annual average in the lower troposphere at 40 degrees northern latitude. Indirect photolysis rate constant estimated to be 0.00000026 cm^3/mol/sec based on OH sensitizer concentration of 1,180,000 mol/cm^3.
Test condition	Temperature for direct photolysis test equaled room temperature
Reference	Meyrahn, H., Pauly, J., Schneider, W., and Warneck, P. (1986). Quantum yields for the photodissociation of acetone in air and an estimate for the lifetime of acetone in the lower troposphere. J. Atmos. Chem. 4:277-291.

Type	air
Light Spect.	279-313 nm
Rel. Intensity	based on intensity of sunlight
Spectrum	lambda (max) >295 nm epsilon (max) 295 nm
GLP	no data
Test substance	no data
Result	Quantum yield: 0.15 (25 torr); 0.08 (> 400 torr) Photolysis half-life is 40 days near the earth surface to 10 days at 200 mbar pressure. Attack by hydroxyl radicals with half-life of 20 days near earth surface to 100 days at 200 mbar pressure.
Reference	Gardner, E.P. (1984). The primary quantum yields of photodecomposition of acetone in air under tropospheric conditions. J. Phys. Chem. 88:5069-5076. Chatfield, R.B., Gardner, E.P., and Calvert, J.G. (1987). Sources and sinks of acetone in the troposphere: Behavior of reactive hydrocarbons and a stable product. J. Geophys. Res. 92:4208-4216.

3.2 Monitoring Data (Environment)

Type	background concentration
Media	air
Remark	Acetone detected at 1.6-4 part per billion by volume (ppbv), 4.8-12 ppbC, average concentration over a 1-yr period in Denver, Colorado, USA.
Reference	Anderson, L.G., Lanning, J.A., and Wolfe, P. (1994). Acetone in the urban atmosphere: A case study in Denver, Colorado. Israel J. Chem. 34:341-353.

Type	background concentration
Media	air
Remark	1.6 ppb (4.8 ppbC) and 1.8 ppb (5.4 ppbC) found in two rural sites in Ontario, Canada, 1988.

Reference	Shepson, P.B., Hastie, D.R., Schiff, H.I., Polizzi, M., Bottenheim, J.W., Anlauf, K., Mackay, G.I., and Karecki, D.R. (1991). Atmospheric concentrations and temporal variations of C_1-C_3 carbonyl compounds at two rural sites in central Ontario. Atmos. Environ. 25A:2001-2015.
Type	background concentration
Media	air
Remark	12 ppb (36 ppbC) in troposphere above Tucson, Arizona; 2.8 ppb (8.4 ppbC) at two rural sites 40 km away.
Reference	Snider, J.R. and Dawson, G.A. (1985). Tropospheric light alcohols, carbonyls, and acetonitrile: Concentrations in the southwestern United States and Henry's Law data. J. Geophys. Res. 90:3797-3805.
Type	background concentration
Media	air
Remark	Range of 4.1-94 part per billion by volume (ppbv), 12.3-282 ppbC, at two urban sites in USA. Additionally, a range of 19.5-89.6 ppbv, (58.5-268.8 ppbC) was reported in a variety of work settings, including indoor air.
Reference	Kelly, T.J., Callahan, P.J., Piell, J., and Evans, G.F. (1993). Method development and field measurements for polar volatile organic compounds in ambient air. Environ. Sci. Technol. 27:1146-1153.
Type	background concentration
Media	air
Remark	Qualitative detection in volcanic gas from Guatemala.
Reference	Stoiber, R.E., Leggett, R.E., Jenkins, T.F., Murrmann, R.P., and Rose, W.I. (1971). Organic compounds in volcanic gas from Santiaguito volcano, Guatemala. Am. Geolog. Soc. Bull. 82:2299-2302.
Type	contaminated site
Media	air
Remark	Acetone detected at 770-4100 parts per billion by volume (ppbv) 2310-12,300 ppbC, around several different manufacturing sites.
Reference	Hoshitia, Y., Nihei, Y., Muto, G. (1981). Pattern display for characterization of trace amounts of odorants discharged from nine odor sources. Analyst 106:1187-1202.
Type	background concentration
Media	air
Remark	6.7-32.3 parts per billion as carbon (ppbC) was detected in seven Florida (USA) sites.
Reference	Lonneman, W.E., Sella, R.L., and Bufalini, J.J. (1978). Ambient air hydrocarbon concentrations in Florida. Env. Sci. Technol. 12:459-463.

Type	background concentration
Media	air
Remark	0.5-20.6 parts per billion as carbon (ppbC) was detected in USA continental and marine areas.
Reference	Duce, R.A., Mohnen, V.A., Zimmerman, P.R., Grosjean, D., Cautreels, W., Chatfield, R., Jaenicke, R., Ogren, J.A., Pelliari, E.D., and Wallace, G.T. (1983). Organic material in the global troposphere. Rev. Geophys. Space Phys. 21:921-952.
Type	background concentration
Media	air
Remark	An average of 470 parts per trillion by volume (pptv) (1410 pptC) of acetone at ground level to 120 pptv (360 pptC) in the upper troposphere was detected.
Reference	Arnold, F., Knop, G., and Ziereis, H. (1986). Acetone measurements in the upper troposphere and lower stratosphere- implications for hydroxyl radical abundances. Nature 321:505-507.
Type	background concentration
Media	air
Remark	4-52 part per billion as carbon (ppbC) was detected at three sites in the USA.
Reference	Arnts, R.R. and Meeks, S.A. (1981). Biogenic hydrocarbon contribution to the ambient air of selected areas. Atmos. Environ. 15:1643-1651.
Type	contaminated site
Media	ground water
Remark	A concentration of 43,700 µg/L was detected onsite at a contaminated landfill; 0.2-0.7 µg/L acetone was found in wells adjacent to the landfill.
Reference	DeWalle, F.B. and Chien, E.S.K. (1981). Detection of trace organics in well water near a solid waste landfill. J. Am. Water Works Assoc. 73:206-211.
Type	contaminated site
Media	air
Remark	20-250 part per billion by volume (ppbv) (60-750 ppbC) was detected in a house near a contaminated landfill.
Reference	Hodgson, A.T., Garbesi, K., Sextro, R.G., and Daisey, J.M. (1992). Soil-gas contamination and entry of volatile organic compounds into a house near a landfill. J. Air Waste Manage. Assoc. 42:277-283.
Type	other
Media	air
Remark	Acetone was detected in seven different product categories. The percentage of products with acetone at the average concentration (w/w%) are as follows:

	23% automotive - 28.1 11% household cleaners - 0.3 51% paints - 29.3 15% fabric & leather - 12.9 16% electronic equipment - 0.3 5% oils, greases, lubricants - 0.2 24% adhesives - 18.8
Reference	Sack, T.M., Steele, D.H., Hammerstrom, K., and Remmers, J. (1992). A survey of household products for volatile organic compounds. Atmos. Environ. 26A:1063-1070.
Type	other
Media	air
Remark	Acetone was found in the homes of smoking and non-smoking adults at average concentrations of 71 and 50 $\mu g/m^3$, respectively.
Reference	Heavner, D.L., Morgan, W.T., and Ogden, M.W. (1996). Determination of volatile organic compounds and respirable suspended particulate matter in New Jersey and Pennsylvania homes and workplaces. Environ. Int. 22:159-183.
Type	other
Media	air
Remark	Acetone was emitted from particle board at rate ranging from 37- 41 $\mu g/m^2/h$.
Reference	Tichenor, B.A. and Mason, M.A. (1988). Organic emissions from consumer products and building materials to the indoor environment. J. Air Pollut Control Assoc. 38:264-268.
Type	other
Media	air
Remark	78.8 ppm (236.4 ppmC) found in smoke from polypropylene burning.
Reference	Woolley, W.D. (1982). Smoke and toxic gas production from burning polymers. J. Macromol. Sci. Chem. A17:1-33.
Type	background concentration
Media	air
Remark	14-66 $\mu g/m^3$ (6-30 ppb) (18-120 ppbC) acetone was detected in a new office building over a period of one year.
Reference	Hodgson, A.T., Daisey, J.M., and Grot, R.A. (1991). Sources and source strengths of volatile organic compounds in a new office building. J. Air Waste Manage. Assoc. 41:1461-1468.
Type	contaminated site
Media	air
Remark	6838-32,500 part per billion by volume (ppbv) (20,514-97,500 ppbC) was detected in the air at municipal landfill sites.

Reference	Brosseau, J. and Heitz, M. (1994). Trace gas compound emissions from municipal landfill sanitary sites. Atmos. Environ. 28:285-293.
Type	contaminated site
Media	water
Remark	Acetone ranged from 9 ppb influent to 41 ppb effluent in a textile finishing plant.
Reference	Gordon, A.W. and Gordon, M. (1981). Analysis of volatile organic compounds in a textile finishing plant effluent. Trans. Ky. Acad. Sci. 42:149-157.
Type	background concentration
Media	water
Remark	0-41 ng/mL acetone was detected in cloud water at a remote continental (USA) site.
Reference	Aneja, V.P. (1993). Organic compounds in cloud water and their deposition at a remote continental site. J. Air Waste Manage. Assoc. 43:1239-1244.
Type	background concentration
Media	water
Remark	0-0.052 mg/L acetone was detected in seawater samples from Florida and the Eastern Mediterranean.
Reference	Corwin, J.F. (1969). Volatile oxygen-containing organic compounds in sea water: Determination. Bull. Marine Sci. 19:504-509.
Type	background concentration
Media	biota
Remark	Acetone is a normal endogenous biochemical that can be routinely detected and measured in body fluids. Detectable amounts of acetone have been found in a variety of biological specimens including whole blood (fetal through adult), cerebrospinal fluid, urine, exhaled air, and breast milk.
Reference	Dowty, B.J., Laseter, J.L., and Storer, J. (1976). The transplacental migration and accumulation in blood of volatile organic compounds. Pediatr. Res. 10:696-701. Sulway, M.J., Trotter, M.D., Trotter, E., and Malins, J.M. (1971). Acetone in uncontrolled diabetes. Postgrad. Med. J. 47(Suppl.):383-387. Zlatkis, A., Bertsch, W., Lichtenstein, H.A., Tishbee, A., Shunbo, F., Liebich, H.M., Coscia, A.M., and Fleischer, N. (1973). Profile of volatile metabolites in urine by gas chromatography-mass chromatography. Anal. Chem. 45:763-767. Pellizzari, E.D., Hartwell, T.D., Harris, B.S.H., Waddell, R.D., Whitaker, D.A., and Erickson, M.D. (1982). Purgeable

organic compounds in mother's milk. Bull. Environ. Contam. Toxicol. 28:322-328.

Type	background concentration
Media	biota
Remark	The normal limit for blood, serum, and plasma acetone in non-fasting adults has been shown to range from 0.8-4.4 mg/L depending on the analytical method applied. The acetone concentration in plasma can be 8-11% greater than the level in whole blood. Infants, pregnant women, and training athletes can have ketone body levels that are elevated 2 to 20-fold above normal due to the ketogenesis resulting from their higher energy requirements.
Reference	Paterson, P., Sheath, J., Taft, P., and Wood, C. (1967). Maternal and foetal ketone concentration in plasma and urine. Lancet II:862-865.

Koeslag, J.H., Noakes, T.D., and Sloan, A.W. (1980). Post-exercise ketosis. J. Physiol. 301:79-90.

Ashley, D.L., Bonin, M.A., Cardinali, F.L. McCraw, J.M., and Wooten, J.V. (1994). Blood concentrations of volatile organic compounds in a nonoccupationally exposed US population and in groups with suspected exposure. Clin. Chem. 40:1401-1404.

Trotter, M.D., Sulway, M.J., and Trotter, E. (1971). The rapid determination of acetone in breath and plasma. Clin. Chem. Acta 35:137-143.

Kimura, M., Kobayashi, K., Matsuoka, A., Hayashi, K., and Kimura, Y. (1985). Head-space gas-chromatographic determination of 3-hydroxybutyrate in plasma after enzymic reactions, and the relationship among the three ketone bodies. Clin. Chem. 31:596-598.

Brega, A., Villa, P., Quadrini, G., Quadri, A., and Lucarelli, C. (1991). High-performance liquid chrom-otographic determination of acetone in blood and urine in the clinical diagnostic laboratory. J. Chromatogr. 553:249-254.

Gavino, V.C., Vinet, B., David, F, Garneau, M., and Brunengraber, H. (1986). Determination of the concen-tration and specific activity of acetone in biological fluids. Anal. Biochem. 152:256-261.

Wang, G., Maranelli, G., Perbellini, L., Raineri, E., and Brugnone, F. (1994). Blood acetone concentration in "normal people" and in exposed workers 16 h after the end of the workshift. Int. Arch. Occup. Environ. Health65:285-289.

Type	background concentration
Media	biota
Remark	Endogenous acetone concentrations in normal human spot urine specimens have been shown to range from 0.3-3.0 mg/L. The urinary concentration of acetone was not found to increase appreciably when test subjects performed light physical exercise. A consistent diurnal trend was observed, however, with higher urine acetone concentrations found in the late evening and early morning than during the day.
Reference	Brega, A., Villa, P., Quadrini, G., Quadri, A., and Lucarelli, C. (1991). High-performance liquid chrom-atographic determination of acetone in blood and urine in the clinical diagnostic laboratory. J. Chromatogr. 553:249-254. Kobayashi, K., Okada, M., Yasuda, Y., and Kawai, S. (1983). A gas chromatographic method for the determination of acetone and acetoacetic acid in urine. Clin. Chem. Acta 133:223-226. Levey, S., Balchum, O.J., Medrano, V., and Jung, R. (1964). Studies of metabolic products in expired air. II. Acetone. J. Lab. Clin. Med. 63:574-584. Pezzagno, G., Imbriani, M., Ghittori, S., and Capodaglio, E. (1988). Urinary concentration, environ-mental concentration, and respiratory uptake of some solvents: Effect of the work load. Am. Ind. Hyg. Assoc. J. 49:546-552. Wang, G., Maranelli, G., Perbellini, L., Raineri, E., and Brugnone, F. (1994). Blood acetone concentration in "normal people" and in exposed workers 16 h after the end of the workshift. Int. Arch. Occup. Environ. Health 65:285-289.
Type	background concentration
Media	biota
Remark	The normal value for endogenous acetone in expired air specimens from adult humans was found to average between 0.7-1.6 mg/L, regardless of whether the subjects were fed or fasted overnight.
Reference	Rooth, G. and Tibbling, G. (1968). Free fatty acids, glycerol and alveolar acetone in obese women during phenformin treatment. Acta Med. Scand. 184:263-267. Rooth, G. and Östenson, S. (1966). Acetone in alveolar air, and the control of diabetes. Lancet II:1102-1105. Levey, S., Balchum, O.J., Medrano, V., and Jung, R. (1964). Studies of metabolic products in expired air. II. Acetone. J. Lab. Clin. Med. 63:574-584.

Crofford, O.B., Mallard, R.E., Winton, R.E., Rogers, N.L., Jackson, J.C., and Keller, U. (1977). Acetone in breath and blood. Trans. Am. Clin. Climatol. Assoc. 88:128-139.

Trotter, M.D., Sulway, M.J., and Trotter, E. (1971). The rapid determination of acetone in breath and plasma. Clin. Chem. Acta 35:137-143.

Jansson, B.O. and Larsson, B.T. (1969). Analysis of organic compounds in human breath by gas chromatography-mass spectrometry. J. Lab. Clin. Med. 74:961-966.

Stewart, R.D. and Boettner, E.A. (1964). Expired-air acetone in diabetes mellitus. New Eng. J. Med. 270:1035-1038.

Tassopoulos, C.N., Barnett, D., and Fraser, T.R. (1969) Breath-acetone and blood-sugar measurements in diabetes. Lancet II:1282-1286.

Phillips, M. and Greenberg, J. (1987). Detection of endogenous acetone in normal human breath. J. Chromatogr. 422:235-238.

Wang, G., Maranelli, G., Perbellini, L., Raineri, E., and Brugnone, F. (1994). Blood acetone concentration in "normal people" and in exposed workers 16 h after the end of the workshift. Int. Arch. Occup. Environ. Health 65:285-289.

Type	other
Media	biota
Remark	Four workers exposed to 30 ppm (71.1 mg/m^3) of acetone for 2 h were found to retain about 80% of the inhaled acetone. The concentration of acetone in the urine increased from about 0.75 mg/L at the beginning of the workshift to about 2.0 mg/L by the end of the shift. The acetone in venous blood increased from 1.0 mg/L at the start of the shift to 3.3 mg/L by the end. Urine and blood acetone levels returned to normal within 24 h.
Reference	Baumann, K. and Angerer, J. (1979). Untersuchungen zur Frage der beruflichen Lösungsmittelbelastung mit Aceton. Krebsgefaehrdung Arbeitsplatz Arbeitsmed. 19:403-408.

Type	other
Media	biota
Remark	Biological monitoring of styrene exposure in the workplace was not affected by co-exposures to acetone. Styrene metabolite concentrations in the urine of 22 workers exposed to styrene and acetone were not affected by 8-h TWA acetone exposures that ranged from about 10-210 ppm (25 to 498 mg/m^3).

Reference	DeRosa, E., Cellini, M., Sessa, G., Saletti, C., Rausa, G., Marcuzzo, G., and Bartolucci, G.B. (1993). Bio-logical monitoring of workers exposed to styrene and acetone. Int. Arch. Occup. Environ. Health 65:S107-S110.

3.3 Transport and Distribution in Environmental Compartments

3.3.1 Transport

Type	volatility
Media	water-air
Method	mass-transfer coefficients measurement
Result	The liquid film mass-transfer coefficient K_L ranged from 0.28-0.54 m/day.
Reference	Rathbun, R.E. and Tai, D.Y. (1982). Volatilization of ketones from water. Water Air Soil Pollut. 17:281-293.

Type	volatility
Media	water-air
Method	acetone measured in model stream
Result	Volatilization coefficient ranged from 82,300-111,000 min^{-1}.
Reference	Rathbun, R.E., Stephans, D.W., and Tai, D.Y. (1991). Fate of acetone in an outdoor model stream with a nitrate supplement, southern Mississippi, U.S.A. J. Hydrol. 123:225-242.

3.3.2 Distribution

Media	water-air
Method	other (measurement)
Remark	Partition between air and seawater at a variety of temperatures was measured and calculated.
Result	Partition coefficient K (m/atm) was 14.8-71.3.
Reference	Zhou, X. and Mopper, K. (1990). Apparent partition coefficients of 15 carbonyl compounds between air and seawater and between air and freshwater: Implications for air-sea exchange. Environ. Sci. Technol. 24:1864-1869.

Media	water sediment
Method	other (measurement)
Result	200-230 ppm acetone was detected in wastewater; acetone was not detected in river water or sediment.
Reference	Jungclaus, G.A., Lopez-Avila, V., and Hites, R.A. (1978). Organic compounds in an industrial wastewater: A case study of their environmental impact. Environ. Sci. Technol.12:88-96.

Media	water-air
Method	other (measurement)
Result	Henry's law constant was 25.6-27.0 m/atm at 25°C.
Reference	Betterton, E.A. (1991). The partitioning of ketones between the gas and aqueous phases. Atmos. Environ. 25A:1473-1477.

3.4 Mode of Degradation

Remark	biological oxidation
Reference	Rathbun, R.E., Stephens, D.W., and Tai, D.Y. (1993). Bacterial degradation of acetone in an outdoor model stream. Environ. Pollut. 79,153-162.
	Rathbun, R.E., Stephans, D.W., and Tai, D.Y. (1991). Fate of acetone in an outdoor model stream with a nitrate supplement, southern Mississippi, U.S.A. J. Hydrol. 123,225-242.
	Taylor, D.G., Trudgill, P.W., Cripps, R.E., and Harris, P.R. (1980). The microbial metabolism of acetone. J. Gen. Microbiol. 118,159-170.

3.5 Biodegradation

Type	aerobic
Inoculum	activated sludge, domestic
Degradation	78% after 28 days
Results	readily biodegradable
Method	OECD Guideline 301 D
GLP	no data
Test substance	no data
Reference	Waggy, G.T., Conway, R.A., Hansen, J.L., and Lessing, R.L. (1994). Comparison of 20-d BOD and OECD closed-bottle biodegradation tests. Environ. Toxicol. Chem. 13:1277-1280.

Type	aerobic
Inoculum	activated sludge, domestic
Concentration	100 mg/L
Degradation	42% after 155 h
Method	other
GLP	no data
Test substance	no data
Reference	Urano, K. and Kato, Z. (1986). A method to classify biodegradabilities of organic compounds. J. Hazard. Materials 3:147-159.

Type	aerobic
Inoculum	activated sludge, domestic
Concentration	500 mg/L
Degradation	0% after 24 h
Results	Under test conditions no biodegradation observed
Method	other
GLP	no
Test substance	no data
Remark	This study used a quite high substrate concentration for a limited period of time (24 h), when contrasted to more current methods.

Reference	Gerhold, R.M. and Malaney, G.W. (1966). Structural determinants in the oxidation of aliphatic compounds by activated sludge. J. Water Pollut. Control Fed. 38:562-579.
Type	aerobic
Inoculum	activated sludge, domestic
Concentration	2.5 mg/L
Degradation	78.2%
Results	readily biodegradable
Method	other
GLP	no
Test substance	no data
Remark	Results based on BOD.
Reference	Lamb, C.B. and Jenkins, G.F. (1952). B.O.D. of synthetic organic chemicals. Proc. Ind. Waste Conf. 36:326-339.
Type	aerobic
Inoculum	activated sludge, domestic, adapted
Concentration	333 mg/L
Degradation	86% after 8 h
Results	readily biodegradable
Method	other
GLP	no
Test substance	no data
Reference	Hatfield, R. (1957). Biological oxidation of some organic compounds. Ind. Eng. Chem. 49:192.
Type	aerobic
Inoculum	activated sludge, domestic, adapted
Degradation	47% after 10 days
Method	other
GLP	no
Test substance	no data
Remark	Early study of a wastewater treatment plant.
Test concentration	250-1000 mg/L.
Reference	Mills, E.J. and Stack, V.T. (1954). Biological oxidation of synthetic organic chemicals. Proc. Ind. Waste. Conf. 38:492-517.
Type	aerobic
Inoculum	activated sludge, domestic, adapted
Degradation	38% after 5 days
GLP	no data
Test substance	no data
Remark	Results based on BOD measurement.
Test concentration	0.4-3.2 mg/L
Reference	Babeu, L. and Vaishnav, D.D. (1987). Prediction of biodegradability for selected organic chemicals. J. Ind. Microbiol. 2:107-115.
Type	anaerobic

Inoculum	inoculum from sediment and groundwater
Concentration	50 mg/L
Degradation	100% after 244 days
GLP	no data
Test substance	no data
Remark	Test concentration reported as ppm carbon.
Remark	Results were comparable in sulfite and nitrate-reducing systems.
Reference	Mormile, M.R., Liu, S., and Suflita, J.M. (1994). Anaerobic biodegradation of gasoline oxygenates: Extrapolation of information to multiple sites and redox conditions. Environ. Sci. Technol. 28:1727-1732.

Type	aerobic
Inoculum	activated sludge, domestic
Concentration	10 mg/L
Degradation	81% after 20 days
GLP	no data
Test substance	no data
Remark	BOD/ThOD ratio.
Reference	Young, R.H.F., Ryckman, D.W., and Buzzell, J.C. (1968). An improved tool for measuring biodegradability. J. Water Pollut. Control Fed. 40:R354-R368.

Type	aerobic
Inoculum	activated sludge, domestic
Concentration	3.2 mg/L
Degradation	38% after 5 days
GLP	no data
Test substance	no data
Remark	results based on BOD.
Reference	Vaishnav, D.D., Boethling, R.S., and Babeu, L. (1987). Quantitative structure-biodegradability relationships for alcohols, ketones and alicyclic compounds. Chemosphere 16:695-703.

Type	aerobic
Inoculum	lab-generated organisms seeded from domestic sludge.
Degradation	100%
GLP	no data
Test substance	no data
Remark	Removal rate was 125 mg/L/day after a 5-day lag.
Concentration	166-500 mg/L.
Reference	Chou, W.L., Speece, R.E., and Siddiqi, R.H. (1978). Acclimation and degradation of petrochemical wastewater components by methane fermentation. In: Biotechnology and Bioengineering Symposium No. 8., C.D. Scott, ed., pp. 391-414. John Wiley and Sons, New York, NY.

3.6 BOD_5, COD or BOD_5/COD Ratio

Method	other
Year	1979
BOD_5	1.85 g/g
COD	1.92 g/g
GLP	no data
BOD_5/COD Ratio	0.96
Method	APHA "Standard Methods" 1989.
Concentrations	3, 7, and 10 mg/L were used.
Remark	In additional testing, BOD_{10}, BOD_{15}, and BOD_{20} were determined (Birdie et. al., 1979). ThOD - 2.21 (based on calculation). BOD_{10} - 76% of ThOD BOD_{15} - 83% of ThOD BOD_{20} - 84% of ThOD
Test condition	COD Method = ASTM D1252-67 (reapproved 1974). BOD_5 Method = APHA Standard Methods No. 219,1971
Reference	Birdie, A.L., Wolff, C.J.M., and Winter, M. (1979). BOD and COD of some petrochemicals. Water Res. 13:627-630.
BOD_5/COD Ratio	no data
BOD_5	56% of ThOD
Concentrations	3, 7, 10 mg/L
Method	APHA Standard Methods 1989.
Reference	Waggy, G.T., Conway, R.A., Hansen, J.L., and Blessing, R.L. (1994). Comparison of 20-d BOD and OECD closed-bottle biodegradation tests. Environ. Toxicol. Chem. 13:1277-1280.

3.7 Bioaccumulation

Species	haddock (adult)
Temperature	7 °C
BCF	0.69
Year	1931
GLP	no
Test condition	static
Reference	Rustung, E., Koren, F., and Föyen, A. (1931). Über Aufnahme und von Aceton im Organismus von Kaltblütern. Biochem. Z. 242:366-376.

4. Ecotoxicity

4.1 Acute/Prolonged Toxicity to Fish

Type	flow through
Species	Salvelinus fontinalis
Exposure Period	96 h
LC_{50}	6070 mg/L
Analyt. Monitoring	no data
GLP	no data

Test Substance	no data
Remark	The exposure process is described in U.S. EPA: Methods for Acute Toxicity Tests with Fish, Macro-invertebrates, and Amphibians. EPA-660/3-75-009. Committee on Methods for Toxicity Tests with Aquatic Organisms (1975). The methods used by Cardwell et.al. (1974) are similar in duration of exposure, type of test vessel, physical/chemical parameters monitored, selection of dilution water, and selection of test species.
Reference	Cardwell, R.D., Foreman, D.G., Payne, T.R., and Wilber, D.J. (1974). Acute and chronic toxicity of four organic chemicals to fish. Project Report to C.E. Stephen, U.S. EPA, Environmental Research Laboratory - Duluth. Duluth, MN.

Type	flow through
Species	Lepomis macrochirus
Exposure Period	96 h
LC_{50}	7300 mg/L
Analyt. Monitoring	no data
GLP	no data
Test Substance	no data
Remark	Test Method similar to U.S. EPA: Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians. EPA-660/3-75-009. Committee on Methods for Toxicity Tests with Aquatic Organisms, 1975.
Reference	Cardwell, R.D., Foreman, D.G., Payne, T.R., and Wilber, D.J. (1974). Acute and chronic toxicity of four organic chemicals to fish. Project Report to C.E. Stephen, U.S. EPA, Environmental Research Laboratory - Duluth. Duluth, MN.

Type	flow through
Species	Pimephales promelas
Exposure Period	96 h
LC_{50}	9100 mg/L
Analyt. Monitoring	no data
GLP	no data
Test Substance	no data
Remark	Test method similar to U.S. EPA: Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians. EPA-660/3-75-009. Committee on Methods for Toxicity Test with Aquatic Organisms, 1975.
Reference	Cardwell, R.D., Foreman, D.G., Payne, T.R., and Wilber, D.J.(1974). Acute and chronic toxicity of four organic chemicals to fish. Project Report to C.E. Stephen, U.S. EPA - Environmental Research Laboratory - Duluth. Duluth, MN.

Type	static
Species	Gambusia affinis
Exposure Period	72 h
LC_{50}	13,000 mg/L
Analyt. Monitoring	no data

GLP	no data
Test substance	no data
Results	24-h LC_{50} = 13,500 mg/L 48-h LC_{50} = 13,000 mg/L Below 11,500 mg/L, the fish showed no permanent distress.
Remark	Method similar to Doudoroff et al., Bioassay methods for the evaluation of acute toxicity of industrial wastes to fish. Sewage Ind. Wastes 23:1380-1397, 1951.
Reference	Wallen, I.E., Greer, W.C., and Lasater, R. (1957). Toxicity to Gambusia affinis of certain pure chemicals in turbid waters. Sewage Ind. Wastes 29:695-711.

Type	flow through
Species	Pimephales promelas
Exposure Period	96 h
LC_{50}	8120 mg/L
Analyt. Monitoring	yes
GLP	no data
Test Substance	no data
Remark	Method similar to: Methods for Measuring the Acute Toxicity of Effluents to Aquatic Organisms. W. Piltier, Bioassay Subcommittee. EPA Biological Advisory Committee, Ecology Branch. EPA-600/4-28-012, 1978.
Reference	Veith, G. (1983). Structure-toxicity relationships for the fathead minnow, Pimaphales promelas: Narcotic industrial chemicals. Can. J. Fish Aquat. Sci. 40:743-748.

Type	static
Species	Oncorhynchus mykiss
Exposure Period	96 h
LC_{50}	5540 mg/L
Analyt. Monitoring	no data
GLP	no data
Test Substance	prescribed by 1.1-1.4
Remark	Method similar to: Methods for Measuring the Acute Toxicity of Effluents to Aquatic Organisms. W. Piltier, Bioassay Subcommittee. EPA Biological Advisory Committee, Ecology Branch, EPA-600/4-28-012, 1978.
Reference	Johnson, W.W. and Finley, M.T. (1980). Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Inver-tebrates. Department of the Interior Fish and Wildlife Service. Resource Publication 137. Washington, DC.

Type	flow through
Species	Pimephales promelas
Exposure Period	96 h
LC_{50}	6210-8120 mg/L
Analyt. Monitoring	yes
GLP	no data
Test substance	no data
Test method	similar to OECD Guideline 204.

Remark	Results from 3 test runs (LC_{50} in mg/L): 24-h: 8830, 9400, 8030 72-h: 8120, 7940, 6400 96-h: 8120, 7280, 6210
Reference	Brooke, L.T., Call, D.J., Geiger, D.L., and Northcott, C.E. (1984). Acute Toxicities of Organic Chemicals to Fathead Minnows (Pimephales promelas). Center for Lake Superior Environmental Studies.
Type	static
Species	Poecilia reticulata
Exposure Period	14 day
LC_{50}	6400 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Test method	similar to U.S. EPA: Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians. EPA-660/3-75-009. Committee on Methods for Toxicity Tests with Aquatic Organisms, 1975.
Reference	Konemann, H. (1981). Quantitative structure-activity relationships in fish toxicity studies. Part 1: Relationship for 50 industrial pollutants. Toxicology 9:209-221.
Type	flow through
Species	Salmo gairdneri
Exposure Period	24 h
LC_{50}	6100 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Acetone (2930 mg/L) produced an increase in ventilation rate, reaching a maximum of 158% of controls at 21 hours for the duration of the exposure period.
Remark	Method similar to that contained in: Sprague, J.B. (1969). Measurement of pollutant toxicity to fish. I. Bioassay methods for acute toxicity. Water Res. 3:793-821.
Reference	Majewski, H.S., Klaverkamp, J.F., and Scott, D.P. (1978). Acute lethality and sub-lethal effects of acetone, ethanol, and propylene glycol on the cardiovascular and respiratory systems of rainbow trout (Salmo gairdneri). Water Res. 13:217-221.
Type	static
Species	Lepomis macrochirus
Exposure Period	96 h
LC_{50}	8300 mg/L
Analyt. Monitoring	no data
GLP	no
Test substance	no data

Remark	Test method similar to Doudoroff, P. (1951). Bioassay methods for the evaluation of acute toxicity of industrial wastes to fish. Sewage Ind. Wastes 23:1380-1397.
Reference	Cairns, J. and Scheier, A. (1968). A comparison of the toxicity of some of the common industrial waste components tested individually and combined. Progressive Fish Culturist 30:3-8.
Type	static
Species	Carassius auratus
Exposure Period	24 h
LC_{50}	>5000 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Method similar to that described in: American Public Health Association. Review papers on measurement of pollutant toxicity to fish. Sprague, J.B. (1969). Bioassay methods for acute toxicity. Water Res. 3:793-821.
Reference	Birdie, A.L., Wolff, C.J.M., and Winter, M. (1979). The acute toxicity of some petrochemicals to goldfish. Water Res.13:623-626.
Type	static
Species	Leuciscus idus
Exposure Period	48 h
LC_{50}	7505-11,300 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Test method similar to: U.S. EPA: Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. EPA-660/3-75-009. Committee on methods for toxicity tests with aquatic organisms, 1975.
Reference	Juhuke, I. and Luedemann, D. (1978). Results of the study of 200 chemical compounds on acute toxicity using the golden orfe test. Z. Wasser Abwasser Forsch. 11:161-164.
Type	flow through
Species	Pimephales promelas
Exposure Period	1 h
LC_{50}	6210-8030 mg/L
Analyt. Monitoring	yes
GLP	no data
Test substance	no data
Remark	Test method similar to U.S. EPA: Methods for acute toxicity test with fish, macroinvertebrates, and amphibians. EPA-660/3-75-009. Committee on Methods for Toxicity Test with Aquatic Organisms, 1975.
Result	Results of 3 test runs are as follows (LC_{50} in mg/L): 24-h: 8830, 9400, 8030 48-h: 8290, 8880, 7940

	72-h: 8120, 7940, 6400 96-h: 8120, 7280, 6210
Test substance	minimum purity 90%; analysis of test article in water from fish exposure tanks.
Reference	Brooke, L.T., Call, D.J., Geiger, D.L., and Northcott, C.E. (1984). Acute toxicities of organic chemicals to fathead minnows (Pimephales promelas). Center for Lake Superior Environmental Studies. University of Wisconsin - Superior. pp. 319.

4.2 Acute Toxicity - Aquatic Invertebrates

Species	Daphnia magna
Exposure Period	48 h
LC_{50}	12,600 & 12,700 mg/L (two laboratories)
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Tests conducted according to a protocol from the Dutch Standard Institute (Adema, 1978).
Reference	Canton, J.H. and Adema, D.M.M. (1978). Repro-ducibility of short-term and reproduction toxicity experiments with Daphnia magna and comparison of the sensitivity of Daphnia magna with Daphnia pulex and Daphnia cucullata in short-term experiments. Hydrobiologia 59:135-140.

Species	Daphnia pulex
Exposure Period	48 h
LC_{50}	8800 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Tests conducted according to a protocol from the Dutch Standard Institute (Adema, 1978).
Reference	Canton, J.H. and Adema, D.M.M. (1978). Repro-ducibility of short-term and reproduction toxicity experiments with Daphnia magna and comparison of the sensitivity of Daphnia magna with Daphnia pulex and Daphnia cucullata in short-term experiments. Hydrobiologia 59:135-140.

Species	Daphnia cucullata
Exposure Period	48 h
LC_{50}	7635 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Tests conducted according to a protocol from the Dutch Standard Institute (Adema, 1978).
Reference	Canton, J.H. and Adema, D.M.M. (1978). Repro-ducibility of short-term and reproduction toxicity experiments with Daphnia magna and comparison of the sensitivity of Daphnia magna

with Daphnia pulex and Daphnia cucullata in short-term experiments. Hydrobiologia 59:135-140.

Species	Daphnia magna
Exposure Period	48 h
LC_{50}	13,500 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Procedure used individuals 12-hours old. The test water was from a local spring-fed pond with an average hard-ness 154.5 mg/L, pH of 7.7, and temperature of 22°C.
Reference	Randall, T.L. and Knopp, P.V. (1980). Detoxification of specific organic substances by wet oxidation. J. Water Pollut. Control Fed. 52:2117-2130.

Species	Daphnia magna
Exposure Period	24 h
LC_{50}	>10,000 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Procedure used individuals 24-hours old. Test used tap water free of chlorine, saturated with oxygen, hardness 16 (German), pH 7.6-7.7, temperature 20-22°C.
Reference	Bringmann, V.G. and Kuhn, R. (1977). Results of the damaging effect of water pollutants on Daphnia magna. Z. Wasser Abwasser Forsch. 10:161-166.

Species	Daphnia pulex
Exposure Period	18 h
LC_{50}	1550 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Test containers selected for compatibility with the size of the test organism. Duplicate test chambers with 10-12 concentrations. Test duration was 18 hours of which 16 hours were fluorescent illumination. Water temperature 23°C plus or minus 2°C. No supplemental food or air.
Reference	Bowman, M.C., Oller, W.L., and Cairns, T. (1981). Stressed bioassay systems for rapid screening of pesticide residues. Part I: Evaluation of bioassay systems. Arch. Environ. Contam. Toxicol. 10:9-24.

Species	Culex restuans (white-dotted mosquito)
Exposure Period	18 h
LC_{50}	7840 mg/L
Analyt. Monitoring	no data
GLP	no data

Test substance	no data
Remark	Test containers selected for compatibility with the size of the test organism. Duplicate test chambers with 10-12 concentrations. Test duration was 18 hours of which 16 hours were fluorescent illumination. Water temperature was 23°C plus or minus 2°C. No food or air added.
Reference	Bowman, M.C., Oller, W.L., and Cairns, T. (1981). Stressed bioassay systems for rapid screening of pesticide residues. Part I: Evaluation of bioassays systems. Arch. Environ. Contam. Toxicol. 10:9-24.

Species	Hyalella azteca
Exposure Period	18 h
LC_{50}	3520 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Test containers selected for compatibility with the size of the test organism. Duplicate test chambers with 10-12 concentrations. Test duration was 18 hours of which 16 hours were fluorescent illumination. Water temperature was 23°C plus or minus 2°C. No food or air added.
Reference	Bowman, M.C., Oller, W.L., and Cairns, T. (1981). Stressed bioassay systems for rapid screening of pesticide residues. Part I: Evaluation of bioassay systems. Arch. Environ. Contam. Toxicol. 10:9-24.

Species	Lithodes antarcticus (southern king crab, larval stage)
Exposure Period	120-192 h.
EC_{50}	1010-4660 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	as prescribed by 1.1-1.4
Test method	American Public Health Association for Static Bioassay Procedures (APHA, AWWA, WPCF) 1976.
Remark	The mortality curve of larvae exposed to 7500 mg/L acetone (acetone controls) did not differ from that of seawater controls.
Result	Results as LC_{50} in mg/L are as follows: 120-h: 4660 144-h: 3880 168-h: 2330 192-h: 1010
Reference	Lombardo, R.J., Ferrari, L., and Vinuesa, J.H. (1991). Effects of lindane and acetone on the development of larvae of the southern King Crab (Lithodes antarcticus). Bull. Environ. Contam. Toxicol. 46:185-192.

Species	Streptocephalus rubricaudatus
Exposure Period	24 h
LC_{50}	64,300 mg/L

Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	The hatching and 24-h toxicity test procedure used dry-stored cysts of S. rubricaudatus (originating from Algeria). Hatching was obtained by hydrating dried cysts in a petri dish in U.S. EPA freshwater medium (1985). After 18 hours incubation (at 25°C), the free-swimming larvae were pipet-transferred into a second petri dish for a supplemental period of 6 h. The test endpoint was death, defined by the complete lack of movement during 10 seconds of observation under a dissection microscope.
Reference	Crisinel, A., Delaunay, L., Rossel, D., and Tanadellas, J. (1994). Cyst-based ecotoxicological tests using Anostracans: comparison of two species of Streptocephalus. Environ. Toxicol. Water Qual. 9:317-326.

Species	Daphnia magna
Exposure Period	48 h
LC_{50}	104,712 mol/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Age of test organism was less than 2 days; number of test organisms per group was 25; test volume was 1 L; temperature was 22°C plus or minus 1°C; hardness was approximately equal to one.
Reference	Hermens, J., Cantor, H., Janssen, P., and DeJong, R. (1984). Quantitative structure-activity relationships and toxicity studies of mixtures of chemicals with anesthetic potency: acute lethal and sublethal toxicity to Daphnia magna. Aquatic Toxicol. 5:143-154.

4.3 Toxicity to Aquatic Plants e.g. Algae

Species	Chlorella pyrenoidosa
Endpoint	see below
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Also tested was the green algae, Scenedesmus quadricauda. Photosynthesis was used as the test criterion and was quantified by monitoring the uptake of $^{14}CO_2$ from $NaH^{14}CO_3$, as previously described by Stratton et al. (1980). Acetone alone was not inhibitory to either S. quadricauda or C. pyrenoidosa. Photosynthetic activity in these species was stimulated above 0.2% acetone while stimulatory activity increased 30-40% at an acetone concentration of 1.0%.
Method	Method similar to: Stratton, G.W. et al. (1980). Bull. Environ. Contam. Toxicol. 24:562.

Reference	Stratton, G.W. and Corke, C.T. (1981). Interactions between acetone and two pesticides toward unicellular green algae. Bull. Environ. Contam. Toxicol. 27:13-16.
Species	Chlorella pyrenoidosa
Endpoint	growth rate
Exposure Period	14 day
EC_{50}	3020 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Exposure Period	10-14 days.
Remark	Growth was monitored by following the increase in optical density over time for 10-14 days using a spectrophotometer equipped with a universal test tube adapter and appropriate filters. Effects of acetone were assayed against the growth of C. pyrenoidosa at five to ten concentrations ranging from 0.1% to 6.0%.
Reference	Stratton, W.S. and Smith, T.M. (1988). Interaction of organic solvents with the green alga Chlorella pyrenoidosa. Bull. Environ. Contam. Toxicol. 40:736-742.
Species	Chlorella pyrenoidosa
Endpoint	Effects on membrane integrity and cell leakage
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Acetone-induced leakage from C. pyrenoidosa was monitored by following the loss of carbon compounds from cells using radioisotopic techniques. The cells were radiolabeled photosynthetically using ^{14}C-sodium bicarbonate. Significant leakage occurred at 1.5% and lower (depending on the exposure period (i.e., 24, 48, or 96 h).
eference	Stratton, G.W. (1989). Effect of the solvent acetone on membrane integrity in the green alga, Chlorella pyrenoidosa. Bull. Environ. Contam. Toxicol. 42:754-760.
Species	Anabaena inaequalis
Endpoint	photosynthetic ability
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Method	Cells were incubated for 2 h and harvested by filtration through 0.45 m membrane filters. Photosynthetic changes were noted by monitoring the uptake of $^{14}CO_2$ from $NaH^{14}CO_3$. The amount of radioactivity incorpor-ated into the cells was determined using a liquid scintillation counter. Percent inhibition was calculated. Anabaena cylindrica and Anabaena variabilis also examined.
Remark	A. inaequalis photosynthetic activity was significantly altered at acetone concentrations of 1000 mg/L and 4000 mg/L, where

	stimulation was observed. A. variabilis photosynthesis was significantly stimulated by acetone concentrations below 10,000 mg/L. No significant stimulation of $^{14}CO_2$ uptake occurred with A. cylindrica, although inhibition was observed above 6000 mg/L acetone. Inhibition was 75% at 8000 mg/L and 95% at 10,000 mg/L.
Reference	Stratton, G.W., Burrell, R.E., Krup, M.L., and Corke, C.T. (1980). Interactions between the solvent acetone and pyrethroid insecticide permethrin on activities of the blue-green alga Anabaena. Bull. Environ. Contam. Toxicol. 24:562-569.
Species	Anabaena inaequalis
Endpoint	nitrogen fixation ability
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Method	Assayed using the acetylene reduction technique. After the addition of a 10% atmosphere of acetylene, the cells were incubated for 5 h and the ethylene produced was assayed by gas chromatography. A. variabilis was not included in these studies due to its inability to fix nitrogen. Anabaena cylindrica and Anabaena variabilis were also examined
Remark	A. inaequalis activity was stimulated by all acetone concentrations from 1000 mg/L to 10,000 mg/L. The degree of stimulation was greater than that observed in photosynthetic studies. A. cylindrica exhibited significantly increased acetylene reduction at levels of acetone less than 4000 mg/L and decreased significantly at levels greater than 5000 mg/L.
Reference	Stratton, G.W., Burrell, R.E., Krup, M.L., and Corke, C.T. (1980). Interactions between the solvent acetone and pyrethroid insecticide permethrin on activities of the blue-green alga Anabaena. Bull. Environ. Contam. Toxicol. 24:562-569.
Species	Skeletonema costatum
Endpoint	growth sensitivity
Analyt. Monitoring	no data
Year	1988
GLP	no data
Test substance	no data
Remark	S. costatum was cultured in growth medium to achieve the selected density of 100,000 cells/mL. Total cell count and total cell volume were measured by use of a Coulter counter.
Result	Classified as practically nontoxic (> 100 mg/L).
Reference	Cowgill, U.M., Milazzo, D.P., and Landenberger, B.D. (1989). Toxicity of nine benchmark chemicals to Skeletonema costatum, a marine diatom. Environ. Toxicol. Chem. 8:451-455.
Species	Scenedesmus quadricauda

Endpoint	toxicity threshold
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Additional Species tested was Microcystis aeruginosa. Test cultures prepared from the dilution series and the control cultures were kept under standardized conditions for 8 days with constant lighting at 27 °C. Cultures were shaken daily and the concentration of the algal suspen-sions of each test culture was measured turbidimetrically.
Result	The chemical concentration causing the onset of cell multiplication inhibition was defined as the toxicity threshold. The toxicity threshold was 7500 mg/L for S. quadricauda and 530 mg/L for M. aeruginosa.
Reference	Bringmann, G. and Kuhn, R. (1978). Testing of substances for their toxicity threshold: model organisms Microcystis (Diplocystis) aeruginosa and Scenedesmus quadricauda. Mitt. Internat. Verein. Limnol. 21:275-284.

4.4 Toxicity to Bacteria

Type	aquatic
Species	Paramaecium caudatum
Exposure Period	4 h
LC_{50}	6800 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Method described in: Stressed bioassay systems for rapid screening of pesticide residues. I. Evaluation of bioassay systems. Environ. Contam. Toxicol. 10:9-24. (1981).
Reference	Rajini, P.S., Krishnakumare, M.K., and Majunder, S.K. (1989). Cytotoxicity of certain organic solvents and organophosphorus insecticides to the ciliated protozoan Paramecium caudatum. Microbios 59:157-163.

Type	other
Species	Uronema parduzci
Endpoint	toxicity threshold
Exposure Period	20 h
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	The protozoan test Species was fed with pure inactive cultures of E. coli to avoid metabolism of the test article by the bacteria. The test period for determination of a toxicity threshold was 20 h. Quantification of bacteria (food) and protozoa (test species) was done by cell counter. A 5% difference in protozoan cell count between test article and control was used to determine the toxicity threshold.
Result	Result is given as a toxicity threshold of 1710 mg/L.

Reference	Bringmann, G. and Kuhn, R. (1980). Determination of the harmful effect of water pollutants on protozoa. II. Bacteriovorous ciliates. Z. Wasser Abwasser Forsch. 13:26-31.
Type	other
Species	Chilomonas paramecium
Endpoint	toxicity threshold
Exposure Period	48 h
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	The flagellate saprozoic protozoan test species was fed pure inactive cultures of E. coli to avoid metabolism of the test article by the bacteria. The test period for determination of a toxicity threshold was 48 h. Quantification of bacteria(food) and protozoa (test species) was by electronic cell counter. A 5% difference in protozoan cell count between test Species and controls was used to determine the toxicity threshold.
Result	Result is reported as a toxicity threshold of 3516 mg/L.
Reference	Bringmann, G. and Kuhn, R. (1980). Determination of biological damage from water pollutants to protozoa. III. Saprozoic flagellates. Z. Wasser Abwasser Forsch. 13:170-173.
Type	other
Species	Entosiphon sulcatum
Exposure Period	72 h
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	The protozoan test Species was fed pure inactive cultures of E. coli to avoid metabolism of the test article by the bacteria. The test period for determination of a toxicity threshold was 72 h. Quantification of bacteria (food) and flagellates (test species) was performed by electronic cell counter. A 5% difference in protozoan cell count between test species and controls was used to determine the toxicity threshold.
Result	Result is reported as a toxicity threshold of 28 mg/L.
Reference	Bringmann, G. and Kuhn, R. (1978). Determination of the biological toxicity of water-bound substances towards protozoa. I. Bacteriovorous flagellates (model organism: Entosiphon sulcatum). Z. Wasser Abwasser Forsch. 11:210-215.
Type	aquatic
Species	Pseudomonas putida
Endpoint	oxygen uptake
Analyt. Monitoring	no data
GLP	no data
Test substance	as prescribed by 1.1-1.4

Remark	Oxygen uptake was measured over a 10-min. period at 27°C before, during, and after sample addition. Growth was determined by inoculating P. putida into medical flats and incubating at 27°C. Thirty minutes before inoculation with acetone, the test cultures were diluted with fresh medium to a density with an absorption of approximately 0.8 at 600 m measured spectrophotometrically. The test solutions were redistributed to medical flats, acetone added, and incubated for 6 hours at 27°C. Growth was terminated by formalin addition and immediately followed by density measurements.
Result	Oxygen uptake over 10 min (EC_{10}) was 1380 mg/L. Growth inhibition over 7 h (EC_{10}) was 540 mg/L.
Reference	Slabbert, J.L. and Grabow, W.O.K. (1986). A rapid water toxicity screening test based on oxygen uptake of Pseudomonas putida. Toxicity Assess. 1:13-26.

Type	aquatic
Species	Escherichia coli
Endpoint	minimal inhibitory concentrations (MIC)
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	Test Species was a mutant strain with enhanced sensitivity to a wide spectrum of toxic substances. The assay is based on the ability of toxicants to inhibit the de novo synthesis of an inducible enzyme, e.g., β-galactosidase, by a rough mutant of E. coli, which is highly sensitive to a wide spectrum of toxic substances.
Result	The minimal inhibitory concentration (MIC) was 25,000 mg/L (defined as the concentration causing 20% toxicity).
Reference	Reinhartz, A., Lampert, I., Herzberg, M., and Fish, F. (1987). A new short-term sensitive bacterial assay kit for the detection of toxicants. Toxicity Assess. 2:193-206.

Type	aquatic
Species	Polytox (proprietary blend of 12 aerobic bacteria strains)
Exposure Period	6 h
IC_{50}	48,000 mg/L
Analyt. Monitoring	no data
GLP	no data
Test substance	no data
Remark	The percent inhibition at different concentrations of acetone was based on the reduction in oxygen uptake rate of spiked reactors compared to that of the control reactor. Plotted against the respective concentrations, the concentration causing 50% inhibition or IC_{50} was determined.
Reference	Nirmalakhandan, N., Arulgnanendran, V., Mohsin, M., Sun, B., and Cadena, F. (1994). Toxicity of mixtures or organic chemicals to microorganisms. Water Res. 28:543-551.

Type	aquatic
Species	activated sludge of a predominantly domestic sewage
EC_{50}	77.4 mg/L
Analyt. Monitoring	no data
Method	ISO 8192
Year	1991
GLP	no data
Test substance	as prescribed by 1.1-1.4
Remark	Activated sludge of a predominantly industrial sewage was also tested.
Result	EC_{50} for the industrial/synthetic sewage was 59.4 mg/L.
Reference	Kilroy, A.C. and Gray, N.F. (1992). The toxicity of four organic solvents commonly used in the pharmaceutical industry to activated sludge. Water Res. 26:887-892.

Type	aquatic
Species	activated sludge
Exposure Period	16 h
EC_{50}	>5000 mg/L
Analyt. Monitoring	no data
Method	OECD Guideline 209
GLP	no data
Test substance	no data
Reference	Alsop, G.M., Waggy, G.T., and Conway, R.A. (1980). Bacterial growth inhibition test. J. Water Pollut. Control Fed. 52:2452-2456.

Type	aquatic
Species	activated sludge of a predominantly domestic sewage
Exposure Period	3 h
EC_{50}	>1000
Analyt. Monitoring	no data
Method	OECD Guideline 209
GLP	no data
Test substance	as prescribed by 1.1-1.4
Reference	Klecka, G.M. and Landi, L.P. (1985). Evaluation of the OECD activated sludge respiration inhibition test. Chemosphere 14:1239-1251.

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species	Lithodes antarcticus
Endpoint	mortality
Exposure	7 day
EC_{50}	>0.75 g/L
Analyt. Monitoring	no data
GLP	no data
Test substance	as prescribed by 1.1-1.4
Method	The experiments were conducted following the recommendations of the APHA, AWWA, WPCF Standard Methods for the examination of water and wastewater, 14th

	ed., Am. Pub. Health Assoc., Washington, D.C. 1976, i.e. 7-day, 48-h static renewal. 8°C and 35 parts per thousand salinity.
Remark	Mortality in the seawater controls was lower than 10% during the first seven days of culture and the acetone controls (0.75 g/L) did not show mortality above that of the seawater controls during this period.
Reference	Lombardo, R.J., Ferrari, L., and Vinuesa, J.H. (1991). Effects of lindane and acetone on the development of larvae of the Southern King Crab (Lithodes antarcticus Jaquinot). Bull. Environ. Contam. Toxicol. 46:185-192.

4.6 Toxicity to Terrestrial Organisms

4.6.2 Toxicity to Terrestrial Plants

Species	Raphanus sativus L. var. Champion 708 (radish)
Endpoint	emergence and growth
Exposure Period	7 day
NOEC	100 mg/L
GLP	no
Test substance	no data
Remark	Also tested were Lactuca sativa L. var. 525 Ithaca M.T.O. (lettuce) and Lolium perenne L. var. Manhattan (rye grass).
Method	The bioassay was most similar to the blotter-sandwich technique, and was designed to determine the dose-response characteristics of acetone on the germination and early growth of three representative terrestrial plants during a 7-day exposure period.
Result	7-day NOEC for all three Species was 100 mg/L.
Reference	Gorsuch, J.W., Kringle, R.O., and Robillard, K.A. Chemical effects on the germination and early growth of terrestrial plants (1990). In: Plants for Toxicity Assessment, ASTM STP 1091. W. Wang, J.W. Gorsuch, and W.R. Lower, eds., pp. 49-58. American Society for Testing and Materials. Philadelphia, PA.

Species	Zea mays L. var. rugosa Bouaf
Endpoint	Total germination and percentage of normal seedlings
Exposure Period	5 sec., 0.25, 0.50, 1.0, 2.0, 4.0, or 8.0 h; immersion in 100% acetone.
GLP	no data
Test substance	as prescribed by 1.1-1.4
Method	The organic solvent infusion technique has been used successfully to improve germination.
Remark	Total germination and percentage of normal seedlings in both cultivars (Florida Staysweet and Crisp-n-Sweet 710) were significantly decreased after 8 h of immersion in acetone. Average seedling dry weight, however, did not decrease. Results indicate that acetone could be used as an infusion agent for fungicides in the seed of some sweet corn cultivars without compromising seed germination or vigor.

Reference	Hung, P.E. (1992). Infusion of shrunken-2 sweet corn seed with organic solvents: effects on germination and vigor. Horticult. Sci. 27:467-470.
Species	Cucumis sativus (long green cucumber)
Endpoint	active dormancy - breaking factor
Exposure Period	various
Year	1993
GLP	no data
Test substance	as prescribed by 1.1-1.4
Method	Dormant and non-dormant seeds were immersed in acetone in glass-stoppered containers at 10°C for various time periods. After treatment the seeds were allowed to air-dry for 24 h in open petri dishes and then used in germination experiments.
Remark	Acetone was found not only to break the dormancy in cucumber seeds, but also to prevent its induction by far-red light. The data also show that prevention of dorm-ancy development as well as breakage of dormancy by acetone are accompanied by a change in the permeability of the cell membrane of the perisperm-endosperm envelope around the embryo.
Reference	Amritphale, D., Dixit, S., and Singh, B. (1993). Effect of acetone on the induction and breakage of secondary dormancy in seeds of cucumber. J. Exp. Botany. 44:1621-1626.

4.6.3 Toxicity Non-Mammalian Terrestrial Species

Species	Coturnix coturnix japonica
Endpoint	mortality
Exposure Period	5 days
LC_{50}	>20,000 ppm
GLP	no data
Test substance	as prescribed by 1.1-1.4
Method	5-day dietary trial with 14-day old coturnix quail.
Remark	Total mortality was 0/45 at 5 days.
Reference	Hill, E. F. and Carmardese, M.B. (1986). Lethal dietary toxicities of environmental contaminants and pesticides to Coturnix. Patuxent Wildlife Research Center. Laurel, MD. pp. 22-23.

4.7 Biological Effects Monitoring

Remark	The bioaccumulation potential of a chemical in muscle tissue from rainbow trout has been shown to be related to the octanol water partition coefficient. The partition coefficient for acetone of -0.24 indicates a high degree of water solubility and low potential to bioaccumulate or biomagnify in the environment.
Reference	Paterson, S. and Mackay, D. (1989). Correlation of tissue, blood and air partition coefficients of volatile organic chemicals. Br. J. Ind. Med. 46:321-328.

Neely, W.B., Branson, D.R., and Blau, G.E. (1974). Partition coefficient to measure bioconcentration potential of organic chemicals in fish. Environ. Sci. Technol. 8:1113-1115.

4.8 Biotransformation and Kinetics

Type	plant
Remark	The objective of the experiment was to determine if acetone inhibits the mutagenic activity of promutagenic dimethylnitrosamine (DMN) and methylbutylnitrosamine in a higher plant, Arabidopsis thaliana. Seeds were immersed for 3 hours at 25°C in 1 mL of acetone mixed with buffer for pretreatment. They were then immersed for 3 hours at 25°C in 2 mL of the mixture containing the mutagens and acetone for treatment. Following treatment, the seeds were rinsed for 30 min in distilled water and sown on soil in a greenhouse.
Result	The frequency of mutations and the degree of sterility induced by DMN was markedly reduced in the presence of acetone.
Reference	Gichner, T. and Veleminsky, J. (1986). Organic solvents inhibit the mutagenicity of promutagens dimethyl-nitrosamine and methylbutylnitrosamine in a higher plant Arabidopsis thaliana. Mutagenesis 1:107-109.

Type	animal (Daphnia magna)
Remark	The hypothesis of constancy of the tissue residues in animals treated with narcotic organic chemicals was tested by determining the effect of body length, time, and ambient concentration on tissue concentration in Daphnia magna narcotized by exposure to toxic levels of acetone.
Result	The lower than expected toxicity of acetone may be due to the degradation of this chemical by Daphnia. Acetone, a simple organic compound, may be readily metabolized by Daphnia. As a result, some of the radioactivity in Daphnia tissues would be associated with accumulated metabolites rather than the original compound, and the narcotizing body burdens of acetone would be over-estimated. Acetone did not exert a significant negative influence on the effective internal concentration. When predicted body burdens for acetone were calculated using mean body sizes, exposure concentrations, and exposure durations, body burden acetone residues of 115 mmole/kg were more than an order of magnitude from the overall mean for all narcotics tested.
Reference	Pawlisz, A.V. and Peters, R.H. (1993). A test of the equipotency of internal burdens of nine narcotic chemicals using Daphnia magna. Environ. Sci. Technol. 27:2801-2806.

Type	other
Remark	This paper reports the results of a research program concerned with the analyses and explanation of differences in sensitivity of species to toxic substances using biological properties of the species. The project aims at the development of predictive

models, which, in analogy to QSARs, are called Quantitative Species Sensitivity Relationships. The distributions of acute toxicity data of different Species were studied for 26 chemicals.

Result: Chemicals with a specific mode of action have large sensitivity ratios whereas inert chemicals with lower toxicity have lower ratios. Acetone had the lowest ratio of all twenty-six chemicals studies.

Reference: Hoekstra, J.A., Vaal, M.A., Notenboom, J., and Sloof, W. (1994). Variations in the sensitivity of aquatic species to toxicants. Bull. Environ. Contam. Toxicol. 53:98-105.

Type: plant (various species)

Remark: This paper describes experiments conducted to test the effects of volatiles including (acetone) on seed deterioration during seed storage. Seeds tested were lettuce, soybean, sunflower, carrot, and rice. It has been shown that the yields of volatiles such as acetone in soybean seeds increase during seed development and decrease to trace levels after reaching yellow maturation. The authors showed in a preliminary study that the evolution of volatiles, such as acetone, is a widespread phenomenon occurring in stored seeds. Many types of dry seeds that were tested continued to evolve volatiles and accumulate them during storage. Acetone was found to have only slight deleterious effects on some species.

Reference: Zhang, M., Maeda, Y., Furihata, Y., Nakamaru, Y., and Esashi, Y. (1994). A mechanism of seed deterioration in relation to the volatile compounds evolved by dry seeds themselves. Seed Sci. Res. 4:49-56.

Type: aquatic (Daphnia magna)

Remark: This work examines the hypothesis that exposure of Daphnia magna to sublethal levels of narcotic contam-inants including acetone may affect subsequent sensitivity of animals. Prior exposure (24 h) of Daphnia to sublethal levels of acetone had no effect on their sensitivity to effective levels of these chemicals. Effective burdens (24-h acute exposure) were independent of the sublethal body burdens (24-h sublethal exposure) and of the sublethal water concentrations ($p < 0.025$). These results imply that animals from polluted sites should be no more resistant to high body residues of pollutants than those from clean sites and that the toxicity of narcotic organic compounds like acetone may be independent of the time course of uptake.

Reference: Pawlisz, A.V. and Peters, R.H. (1995). Effects of sublethal exposure on lethal body burdens of narcotic organic chemicals in Daphnia magna. Environ. Sci. Technol. 29:613-621.

4.9 Additional Reports

Remark	The objective of this paper is to compare the usefulness of a representative of the Urodela (Ambystoma mexicanum) and Anura (Xenopus laevis) species as biological indicators in toxicological bioassays. Toxicity test conditions were as follows: static, 1-L size, 20°C plus or minus 1°C, circadian light and dark schedule, 48-h exposure for acetone. The 48-h LC_{50} for A. mexicanum was 20,000 mg/L and the over 48-h LC_{50} for A. laevis was 24,000 mg/L.
Reference	Sloaff, W. and Baesselman, R. (1980). Comparison of the usefulness of Mexican Axolotl (Ambystoma mexicanum) and the clawed toad (Xenopus laevis) in toxicological bioassays. Bull. Environ. Contam. Toxicol. 24:439-443.
Remark	The effects of acetone on the growth of four fungi were determined to be as follows: EC_{50} for Polyporous hirsutus was greater than 2.0%, Pestalotia sp. was 1.25%, Sclerotinia homeocarpa was 0.88%, and Fusarium oxysporum was 1.8%. It was concluded that acetone was a moderately fungitoxic compound, but the specific mode of action was not elucidated.
Reference	Burrell, R.E. and Corke, C.T. (1980). Interactions of the solvent acetone with the fungicides benomyl and captan in fungal assays. Bull. Environ. Contam. Toxicol. 25:554-561.
Remark	This paper provides the 96-h TL_m (50% survival) for Lepomis macrochirus (bluegill sunfish) of 8300 ppm and the 120-h TL_m (50% reduction in number of cells produced) for the diatom Nitzschia linearis (widely distributed in unpolluted soft fresh waters of the U.S.) of 11,493-11,727 ppm acetone.
Reference	Patrick, R., Cairns, J., and Scheir, A. (1968). The relative sensitivity of diatoms, snails, and fish to twenty common constituents of industrial wastes. Progressive Fish Culturist 30:137-140.
Remark	Acetone is often used as a carrier solvent in aquatic bioassays at 100 ppm without affecting the evaluation of the test article. This paper provides comparative chronic data for Daphnia magna and Pimephales promelas. Endpoints evaluated include: survival of adults, number of young per adult, primiparous instar, days to primiparous instar, and total number of broods for the daphnid. Fish endpoints included: embryo survival, hatching rate, larval survival, length and weight. Differences between the solvent control (acetone and dilution water) and control dilution water were minimal.
Reference	McCarthy, J.F. and Whitmore, D.K. (1985). Chronic toxicity of di-n-butyl and di-n-octyl phthalate to Daphnia magna and the fathead minnow. Environ. Toxicol. Chem. 4:167-179.
Remark	Static acute and flow-through toxicity tests were performed with Daphnia magna. The 48-h LC_{50} value for acetone was 39,000 µL/L. The maximum acceptable toxicant concentrations determined during the chronic toxicity test with

acetone were between 1400 and 2800 µL/L. Acetone was sufficiently low in toxicity to suggest that the recommended usage limits for acetone as a co-solvent (500 µL/L during acute toxicity tests; 100 µL/L during chronic toxicity tests).

Reference
LeBlanc, G.A. and Surprenant, D.C. (1983). The acute and chronic toxicity of acetone, dimethylformamide, and triethylene glycol to Daphnia magna (Straus). Arch. Environ. Contam. Toxicol. 12:305-310.

Remark
A multi-species test procedure was used to measure the acute aquatic effects of acetone on seven aquatic species simultaneously: Asellus intermedius (pillbug), Daphnia magna (water flea), Dugesia tigrina (flatworm), Gammarus fasciatus (sideswimmer), Helisoma trivolvis (snail), Lumbriculus variegatus (segmented worm) and Pimephales promelas (fathead minnow). These species were chosen because of their ecological importance diversity, and amenability to laboratory culturing. The 96-h static LC_{50} for all species was > 100 mg/L.

Reference
Ewell, W.S., Gorsuch, J.W., Kringle, R.O., Robillard, K.A., and Spiegel, R.C. (1986). Simultaneous evolution of the acute effects of chemicals on seven aquatic species. Environ. Toxicol. Chem. 5:831-840.

Remark
The test species was Xenopus laevis and the endpoint was the minimum concentration inhibiting growth. The method was the frog embryo teratogenesis assay Xenopus (FETAX), as described by Damont et al. (1983). The 96-h bioassay determines the relative teratogenic potential. The purpose of this experiment was to determine whether carrier solvents interacted with the teratogens t-retinoic acid and 6-aminonicotinamide to affect survival, development, and growth of Xenopus embryos.

Result
The 96-h minimum concentrations that inhibited growth were: 18,000 mg/L for trial 1, 15,000 mg/L for trial 2, and 10,000 mg/L for trial 3.

Reference
Rayburn, J.R. Fort, D.J., McNew, R., and Bantel, J.A. (1991). Synergism and antagonism induced by three carrier solvents with t-retinoic acid and 6-aminonico-tinamide using FETAX. Bull Environ. Contam. Toxicol. 46:625-632.

Remark
The test species was Xenopus laevis and the endpoint was the reproduction rate for 12 weeks post-hatch at 0.10% acetone. The method uses groups of eggs that were put either in 800-mL jars or 3-L glass containers and maintained in aerated tap water at 22°C (plus or minus 1°C) under 16-h photoperiod conditions. According to the volume of water the eggs were reared in groups of 10 or 25. After hatching, tadpoles were fed Infusyl tablets. Each jar or tank was covered with a glass plate in order to limit evaporation. Water was changed weekly. Daily monitoring of egg and tadpole mortality was conducted

	throughout the first week of treatment. The metamorphosis pattern was investigated on surviving tadpoles.
Result	Growth by weight and development were slightly delayed in animals at the beginning of treatment (premetamor-phosis). After metamorphosis, the weight of juvenile Xenopus was higher than that of the water controls. It was speculated that acetone might first delay develop-ment; then because of feeding habits or other reasons, tadpoles could regain normal weight gain and even show a tendency for increased growth.
Reference	Marchal-Segault, D. and Tamade, F. (1981). The effects of lindane, an insecticide, on hatching and postembryonic development of Xenopus laevis (Daudin) Anauran Amphibian. Environ. Res. 24:250-258.

5. Toxicity

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type	LD_{50}
Species	rat
Value	ca. 5800 mg/kg
GLP	no data
Test substance	no data
Reference	Freeman, J.J. and Hayes, E.P. (1985). Acetone potentiation of acute acetonitrile toxicity in rats. J. Toxicol. Environ. Health 15:609-621.

Type	LD_{50}
Species	rat
Value	ca. 8400 mg/kg
GLP	no
Test substance	no data
Reference	Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. (1962). Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

Type	LD_{50}
Species	rat
GLP	no
Test Substance	analytical grade acetone (ACS specifications).
Remark	Groups of 6-12 male and female Sprague-Dawley rats of various ages were intubated with neat acetone. They were observed for 1 week. LD_{50} values in g/kg (95% confidence limits) were: newborn, 1.7 (1.3-3.0), 14-day-old, 4.4 (3.1-6.3), young adults [80-160 g], 7.2 (5.4-9.5), older adults [300-470 g], 6.7 (6.1-7.3).
Reference	Kimura, E.T., Ebert, D.M., and Dodge, P.W. (1971). Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704.

Type	LD_{50}
Species	mouse
Value	ca. 5250 mg/kg
GLP	no data
Test substance	no data
Remark	Male ddY mice weighing 24-27 g were intubated with acetone following ip injection of 0.16 mL of olive oil/g. LD_{50} value of 5250 mg/kg was reported with a 95% confidence range of 3580-7700 mg/kg.
Reference	Tanii, H., Tsuji, H., and Hashimoto, K. (1986). Structure-toxicity relationship of monoketones. Toxicol. Lett. 30:13-17.

5.1.2 Acute Inhalation Toxicity

Type	LC_0
Species	rat
Exposure Time	30 minute
Value	16,000 ppm
GLP	no
Test substance	no data
Remark	Female rats were exposed (whole body exposure) to acetone at nominal air concentrations of the following: 6/6 rats died at 32,000 ppm; 1/6 animals exposed to 16,000 ppm acetone for 4 hours also died.
Reference	Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel J.A. (1962). Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

Type	LC_{50}
Species	rat
GLP	no
Test substance	no data
Remark	LC_{50} values with 95% confidence intervals for 4-hr and 8-hr exposures were 32,000 ppm (27,400-37,200) and 21,000 ppm (17,900-24,800). Exposure was to female Carworth Farms-Nelson rats.
Reference	Pozzani, U.C., Weil, C.S., and Carpenter, C.P. (1959). The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Am. Ind. Hyg. Assoc. J. 20:364-369.

5.1.3 Acute Dermal Toxicity

Type	LD_0
Species	rabbit
Value	>7400 mg/kg
GLP	no
Test substance	no data

Remark	Exposure time was 24 hours. Both sexes were used; skin was abraded. Test substance was "practical" grade.
Reference	Roudabush, R.L., Terhaar, C.J., Fassett, D.W., and Dziuba, S.P. (1965). Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicol. Appl. Pharmacol. 7:559-565.

Type	LD_0
Species	guinea pig
Value	> 7400 mg/kg
Method	other
GLP	no
Test substance	no data
Remark	Male Hartley-derived guinea pigs were used; abraded and intact skin was exposed for 24 h to a "practical" grade of acetone.
Reference	Roudabush, R.L., Terhaar, C.J., Fassett, D.W., and Dziuba, S.P. (1965). Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicol. Appl. Pharmacol. 7:559-565.

Type	LD_{50}
Species	rabbit
Value	>15,700 mg/kg
GLP	no
Test substance	no data
Remark	Exposure was for a 24-h period. The hair was completely clipped from the trunk of four male albino rabbits. The dose was injected under an impervious plastic film (method of Draize et al., J. Pharmacol. Exp. Therap. 82:377, 1944). Animals were observed for 14 days.
Reference	Smyth, H.F., Carpenter, C.P., Weil, C.S. (1962). Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

5.2. Corrosiveness and Irritation

5.2.1 Skin Irritation

Species	rabbit
Result	not irritating
Classification	not irritating
GLP	no
Test substance	no data
Remark	Exposure time was 24 h. Acetone, 0.01 mL, was applied to the shaved stomach of 5 rabbits.
Reference	Smyth, H.F., Carpenter, C.P., and Weil, C.S. (1962). Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

5.2.2 Eye Irritation

Species	rabbit
Result	highly irritating
Classification	irritating
GLP	no
Test substance	no data
Method	20 µL of acetone was added to the center of cornea and the eye was read 18-24 h later and scored after staining with fluorescein.
Results	The dose administered was 15.8 mg. Acetone was assigned a rating of Grade 5 in system with maximum of Grade 10. The 10-grade ordinal series is based upon the degree of corneal necrosis that results from instillation of various volumes and concentrations of a chemical. Grade 1 indicates at most a very small area of necrosis resulting from 0.5 mL of undiluted chemical in the eye. Grade 5 indicates a severe burn from 0.005 mL, and grade 10 indicates a severe burn from 0.5 mL of a 1% solution in water or propylene glycol.
Reference	Carpenter, C.P. and Smyth, H.F. (1946). Chemical burns of the rabbit cornea. Am. J. Ophthamol. 29:1363-1372. Smyth, H.F., Carpenter, C.P., and Weil, C.S. (1962). Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

Species	rabbit
Result	highly irritating
Classification	irritating
Method	Draize Test
GLP	no data
Test substance	no data
Remark	0.1 mL of acetone was placed in the conjunctival sac and the eye was scored at 24 h. The data from this study indicate that corneal thickening is directly related to eye irritation and damage (r=0.86). Acetone eye swelling (215%) was rated as severe. Irritancy ratings for aqueous solutions were: 3, 10, and 30% acetone, mild irritation; 1% acetone, mild/slight irritation; corneal thickening ratings for 1, 3, 10, and 30% aqueous acetone solutions were all mild.
Reference	Kennah, H.E.. Hignet, S., Laux, P.E., Dorko, J.D., and Barrow, C.S. (1989). An objective procedure for quantifying eye irritation based upon changes of corneal thickness. Fund. Appl. Toxicol. 12:258-268.

5.3 Sensitization

Type	Mouse ear swelling test
Species	mouse
Result	not sensitizing
Classification	not sensitizing
GLP	no data

Test substance	no data
Method	Following removal of hair with clippers, mice are injected twice intradermally in the test area with Freund's complete adjuvant. The mice are tape stripped in the application area, and the chemical or solution (0.1 mL) is applied topically. Stripping and application of the Test substance is repeated on three additional consecutive days. Seven days later, 20 µL of test compound or solution is applied to the left ear and 20 µL of the vehicle (if any) is applied to the right ear. Twenty-four and 48-h later, the ear thicknesses are measured while the animals are under light ether anesthesia.
Remark	This test was reported to have correctly identified 48/49 known human sensitizers and 23/23 known human nonsensitizers. The missed compound was a weak human sensitizer. Acetone was also not a sensitizer in a modified MEST that used a patch-test procedure for the sensitization step.
Result	Acetone was not a sensitizer in a similar mouse ear sensitization test (Descotes, 1988) or in a modification of the guinea pig maximization test of Magnusson and Kligman (Nakamura et al., 1994).
Reference	Gad, S.C., Dunn, B.J., Dobbs, D.W., Reilly, C., and Walsh, R.D.(1986). Development and validation of an alternative dermal sensitization test: The mouse ear swelling test (MEST). Toxicol. Appl. Toxicol. 84:93-114. Descotes, J. (1988). Identification of contact allergens: The mouse ear sensitization assay. J. Toxicol. Cutaneous Ocular Toxicol. 7:262-272. Nakamura, A., Momma, J., Sekiguchi, H., Noda, T., Yamano, T., Kaniwa, M., Kojima, S., Tsuda, M., and Kurokawa, Y. (1994). A new protocol and criteria for quantitative determination of sensitization potencies of chemicals by guinea pig maximization test. Contact Dermatitis 31:72-85.

5.4 Repeated Dose Toxicity

Species	mouse
Strain	B6C3F1
Sex	male/female
Route of Administration	drinking water
Exposure Period	14 days and 13 weeks
Frequency of Treatment	ad libitum
Post Exposure Observation Period	none
Doses	14 days: 0.5, 1.0, 2.0, 5.0, and 10.0%; 5 mice/sex. 13-week females: 0.25, 0.5, 1.0, 2.0, and 5.0%; 10 mice each. 13-week males: 0.125, 0.25, 0.5, 1.0, and 2.0%; 10 mice each.
Control Group	Yes
Method	OECD Guideline 407 OECD Guideline 408 was used for the 13-week studies.

GLP	yes
Test substance	as prescribed by 1.1-1.4
Remark	NOEL: 1% (males: 14 days, 1579 mg/kg; 13 weeks, 2258 mg/kg; females: 14 days, 3023 mg/kg; 13 weeks, 4156 mg/kg.
Remark	LOEL: 2% (males: 14 days, 3896 mg/kg; 13 weeks, 4858 mg/kg; females: 14 days, 5481 mg/kg; 13 weeks, 5945 mg/kg.
Remark	Mice, 6-7 weeks old at start of the study, were housed individually. Drinking water containing acetone and NIH 07 feed were provided ad libitum. The time-weighted average dosages were: 14-day males, 965, 1579, 3896, 6348, 10,314 mg/kg; 14-day females, 1569, 3023, 5481, 8804, 12,725 mg/kg; 13-week males, 380, 611, 1353, 2258, 4858 mg/kg; 13-week females, 892, 2007, 4156, 5945, 11,298 mg/kg. Body weights were determined weekly and water consumption twice weekly. At necropsy, liver, right kidney, right testis, heart, thymus, brain, lungs, and, at 13 weeks only, spleen were taken for determination of weights and histopathology. Blood samples were obtained before the 13-week sacrifice for measurement of hematological indices. Male reproductive endpoints were assessed and stage and length of the estrous cycle were evaluated in females.
Result	Water consumption, and thus acetone dose, was reduced at acetone concentrations of 5% and above. There were no deaths during the studies. Body weight gain was depressed in mice given 10% acetone in the 14-day study only. There were no treatment-related clinical signs of toxicity. Absolute and relative liver weights in female mice only were significantly elevated in the 13-week 5% group; similar increases were seen in the 14-day animals. Hematological changes observed in the 13-week animals were increased hematocrit in 5% females ($p < 0.01$), increased hemoglobin in 2% ($p < 0.05$) and 5% ($p < 0.01$) females and 0.5, 1.0, and 2% males ($p < 0.05$). Histopathological alterations were seen only in mice during the 14-day studies; these included centrilobular hepatocellular hypertrophy in 5 of 5 male mice in each of the 2, 5, and 10% groups, 2 of 5 females in the 5% group, and 5 of 5 females in the 10% group. There were no changes in male or female reproductive indices.
Reference	Dietz, D.D., Leininger, J.R., Rauckman, E.J., Thompson, M.B., Chapin, R.E., Morrissey, R.L., and Levine, B.S. (1991). Toxicity studies of acetone administered in the drinking water of rodents. Fund. Appl. Toxicol. 17:347-360.
Species	rat
Strain	Fischer 344
Sex	male/female
Route of Administration	drinking water
Exposure Period	14 days and 13 weeks
Frequency of Treatment	ad libitum
Post Exposure	

Observation Period	none
Doses	14-day: 0.5, 1.0, 2.0, 5.0, 10%; 5/sex/dose level. 13-week: 0.25, 0.5, 1.0, 2.0, 5.0%; 10/sex/dose level.
Control Group	Yes
Method	OECD Guideline 407 OECD Guideline 408 was used for the 13-week studies.
GLP	yes
Test substance	as prescribed by 1.1-1.4
Remark	Rats, 6-7 weeks old at start of the study, were housed 5 per cage. Drinking water containing acetone and NIH 07 feed were provided ad libitum. The time-weighted average doses were: 14-day males, 714, 1616, 2559, 4312, and 6942 mg/kg; 14-day females, 751, 1485, 2328, 4350, 8560 mg/kg; 13-week males, 200, 400, 900, 1700, and 3400 mg/kg; 13-week females, 300, 600, 1200, 1600, and 3100 mg/kg. Body weights were determined weekly and water consumption twice weekly. At necropsy, liver, right kidney, right testis, heart, thymus, brain, lungs, and, at 13 weeks only, spleen were taken for determination of weights and histopathology. Blood samples were obtained before the 13-week sacrifice for measurement of hematological indices. Male reproductive endpoints were assessed, and stage and length of the estrous cycle were evaluated in females.
Remark	NOEL was 2% for 14-day (males: 2%, 2559 mg/kg; females: 5%, 4350 mg/kg); 1% for 13-week (males: 1%, 900 mg/kg; females: 5%, 3100 mg/kg). LOEL was 5% for 14-day (males: 5%, 4312 mg/kg; females: 10%, 8560 mg/kg); 2% for 13-week (males: 2%, 1700 mg/kg).
Result	No deaths were seen during the study. Water consumption, and thus the acetone dose, was reduced in rats given 5% or greater level of acetone. Body weights were depressed in male and female rats given 5 or 10% acetone in both the 14-day and 13-week studies. There were no treatment-related clinical toxic signs during the studies. During the 13-week study, relative kidney (both sexes), liver (both sexes), and testis weights were found in the 2 and 5% groups. Similar increases were reported to have occurred in the 14-day study at the same or lower doses (numbers not given). Hematological effects included mild lymphocytosis in male rats at 2% and male and males at 5%, decreased erythrocyte counts and hemoglobin levels at 2 and 5% and reticulocyte counts at 0.5% in male rats, and increased mean corpuscular hemoglobin and mean cell volume at 1% and higher in males and in 5% females. Platelet counts were mildly depressed in males and females in the 5% dose groups. Histopathologic lesions included bone marrow hypoplasia in 5 of 5 male rats given 10% acetone in the 14-day study. Dose-related increases in the incidence and severity of nephropathy, similar to that seen in aging rats, were seen in male rats. Minimal-to-mild splenic pigmentation was seen in male rats at the 2% and 5% dose levels in the 13-week studies. Acetone exposure of male rats for 13 weeks resulted in

	depressed sperm motility, cauda epididymal weight, and epididymal weight and an increased incidence of abnormal sperm. There was no indication of changes in vaginal cytology suggestive of changes in the estrous cycle.
Reference	Dietz, D.D., Leininger, J.R., Rauckman, E.J., Thompson, M.B., Chapin, R.E., Morrissey, R.L., and Levine, B.S. (1991). Toxicity studies of acetone administered in the drinking water of rodents. Fund. Appl. Toxicol. 17:347-360.
Species	rat
Strain	Sprague-Dawley
Sex	male/female
Route of Administration	gavage
Exposure Period	93, 94, or 95 days (interim sacrifice at 46 or 47 days)
Frequency of Treatment	once/day
Post Exposure	
Observation Period	1 day
Doses	100, 500, 2500 mg/kg; 30 M/30 F per dose levelControl Groupyes
Method	OECD Guideline 408
GLP	yes
Test substance	as prescribed by 1.1-1.4
Remark	Thirty male and 30 female 31-day-old rats were housed individually. Animals were dosed once/day by oral gavage with solutions of 0, 1.0, 5.0, or 25% acetone in reagent grade water. Dosing volumes were adjusted weekly for body-weight changes. Animals were dosed for 46-47 days (interim sacrifice) or 93-95 days (final sacrifice). Retroorbital blood samples and urine were collected prior to interim sacrifice of 10 males and 10 females from each group at 46-47 days and 20 males and 20 females from each group at 94-96 days (one day after end of dosing period). Ophthalmic examinations were conducted prior to study termination. Extensive gross pathological examination was performed at necropsy at which time organs were removed for determination of weights at final sacrifice. Approximately 26 organs or tissues and all tissue masses were removed at final necropsy and prepared for histological examination.
Result	One control female (day 85), one 100 mg/kg female (day 3), two 2500 mg/kg males (days 6 and 36), and three 2500 mg/kg females (days 3, 3, and 56) died during the study; deaths of 5 of the 6 were ascribed to dosing errors. No toxicologically significant effects on body weight or food intake were seen. Clear salivation and clear salivation prior to dosing were seen in both sexes in the 2500 mg/kg group. Hemoglobin, hematocrit, and mean cell volume were significantly increased in males of the 2500 mg/kg group at the interim sacrifice. At the final sacrifice, hemoglobin, hematocrit, mean cell volume, and mean cell hemoglobin were significantly elevated in 2500 mg/kg males and hemoglobin and hematocrit in 2500 mg/kg females. Statistically sig-nificant differences at final sacrifice

included decreased platelet count in 2500 mg/kg males, increased mean cell volume in 500 mg/kg females, increased alanine amino-transferase in 2500 mg/kg females at the interim sacrifice and in males at the final sacrifice, depressed glucose and potassium levels in 2500 mg/kg males at the final sacrifice. Other statistically significant and nonsignificant changes were reported in 2500 mg/kg males and females at the final sacrifice, but these were not considered toxi-cologically significant. Statistically significant organ weight changes included increased kidney weights in 500 and 2500 mg/kg females, increased kidney-to-body and -brain weight ratios for males and females in the 2500 mg/kg group, increased liver/body weight ratio in 2500 mg/kg males, increased liver weights, and liver-to-body and -brain ratios in 2500 mg/kg females, depressed brain weights in 2500 mg/kg males, and increased heart/brain weight ratio in 2500 mg/kg females. Histopathological findings included renal proximal tubule degeneration in control and exposed animals of both sexes and intracyto-plasmic droplets or granules (hyaline droplets) in the proximal tubular epithelium in control and exposed animals, predominantly in males. (Kidney lesions are expected components preceding the development of chronic progressive glomerulonephtopathy, a common aging syndrome in Sprague-Dawley rats.) Although the incidence levels for both of these lesions were similar in control and exposed animals, the severity of distribution was markedly altered with increasing dose. In male rats, testicular interstitial edema was seen in both control and test animals with similar incidence and severity. Reactive hyperplasia of the mesenteric and mandibular lymph nodes and splenic granular pigmentation was seen more commonly in 2500 mg/kg male rats; these increases were not statistically or biologically significant.

Reference	Mayhew, D.A. and Morrow, L.D. (1988). Ninety-day gavage study in albino rats using acetone. United States Environmental Protection Agency Contract No. 68-01-7075. American Biogenic Corporation Study 410-2313.
Species	rat
Strain	Sprague-Dawley
Sex	male
Route of Administration	inhalation
Exposure Period	2, 4, and 8 weeks
Frequency of Treatment	3 h/day, 5 days/wk
Post Exposure Observation. Period	2 weeks (following 8-week exposure only)
Doses	19,000 ppm; 9 animals (total)/time-of-exposure group
Control Group	yes
GLP	no data
Test substance	ACS Grade, Instr-Analyzed (J.T. Baker)
Remark	Groups of rats were exposed to 19,000 ppm of acetone for 3 h per day. Exposures were repeated 5 times per week for 2, 4, or

	8 weeks. At 2, 4, and 8 weeks of exposure and 2 weeks postexposure, groups of 5 exposed animals and 5 controls were weighed and anesthetized (pentobarbital), and blood was withdrawn for deter-mination of serum glutamic-oxaloacetic transaminase (SGOT, lactic dehydrogenase (LDH), and blood urea nitrogen (BUN). The rats were killed, and the whole brain, lungs, kidneys, and liver were removed and weighed. Lungs were also weighed dry to determine fluid content, and triglyceride was determined in liver. At each time interval, 4 exposed rats and 4 controls were killed, and liver, heart, lung, kidney, and brain were taken for histopathological examination.
Result	Body weight gain was slightly, but nonsignificantly ($p>0.05$), depressed throughout the exposure period and 2 weeks postexposure. Brain and kidney weights were depressed during the exposure period only. Nonsignif-icant increases in SGOT (AST) were seen at 2, 4, and 8 weeks. No other effects were seen. Although body, brain, and kidney weights were depressed and SGOT was slightly elevated, there were no statistically significant findings with respect to any toxicological index meas-ured. There were no untoward histopathological findings.
Reference	Bruckner, J.V. and Peterson, R.G. (1981). Evaluation of toluene and acetone inhalant abuse. II. Model develop-ment and toxicology. Toxicol. Appl. Pharmacol. 61:302-312.

5.5 Genetic Toxicity in Vitro

Type	chromosomal aberration
System of Testing	Chinese hamster lung fibroblast cell line CHL (Cancer Research Institute: Tokyo)
Concentration	40 mg/mL
Metabolic Activation	with and without
Result	positive
GLP	no data
Test substance	no data
Remark	Cells were exposed to chemical for 24 or 48 h. Colcemid added 2 h before harvesting cells, which were trypsin-ized, suspended in hypotonic KCl for 13 min, and separated by centrifuging. The cells were fixed with acetic acid-methanol and fixed on glass slides, which were air dried. The cells were stained with Giemsa, and 100 metaphases were scored for polyploid cells and structural chromosomal aberrations.
Result	Acetone produced 6.0% polyploid cells at 48 h, and 28.0% cells with structural aberrations were at 24 h. The authors consider an incidence of less than 4.9% aberrations to be negative and greater than 10% to be positive. The dose at which structural aberrations were detected in 20% of the metaphases observed (D20) was 36.9 mg/mL. The authors noted that the test was positive at 48 h also, but negative in the presence of S9 mix. Control and solvent-control (saline,

	DMSO, ethanol, sodium carboxymethyl cellulose) incidences of aberrations were said to be 3% or less.
Reference	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matsuoka, A. (1984). Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol. 22:623-636.
Type	chromosomal aberration
System of Testing	Chinese hamster ovary cells
Concentration	0.5-5.0 mg/mL
Metabolic Activation	with and without
Result negative	
GLP	no data
Test substance	as prescribed by 1.1-1.4
Remark	Cells were exposed to chemical for 8 h, washed to remove the test chemical, and treated with colcemid for 2.0-2.5 h before cell harvest. The method of Galloway et al., Environ. Mutagen. 7,1985 was followed except that the total duration of 10-12 h. The cells were fixed with 3:1 acetic acid-methanol and stained with 5% Giemsa on glass slides. Simple, complex, and "other" aberrations were determined on 100-200 cells. Chromatid and chromosome gaps were recorded but were not used in the analysis.
Result	Acetone produced 0-3.5% simple aberations and 0-2% complex aberations, and a total percentage of 1.5-4.0% for the three dose levels tested. The results were equal to or less than the values observed with untreated control cells.
Reference	Loveday, K.S., Anderson, B.E., Resnick, M.A., and Zeiger, E. (1990). Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V: Results with 46 chemicals. Environ. Mol. Mutagen. 16:272-303.
Type	sister chromatid exchange
System of Testing	Chinese hamster ovary cells
Concentration	0.05-5.0 mg/mL
Metabolic Activation	with and without
Result negative	
GLP	no data
Test substance	as prescribed by 1.1-1.4
Remark	Cells were exposed to chemical for 2 h before adding bromodeoxyuridine (BrdUrd), which was incubated for 24 h. After 26 h fresh medium with BrdUrd and colcemid was added for an additional 2-2.5 h at 37°C. Cells were examined for signs of toxicity (confluence in the monolayer) before harvesting. Cells were separated by centrifugation, fixed with 3:1 acetic acid-methanol, fixed on glass slides, and stained with Hoechst 33258 and then 5% Giemsa. Fifty (50) second division metaphase cells were scored for sister chromatid exchanges (SCEs).
Result	Acetone produced 8.5-8.7 SCEs per cell when tested without activation at the three dose levels examined. When tested with

	activation 6.4-7.5 SCEs per cell were observed. The results were equal to or less than the values observed with untreated control cells. A postive trend test with at 20% increase in chromatid exchanges with at least one dose was required for a positive response.
Reference	Loveday, K.S., Anderson, B.E., Resnick, M.A., and Zeiger, E. (1990). Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V: Results with 46 chemicals. Environ. Mol. Mutagen. 16:272-303.
Type	two-stage cell transformation assay
System of Testing	BALB/3T3 clone A31-1-1 (JCRB0601)
Concentration.	0.5%
Metabolic Activation	without
Result negative	
GLP	no data
Test substance	no data
Method	BALB/3T3 cells in culture were treated with test chem-ical (but not acetone) for 72 h. The chemical was removed, and the cells were grown in medium for 3 days. The promoter 12-O-tetradecanoylphorbol 13-acetate (TPA) or 0.5% acetone was added. After two weeks, the promoter was removed, and the cells were grown for 3 weeks at which time they were collected and stained with Giemsa.
Remark	Acetone caused no transformation when applied during the promotion phase to cells treated with DMSO. It is not clear that cells were treated with acetone alone or with acetone followed by TPA. TPA was, however, applied to the cells in acetone solution.
Reference	Sakai, A. and Sato, M. (1989). Improvement of carcin-ogen identification in BALB/3T3 cell transformation by application of a 2-stage method. Mutat. Res. 214:285-296.
Type	minimal inhibitory concentration
System of Testing	trp- E. coli, 3 strains: WP2 (wild-type, repair proficient), WP67 (uvr- polA-), and CM871 (uvrA- recA- lexA-).
Concentration.	Up to 40 mg/well
Metabolic Activation	with and without
Result	negative
GLP	no data
Test substance	no data
Method	Six replicates (rows) of eight twofold dilutions of each compound were prepared in Microtiter plates. Three rows were filled with phosphate-buffered saline and three with S9 mix. One strain of each of the three bacteria was added to each of the eight wells in one of the rows. The plates were incubated at 37°C and observed for increases in turbidity or the formation of a pellet of settled cells. Apparently positive results were confirmed by subculture on agar plates. Method is liquid micromethod modification of the rec-assay system with B.

	subtilis (Kada et al., 1981) and the E. coli system of McCarroll et al. (1981).
Remark	Method results in a minimal inhibitory concentration (MIC). The MIC for acetone under each condition of strain and activation (six values) was > 40 mg/well. A ratio between the MICs in repair-proficient (WP2) and repair-deficient (WP67 and CM871) strains greater than 2 was considered to be significant in the test. Although these ratios could not be obtained for acetone (since all values were "> 40 mg"), the values suggest that acetone would be an extremely weak DNA-damaging agent if it were positive. The overall accuracy for predicting car-cinogenicity for the DNA-repair test was 72.4% for a battery of 75 of the 135 compounds for which clear carcinogenicity data were available and that included several compounds reported to be nonmutagenic carcin-ogens or noncarcinogenic mutagens.
Reference	De Flora, S., Zanacchi, P., Camoirano, A., Bennicelli, C., and Badolati, G.S. (1984). Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test. Mutat. Res. 133:161-198. Kada, T., Hirano, K., and Shirasu, Y. (1980). Screening of environmental chemical mutagens by the Rec-assay system with Bacillus subtilis. In: De Serres, F.J. and Hollaender, A. (Eds.). Chemical Mutagens, Vol. 6, Plenum, New York, 149-173. McCarroll, N.E., Piper, C.E., and Keech, B.H. (1981). An E. coli microsuspension assay for the detection of DNA damage induced by direct-acting agents and promutagens. Environ. Mutagen. 3:429-444.
Type	mitotic chromosomal malsegregation, mitotic recombination, and point mutations.
System of Testing	Saccharomyces cerevisiae diploid strain D61.M
Concentration.	6.82-7.83%
GLP	no data
Test substance	no data
Remark	Chemicals were at least 97%
Results	Positive for aneuploidy; negative for mitotic recombination and point mutations.
Method	Chemicals were pipetted directly into growing cultures in peptone-glucose-yeast extract (YEPD) medium and incubated at 28°C for 4 h, placed in an ice bath for < 16 h, and then incubated at 28°C on a shaker for 4 h (cold-interruption procedure). Samples of cultures were plated on a selective cyclohexamide medium. After 6-7 days, the plates were scored for colony color and numbers. Red colonies reflect cumulative effects of events like point mutations, mitotic recombinations, and deletion of chromosomal fragments. White colonies

	contain presumptive monosomics; these are confirmed by establishment of a requirement for leucine.
Remark	Acetone gave inconsistent results with the original protocol, which did not have the ice-storage step. The authors found that storage in ice for 16 h or more fol-lowing the initial incubation gave repeatable positive results (Zimmermann et al. 1984). Most of the cyclohex- amide-resistant colonies were white and almost all of these were leucine requiring, indicating that these colonies were monosomics. Red resistant colonies did not increase and were not significantly leucine requiring, indicating that acetone did not induce point mutations or recombinations under the test conditions.
Remark	Using the method of Zimmermann et al. (1985), Mayer and Goins (1994) reported that concentrations of acetone up to 459 mM (2.7%) did not cause chromosome loss or mutations in S. cerevisiae D61.M. In an interlaboratory comparison of mitotic chromosome loss in S. cerevisiae, acetone was positive in one laboratory at levels of ca. 45-55 mg/mL using the cold-interruption procedure of Zimmermann et al. (1985) but negative in a second lab-oratory. Both laboratories reported acetone negative using the standard procedure with overnight incubation at 28°C (Whittaker et al., 1989). Acetone was positive for production of aneuploidy in S. cerevisiae using the cold-interruption procedure of Zimmermann et al. (1985) at levels > 40 mg/mL. It was negative using the standard procedure and did not produce other genetic effects (gene mutation, mitotic recombination, etc.) with either protocol (Albertini, 1991). The merokinetic effect (multipolarity) of acetone on chromosome division of human leukocytes was reported by Kabarity (1969). Acetone caused the formation of multiple-spindle apparatus leading to the movement of each part of the centrosome to one pole. The author concluded that lymphoma TK+/- 3.7.2C cells
Concentration.	10-30 mg/mL
Metabolic Activation	without
	Resul0 Reference EHRT (1987). Screening of Priority Chemicals for Reproductive Hazards. Environmental Health Research and Testing, Inc. Cincinnati, OH. Project No. ETOX-85-

EXTRACT FROM IRPTC LEGAL FILES

File: 17.01 LEGAL **rn : 3971**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : AUS type : REC

subject	specification	descriptor
AIR	OCC	TLV

TWA: 1780MG/M3 (750PPM) STEL: 2375MG/M3 (1000PPM)
entry date: MCH 1985

original : ILO , , , , ,
amendment: AOHGN*, APPROVED OCCUPATIONAL HEALTH GUIDE THRESHOLD LIMIT VALUES, , , , 1983

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File: 17.01 LEGAL **rn : 14731**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : BEL type : REC

subject	specification	descriptor
AIR	OCC	TLV

TWA: 1780MG/M3 (750PPM); STEL: 2375MG/M3 (1000PPM)
entry date: JUL 1987

original : ILO , , , , ,
amendment: TLVBE*, THRESHOLD LIMIT VALUES(TOLERABLE LIMIT VALUES), , , , 1984

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File: 17.01 LEGAL **rn : 15424**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : FIN type : REC

subject	specification	descriptor
AIR	OCC	MPC

TWA: 1200MG/M3 (500PPM) STEL: 1500MG/M3 (625PPM)
entry date: MAY 1989

original : ILO , , , , ,
amendment: APWFI*, HTP-ARVOT (LIST OF LIMIT VALUES FOR CONCENTRATIONS OF TOXIC SUBSTANCES KNOWN TO BE HARMFUL TO HEALTH), 25 , , 10 ,

1988

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File: 17.01 LEGAL **rn : 16007**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : HUN type : REG

subject	specification	descriptor
AIR	OCC	MAC

TWA: 200MN/M3; STEL(30 MIN): 1000MG/M3
entry date: MCH 1985

original : ILO , , , , ,
amendment: HSMSZ*, HUNGARIAN STANDARD MSZ NO., 21461-78 , , , 1978

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File: 17.01 LEGAL **rn : 16192**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : ITA type : REC

subject	specification	descriptor
AIR	OCC	TLV

1000MG/M3 (420PPM)
entry date: MCH 1985

original : ILO , , , , ,
amendment: TLVIT*, VALORI LIMITE PONDERATI(APPRAISED LIMIT VALUES), , ,

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File: 17.01 LEGAL **rn : 16428**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : NLD type : REC

subject	specification	descriptor
AIR	OCC	MXL

TWA: 1780MG/M3 (750PPM)
entry date: JUN 1987

original : ILO , , , , ,
amendment: NMACN*, NATIONALE MAC-LIST(NATIONAL MAC-LIST), , , , 1986

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File: 17.01 LEGAL **rn : 16943**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : POL type : REG

subject	specification	descriptor
AIR	OCC	MPC

TWA: 200MG/M3
entry date: MCH 1985

original : ILO , , , , ,
amendment: OMLWS*, ORDINANCE OF THE MINISTER OF LABOUR, WAGES AND SOCIAL AFFAIRS, 22DEC , , , 1982

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File: 17.01 LEGAL **rn : 17169**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : ROM type : REG

subject	specification	descriptor
AIR	OCC	MPC

TWA: 1000MG/M3; CLV: 1500MG/M3
entry date: MCH 1985

original : ILO , , , , ,
amendment: OMHRO*, ORDINANCE OF THE MINISTRY OF HEALTH, 60 , , , 1975

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File: 17.01 LEGAL **rn : 17543**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : CHE type : REG

subject	specification	descriptor
AIR	OCC	MAK

TWA: 1780MG/M3 (750PPM)
entry date: DEC 1987

original : ILO , , , , ,
amendment: ZWACH*, ZULAESSIGE WERTE AM ARBEITSPLATZ(PERMITTED VALUES IN THE WORKPLACE), , , , 1987

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File: 17.01 LEGAL **rn : 18086**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : YUG type : REG

subject	specification	descriptor
AIR	OCC	MAC

TWA: 800MG/M3 (336PPM)
entry date: MCH 1985

original : ILO , , , , ,
amendment: ORYUG*, ORDINANCE, 24-3698/1 , , , 1971

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File: 17.01 LEGAL **rn : 50877**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : IMO type : REG

subject	specification	descriptor
AQ	EMI	PRMT
AQ	MARIN	PRMT

This substance is presently considered to present no harm to human health, marine re sources, amenities or other legitimats uses of the sea when discharged into the sea from tank cleaning or deballasting operations
entry date: APR 1993

original : IMODC*, , , , , 1992

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File: 17.01 LEGAL **rn : 100031**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : ARG type : REG

subject	specification	descriptor
AIR	OCC	MPC

8H-TWA : 1780 MG/M3 (750 PPM), 15MIN-STEL : 2375 MG/M3 (1000 PPM)
(MAXIMUM 4 TIMES/DAY WITH INTERVALS OF A LEAST 60 MINUTES)
entry date: OCT 1991 effective date: 29MAY1991

title: LIMIT VALUES FOR CHEMICAL SUBSTANCES IN THE WORKING ENVIRONMENT-RESOLUTION NO. 444/1991 OF THE MINISTRY OF WORK AND SOCIAL SECURITY (AMENDING REGULATION DECREE NO. 351/1979 UNDER LAW NO. 19587/1972: HYGIENE AND SAFETY AT WORK)
original : ARGOB*, Boletin Oficial de la Republica Argentina(Argentinian Official Bulletin), 24170 , I , 1 , 1979
amendment: ARGOB*, Boletin Oficial de la Republica Argentina(Argentinian Official Bulletin), 27145 , I , 4 , 1991

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File: 17.01 LEGAL **rn : 300477**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : CAN type : REG

subject	specification	descriptor
AIR	OCC	TLV

TWA: 750 PPM, 1,780 MG/M3; STEL: 1,000 PPM, 2,375 MG/M3. PRESCRIBED BY THE CANADA OCCUPATIONAL SAFETY AND HEALTH REGULATIONS, UNDER THE CANADA LABOUR CODE (ADMINISTERED BYTHE DEPARTMENT OF LABOUR). THE REGULATIONS STATE THAT NO EMPLOYEE SHALL BE EXPOSED TO A CONCENTRATION OF AN AIRBORNE CHEMICAL AGENT IN EXCESS OF THE VALUE FOR THAT CHEMICAL AGENT ADOPTED BY ACGIH (AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS) IN ITSPUBLICATION ENTITLED: "THRESHOLD LIMIT VALUE AND BIOLOGICAL EXPOSURE INDICES FOR 1985-86".
entry date: MCH 1991 effective date: 13MCH1986

amendment: CAGAAK, Canada Gazette Part II, 120 , 6 , 1105 ,

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File: 17.01 LEGAL **rn : 301601**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : CAN type : REG

subject	specification	descriptor
TRNSP LABEL PACK		CLASS RQR

PIN (PRODUCT IDENTIFICATION NO.): UN1090. CLASS (3.1): FLAMMABLE LIQUID. SPECIAL PROVISIONS: 99. PACKING GROUP II, (I=GREAT DANGER, III=MINOR DANGER). MAXIMUM AMOUNT PER PACKAGE THAT MAY BE TRANSPORTED ON PASSENGER AIRCRAFT OR VEHICLE: 5 L. MAXIMUM AMOUNT PER PACKAGE THAT MAY BE TRANSPORTED ONA CARGO AIRCRAFT: 60 L. PRESCRIBED BY THE TRANSPORTATION OF DANGEROUS GOODS REGULATIONS, UNDER THE TRANSPORTATION OF DANGEROUS GOODS ACT (ADMINISTERED BY THE DEPARTMENT OF TRANSPORT). THE ACT AND REGULATIONS ARE INTENDED TO PROMOTE SAFETY INTHE TRANSPORTATION OF DANGEROUS GOODS IN CANADA, AS WELL AS PROVIDE ONE COMPREHENSIVE SET OF RULES APPLICABLE TO ALL MODES OF TRANSPORT ACCROSS CANADA. THESE ARE BASED ONUNITED NATIONS RECOMMENDATIONS. THE ACT AND REGULATIONS SHOULD BE CONSULTED FOR DETAILS. RECORDS ARE ENTERED UNDER THE PROPER SHIPPINGNAME FOUND IN THE REGULATIONS; THIS MAY INCLUDE VERY GENERAL GROUPS OF CHEMICAL SUBSTANCES.
entry date: OCT 1991 effective date: 06DEC1990

amendment: CAGAAK, Canada Gazette Part II, 124 , 26 , 5523 ,

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File: 17.01 LEGAL **rn : 302345**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : CAN type : REG

subject	specification	descriptor
GOODS	CONSM	RQR
LABEL		PRO
SALE		
IMPRT		

IT IS PROHIBITED TO SELL, ADVERTISE OR IMPORTINTO CANADA ADHESIVES, CLEANING SOLVENTS, THINNING AGENTS AND DYES CONTAINING ACETONE, WHEN PACKAGED AS CONSUMER PRODUCTS, UNLESS DETAILED LABELLING REQUIREMENTS ARE MET. THIS PROHIBITION IS PRESCRIBED BY SCHEDULE I OF THE HAZARDOUS PRODUCTS ACT (HPA), ADMINISTERED BY THE DEPARTMENT OF CONSUMER AND CORPORATE AFFAIRS. IT AUTHORIZES THE PROHIBITION OF PRODUCTS THAT ARE LIKELY TO BEOF DANGER TO THE HEALTH AND SAFETY OF THE PUBLIC.
entry date: MAY 1991 effective date: 01NOV1988

amendment: CAGAAK, Canada Gazette Part II, 122 , 24 , 4625 ,

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File: 17.01 LEGAL **rn : 302508**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : CAN type : REG

subject	specification	descriptor
USE	OCC	RQR
STORE		
LABEL		

INGREDIENT DISCLOSURE LIST CONCENTRATION 1% WEIGHT/WEIGHT. THE WORKPLACE HAZARDOUS MATERIALS INFORMATION SYSTEM (WHMIS) IS A NATIONAL SYSTEM TO PROVIDE INFORMATION ON HAZARDOUS MATERIALS USED IN THE WORKPLACE. WHMIS IS IMPLEMENTED BY THE HAZARDOUS PRODUCTS ACT AND THE CONTROLLED PRODUCTS REGULATIONS (ADMINISTERED BY THE DEPARTMENT OF CONSUMER AND CORPORATE AFFAIRS). THE REGULATIONS IMPOSE STANDARDS ON EMPLOYERS FORTHE USE, STORAGE AND HANDLING OF CONTROLLED PRODUCTS AND ADDRESS LABELLING AND IDENTIFICATION, EMPLOYEE INSTRUCTION AND TRAINING, AS WELL AS THE UPKEEP OF A MATERIALS SAFETY DATA SHEET (MSDS). THE PRESENCE IN A CONTROLLED PRODUCT OF AN INGREDIENT IN A CONCENTRATION EQUAL TO OR GREATER THAN SPECIFIED IN THE INGREDIENT DISCLOSURE LIST MUST BE DISCLOSED IN THE SAFETY DATA SHEET.
entry date: APR 1991 effective date: 31DEC1987

amendment: CAGAAK, Canada Gazette Part II, 122 , 2 , 551 ,

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File: 17.01 LEGAL **rn : 400270**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : CSK type : REG

subject	specification	descriptor
AIR	AMBI	CLASS

THE SUBSTANCE IS CLASSIFIED IN THE FOURTH GROUP OF AIR POLLUTANTS (ORGANIC GASES AND VAPOURS)
entry date: JAN 1992 effective date: 1OCT1991

title: PROVISION OF FEDERAL COMMITTEE FOR ENVIRONMENT TO ACT NO. 309 FROM 9 JULY 1991 ON AIR PROTECTION AGAINST AIR POLLUTANTS
original : SZCSR*, Sbirka Zakonu Ceskoslovenske Socialisticke Republiky(Collection of the Law of Czechoslovak Socialist Republic), , 84 , 2061 , 1991

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File: 17.01 LEGAL **rn : 400406**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : CSK type : REG

subject	specification	descriptor
WASTE	INDST	CLASS
		RQR

THE SUBSTANCE IS CLASSIFIED AS HAZARDOUS WASTE COMPONENT. IT IS OR CAN BE DANGEROUS TO HUMAN HEALTH OR ENVIRONMENT. QUANTITY, SPECIFICATION, USE OR DISPOSAL OF THE WASTE MUST BE REPORTED TO AUTHORITIES. TRANSPORT AND DISPOSAL OF THE WASTE MUST BE PERFORMED IN ACCORDANCE WITH SPECIAL DIRECTIVE
entry date: JAN 1992 effective date: 1AUG1991

title: PROVISION OF FEDERAL COMMITTEE FOR ENVIRONMENT WHICH DECLARES

WASTE CLASSIFICATION AND CATALOGUE
original : SZCSR*, Sbirka Zakonu Ceskoslovenske Socialisticke Republiky(Collection of the Law of Czechoslovak Socialist Republic), , 69 , 1650 , 1991

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File: 17.01 LEGAL **rn : 400540**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : CSK type : REG

subject	specification	descriptor
AIR	OCC	MAC

TWA: 800.0MG/M3; CLV: 4000.0MG/M3
entry date: DEC 1991 effective date: MCH1985

title: DIRECTIVE NO. 46/1978 ON HYGIENIC REQUIREMENTS ON OCCUPATIONAL ENVIRONMENT
original : HPMZC*, HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 39 , , , 1978
amendment: HPMZC*, HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 58 , , , 1985

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File: 17.01 LEGAL **rn : 401111**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : CSK type : REG

subject	specification	descriptor
FOOD		MPC

LIMIT OF ADDITIVE PRESENT DUE TO PRODUCTION, PACKING, TRANSPORT AND STORAGE OF FOOD PRODUCTS: 5G/KG.
entry date: DEC 1991 effective date: 1JUL1986

title: DIRECTIVE NO. 50/1978 ON FOREIGN SUBSTANCES IN FOODSTUFFS
original : HPMZC*, HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 43 , , , 1978
amendment: HPMZC*, HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 61 , , , 1986

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File: 17.01 LEGAL **rn : 500483**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : DEU type : REC

subject	specification	descriptor
AQ USE	INDST	CLASS RQR

THIS SUBSTANCE IS CLASSIFIED AS IN GENERAL NOT HAZARDOUS TO WATER (WATER-HAZARD CLASS: WGK 0). (THE DIFFERENT CLASSES ARE: WGK 3 = VERY HAZARDOUS; WGK 2 = HAZARDOUS; WGK 1 = SLIGHTLY HAZARDOUS; WGK 0 = IN GENERAL NOT HAZARDOUS.) THE CLASSIFICATION FORMS THE BASIS FOR WATER-PROTECTION REQUIREMENTS FOR INDUSTRIAL PLANTS IN WHICH WATER-HAZARDOUS SUBSTANCES ARE HANDLED.
entry date: DEC 1991

title: ADMINISTRATIVE RULES CONCERNING WATER-HAZARDOUS SUBSTANCES (VERWALTUNGSVORSCHRIFT WASSERGEFAEHRDENDE STOFFE)
original : GMSMA6, Gemeinsames Ministerialblatt. Joint Ministerial Papers, , 8 , 114 , 1990

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File: 17.01 LEGAL **rn : 502155**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : DEU type : REG

subject	specification	descriptor
AIR	EMI	MPC

THIS SUBSTANCE BELONGS TO CLASS III. THE AIR EMISSIONS OF ORGANIC COMPOUNDS MUST NOT EXCEED (AS THE SUM OF ALL COMPOUNDS IN ONE CLASS) THE FOLLOWING MASS CONCENTRATIONS: CLASS I - 20 MG/M3 AT A MASS FLOW OF >= 0.1 KG/H; CLASS II - 100 MG/M3 AT A MASS FLOW OF >= 2 KG/H; CLASS III - 150 MG/M3 AT A MASS FLOW OF >= 3 KG/H. IF COMPOUNDS FROM DIFFERENT CLASSES ARE PRESENT, THE MASS CONCENTRATION MUST NOT EXCEED 150 MG/M3 AT A TOTAL MASS FLOW OF >= 3 KG/H.
entry date: JAN 1992 effective date: 01MCH1986

title: TECHNICAL GUIDELINES FOR AIR POLLUTION CONTROL (TECHNISCHE ANLEITUNG ZUR REINHALTUNG DER LUFT)
original : GMSMA6, Gemeinsames Ministerialblatt. Joint Ministerial Papers, , 7 , 93 , 1986

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File: 17.01 LEGAL **rn : 502438**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000

area : DEU type : REC

subject	specification	descriptor
AIR	OCC	MAK

8H-TWA: 1000 ML/M3 (PPM); 2400 MG/M3 (20C, 101.3 KPA). SUBSTANCE ELICITING VERY WEAK EFFECTS. 60MIN-STEL: 2000 ML/M3 (PPM); 4800 MG/M3; CEILING VALUE; 3X/SHIFT. VAPOUR PRESSURE: 24 KPA AT 20 C.
entry date: JAN 1992

title: MAXIMUM CONCENTRATIONS AT THE WORKPLACE AND BIOLOGICAL TOLERANCE VALUES FOR WORKING MATERIALS (MAXIMALE ARBEITSPLATZKONZENTRATIONEN UND BIOLOGISCHE ARBEITSSTOFFTOLERANZWERTE)
original : MPGEDF, MITTEILUNG DER SENATSKOMMISSION ZUR PRUEFUNG GESUNDHEITSSCHAEDLICHER ARBEITSSTOFFE (DEUTSCHE FORSCHUNGSGEMEINSCHAFT), XXVII , , 17 , 1991

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File: 17.01 LEGAL **rn : 510565**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : DEU type : REG

subject	specification	descriptor
CLASS		CLASS
LABEL		RQR
PACK		RQR

CLASSIFICATION AND LABELLING IN GERMANY IS GENERALLY THE SAME AS FOR THE EEC (SEE OJEC** L180, 1991). HOWEVER, SLIGHT MODIFICATIONS MAY BE INTRODUCED FOR SOME SUBSTANCES IN THE GERMAN LEGISLATION.
entry date: APR 1992 effective date: 15JUN1991

title: ORDINANCE ON HAZARDOUS SUBSTANCES. (GEFAHRSTOFFVERORDNUNG)
original : BGZBAD, Bundesgesetzblatt (Federal Law Gazette), , I , 1931 , 1991

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File: 17.01 LEGAL **rn : 612864**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : GBR type : REG

subject	specification	descriptor
TRNSP		CLASS
LABEL		RQR

LABELLING OF ROAD TANKERS: FLAMMABLE LIQUID. EMERGENCY ACTION CODE: 2(Y)E

entry date: JAN 1983 effective date: 28MCH1979

title: HAZARDOUS SUBSTANCES (LABELLING OF ROAD TANKERS) REGULATIONS 1978
original : GBRSI*, STATUTORY INSTRUMENTS, 1702 , , , 1978

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File: 17.01 LEGAL **rn : 650642**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : GBR type : REG

subject	specification	descriptor
TRNSP	MARIN	RQR
AQ	MARIN	RQR
AQ	EMI	RQR

CLASSIFIED AS A NON-POLLUTING LIQUID SUBSTANCE. DOCUMENTARY EVIDENCE OF ASSESSMENT AND APPROVAL REQUIRED BY A CARRIER. DISCHARGE INTO THE SEA IS NOT PROHIBITED.
entry date: 1992 effective date: 06APR1987

title: THE MERCHANT SHIPPING (CONTROL OF POLLUTION BY NOXIOUS LIQUID SUBSTANCES IN BULK) REGULATIONS 1987, SCHEDULE 2
original : GBRSI*, STATUTORY INSTRUMENTS, 551 , , 15 , 1987
amendment: GBRSI*, STATUTORY INSTRUMENTS, 2604 , , 2 , 1990

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File: 17.01 LEGAL **rn : 665433**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : GBR type : REG

subject	specification	descriptor
AIR	OCC	OES

8H-TWA: 1780MG/M3 (75PPM); STEL(10MIN-TWA): 3560MG/M3 (3560PPM)
entry date: 1992 effective date: 01JAN1992

title: EH40 OCCUPATIONAL EXPOSURE LIMITS FOR USE WITH THE CONTROL OF SUBSTANCES HAZARDOUS TO HEALTH REGULATIONS
original : GBRSI*, STATUTORY INSTRUMENTS, 1657 , , 10 , 1988
amendment: GNHSE*, GUIDANCE NOTE FROM THE HEALTH AND SAFETY EXECUTIVE, EH40 , , 11 , 1992

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File: 17.01 LEGAL **rn : 762000**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : IND type : REG

subject	specification	descriptor
MANUF		RQR
SAFTY		RQR
STORE		RQR
IMPRT		RQR

These rules define the responsabilities of occupiers of any industrial activity in which this toxic and hazardous substance may be involved. These responsabilities encompass: (a) assessment of major hazards (causes, occurrence, frequency); (b) measures to prevent accidents and limit eventual impairment to human health and pollution of the environment; (c) provision of relevant factual knowledge and skills to workers in order to ensure health and environmental safety when handling equipments and the foregoing chemical; (d) notification of the competent authorities in case of major accidents; (e) notification of sites to the competent authorities 3 months before commencing; (f)preparation of an on-site emergency plan as to how major accidents should be coped with; (g) provision of competent authorities with information and means to respond quickly and efficiently to any off-site emergency; (h) provision of information to persons outside the site, liable to be affected by a major accident; (i) labelling of containers as to clearly identify contents, manufacturers, physical, chemical and toxicological data; (j) preparation of a safety data sheet including any significant information regarding hazard of this substance and submission of safety reports to the competent authorities; (k) for the import of a hazardous chemical to India, importers must supply the competent authorities with specified information regarding the shipment.
entry date: SEP 1992 effective date: 27NOV1989

title: THE MANUFACTURE, STORAGE AND IMPORT OF HAZARDOUS CHEMICALS RULES. 1989
original : GAZIN*, THE GAZETTE OF INDIA, 787 , , , 1989

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File: 17.01 LEGAL **rn : 800148**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : JPN type : REC

subject	specification	descriptor
AIR	OCC	MAC

TWA: 470MG/M3 (200PPM)
entry date: DEC 1991

title: MAXIMUM ALLOWABLE CONCENTRATIONS RECOMMENDED BY THE JAPANESE ASSOCIATION OF INDUSTRIAL HEALTH.
original : SAIGBL, Sangyo Igalu (Japanese Journal of Industrial Health), 33 , 4 , 277-287 , 1991

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File: 17.01 LEGAL **rn : 1010048**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : MEX type : REG

subject	specification	descriptor
AIR	OCC	MXL

AT ANY WORKPLACE WHERE THIS SUBSTANCE IS PRODUCED, STORED OR HANDLED A MAXIMUM PERMISSIBLE LEVEL OF 2400MG/M3 (1000PPM) MUST BE OBSERVED FOR A PERIOD OF 8 HOURS OR 3000MG/M3 (1260PPM) FOR 15 MINUTES FOUR TIMES A DAY WITH INTERVALS OF AT LEAST 1 HOUR.
entry date: DEC 1991 effective date: 28MAY1984

title: INSTRUCTION NO.10 RELATED TO SECURITY AND HYGIENIC CONDITIONS AT WORKPLACES. (INSTRUCTIVO NO. 10, RELATIVO A LAS CONDICIONES DE SEGURIDAD E HIGIENE DE LOS CENTROS DE TRABAJO).
original : DOMEX*, Diario Oficial, , , , 1984
amendment: DOMEX*, Diario Oficial, , , , 1989

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File: 17.01 LEGAL **rn : 1120809**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : RUS type : REG

subject	specification	descriptor
AIR	OCC	MAC CLASS

CLV: 200.0MG/M3 (VAPOUR) HAZARD CLASS: IV
entry date: MAY 1990 effective date: 01JAN1989

amendment: GOSTS*, GOSUDARSTVENNYI STANDART SSSR(STATE STANDARD OF USSR), 12.1.005 , , , 1988

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File: 17.01 LEGAL **rn : 1122198**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : RUS type : REG

subject	specification	descriptor
AIR	AMBI	MAC

0.35MG/M3 1X/D, 0.35MG/M3 AV/D.
entry date: SEP 1985 effective date: AUG1984

amendment: PDKAV*, PREDELNO DOPUSTIMYE KONTSENTRATSII (PDK) ZAGRYAZNYAYUSHCHIKH VESHCHESTV V ATMOSFERNOM VOZDUKHE NASELENNYKH MEST (MAXIMUM ALLOWABLE CONCENTRATIONS (MAC) OF CONTAMINANTS IN THE AMBIENT AIR OF RESIDENTIAL AREAS), 3086-84 , , , 1984

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File: 17.01 LEGAL **rn : 1122704**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : RUS type : REG

subject	specification	descriptor
AQ	SURF	MAC CLASS

2.2MG/L HAZARD CLASS: III
entry date: JUL 1990 effective date: 1JAN1989

amendment: SPNPV*, SANITARNYE PRAVILA I NORMY OKHRANY POVERKHNOSTNYKH VOD OT ZAGRIAZNENIA (HEALTH REGULATION AND STANDARDS OF SURFACE WATER PROTECTION FROM CONTAMINATION), 4630-88 , , , 1988

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File: 17.01 LEGAL **rn : 1200096**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : SWE type : REG

subject	specification	descriptor
AIR	OCC	HLV

1D-TWA: 600MG/M3 (250PPM). 15MIN-STEL: 1200MG/M3 (500 PPM)
entry date: 1992 effective date: 01JUL1991

title: HYGIENIC LIMIT VALUES.
original : AFS***, ARBETARSKYDDSSTYRELSENS FOERFATTNINGSSAMLING, 1990:13 , , 5-64 , 1990

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File: 17.01 LEGAL **rn : 1302002**

systematic name:2-Propanone
common name :acetone

reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : USA type : REG

subject	specification	descriptor
FOOD	ADDIT	RSTR
TRANS		RSTR
STORE		RSTR
PACK		RSTR

; Summary - THIS SUBSTANCE IS INCLUDED ON A LIST OF SUBSTANCES USED TO PREPARE ADHESIVES WHICH MAY BE SAFELY USED AS COMPONENTS OF ARTICLES INTENDED FOR USE IN PACKAGING, TRANSPORTATION, OR HOLDING FOOD IN ACCORDANCE WITH THE FOLLOWING PRESCRIBED CONDITIONS: SUBSTA NCE MUST BE SEPARATED FROM THE FOOD BY A FUNCTIONAL BARRIER, MUST NOT EXCEED LIMITS OF GOOD MANUFACTURING PRACTICE USED WITH DRY FOODS, OR NOT EXCEED TRACE AMOUNTS AT SEAMS AND EDGE EXPOSURES WHEN USED WITH FATTY AND AQUEOUS FOODS. ALSO REGULATED BY SEA M INTEGRITY, LABELING STANDARDS, AND ANY PROVISION UNDER 21 CFR 175
entry date: NOV 1991 effective date: 1977

title: SUBSTANCES FOR USE ONLY AS COMPONENTS OF ADHESIVES
original : FEREAC, Federal Register, 42 , , 14534 , 1977
amendment: CFRUS*, Code of Federal Regulations, 21 , 175 , 105 , 1988

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File: 17.01 LEGAL **rn : 1309525**

systematic name:2-Propanone
common name :acetone
reported name :2-PROPANONE
cas no :67-64-1 rtecs no :AL3150000
area : USA type : REG

subject	specification	descriptor
CLASS	INDST	RQR
AIR	EMI	RQR
AQ	EMI	RQR

5000 (2270); Summary - RELEASES OF THIS HAZARDOUS SUBSTANCE, IN QUANTITIES EQUAL TO OR GREATER THAN ITS REPORTABLE QUANTITY (RQ), REPORTED AS [LBS (KG)!, ARE SUBJECT TO REPORTING TO THE NATIONAL RESPONSE CENTER UNDER THE COMPREHENSIVE ENVIRONMENTAL RESPONSE, COMPENSATION, AND LIABILITY ACT. (#)- RQ IS SUBJECT TO CHANGE
entry date: SEP 1991 effective date: 1990

title: CERCLA: LIST OF HAZARDOUS SUBSTANCES AND REPORTABLE QUANTITIES
original : CFRUS*, Code of Federal Regulations, 40 , 302 , 4 , 1990
amendment: CFRUS*, Code of Federal Regulations, 40 , 302 , 4 , 1990

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File: 17.01 LEGAL **rn : 1323003**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE

cas no :67-64-1 rtecs no :AL3150000
area : USA type : REG

subject	specification	descriptor
CLASS	PESTI	RQR
MANUF	PESTI	PRMT
FOOD	ADDIT	RQR

CASE NAME ACETONE; Summary - THIS SUBSTANCE IS INCLUDED ON A LIST OF ACTIVE INGREDIENTS CONTAINED IN A PRODUCT FIRST REGISTERED BEFORE NOVEMBER 1, 1984, FOR WHICH A REGISTRATION STANDARD HAS NOT BEEN ISSUED. PUBLICATION OF THIS LIST INITIATES AN ACCELERATED REREGISTRATION AND DATA C ALL-IN FOR PRODUCTS CONTAINING THE LISTED ACTIVE INGREDIENTS.
entry date: JAN 1992 effective date: 1989

title: FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT PESTICIDES REQUIRED TO BE REREGISTERED; LIST D
original : FEREAC, Federal Register, 54 , 204 , 43388 , 1989
amendment: FEREAC, Federal Register, 54 , 204 , 43388 , 1989

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File: 17.01 LEGAL **rn : 1324017**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : USA type : REG

subject	specification	descriptor
AQ	GRND	MONIT
AQ	GRND	MXL

; Summary - THIS LIST IS REQUIRED ONLY FOR GROUND-WATER MONITORING AT RCRA LAND BASED HAZARDOUS WASTE DISPOSAL UNITS. THIS FINAL RULE WILL REQUIRE THAT AN ANALYSIS OF ALL THE CONSTITUENTS OF THIS LIST BE PERFORMED ON THE GROUND WATER TAKEN FROM WELLS SURROUNDING TH OSE UNITS. THIS ANALYSIS TAKES PLACE WHEN GROUND-WATER CONTAMINATION IS FIRST DETECTED, AND THEN AGAIN ONCE PER YEAR 40 CFR 264. WHEN A LISTED CONSTITUENT IS FOUND TO BE PRESENT A BACKGROUND VALUE MUST BE SET IN COMPLIANCE WITH 40 CFR 264.98(H)(2) UNLE SS OTHERWISE STATED.
entry date: SEP 1991 effective date: 1987

title: LIST (PHASE 1) OF HAZARDOUS CONSTITUENTS FOR GROUND-WATER MONITORING FINAL RULE: INCLUDING MAXIMUM CONCENTRATION OF CONSTITUENT: FOR GROUNDWATER PROTECTION.
original : FEREAC, Federal Register, 52 , , 25947 , 1987
amendment: CFRUS*, Code of Federal Regulations, 40 , 264 , , 1990

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File: 17.01 LEGAL **rn : 1325006**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE

cas no :67-64-1 rtecs no :AL3150000
area : USA type : REC

subject	specification	descriptor
SAFTY	OCC	MXL
USE	OCC	MXL

20000 PPM
entry date: OCT 1991 effective date: JUN1990

title: POCKET GUIDE TO CHEMICAL HAZARDS
original : XPHPAW, US PUBLIC HEALTH SERVICE PUBLICATION, 90 , 117 , 30 , 1990
amendment: XPHPAW, US PUBLIC HEALTH SERVICE PUBLICATION, 90 , 117 , 30 , 1990

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File: 17.01 LEGAL **rn : 1332196**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : USA type : REG

subject	specification	descriptor
WASTE	INDST	CLASS
STORE		RQR
TRNSP	REMOV	RQR

IGNITABLE; Summary - THIS CHEMICAL, IF DISCARDED, MUST BE TREATED AS AN ACUTE HAZARDOUS WASTE. ACUTE HAZARDOUS WASTES REGULATIONS ARE MORE RESTRICTIVE FOR EXCLUSION. ANY RESIDUE OF THIS CHEMICAL LABELED AS ACUTELY HAZARDOUS AND REMAINING IN A CONTAINER, OR AN INNER LINER R EMOVED FROM A CONTAINER, IS CONSIDERED A HAZARDOUS WASTE IF DISCARDED UNLESS TRIPLE RINSING OR OTHER CLEANING MEASURES ARE TAKEN (40 CFR 261.33E).
entry date: JAN 1992 effective date: 1980

title: RCRA-RESOURCE AND CONSERVATION RECOVERY ACT: DISCARDED COMMERCIAL CHEMICAL PRODUCTS, OFF-SPECIFICATION SPECIES, CONTAINER RESIDUES, AND SPILL RESIDUES THEREOF.
original : FEREAC, Federal Register, 45 , , 78541 , 1980
amendment: CFRUS*, Code of Federal Regulations, 40 , 261 , 33 , 1990

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File: 17.01 LEGAL **rn : 1332565**

systematic name:2-Propanone
common name :acetone
reported name :2-PROPANONE
cas no :67-64-1 rtecs no :AL3150000
area : USA type : REG

subject	specification	descriptor
WASTE	INDST	CLASS
STORE		RQR
TRNSP	REMOV	RQR

IGNITABLE; Summary - THIS CHEMICAL, IF DISCARDED, MUST BE TREATED AS AN ACUTE HAZARDOUS WASTE. ACUTE HAZARDOUS WASTES REGULATIONS ARE MORE RESTRICTIVE FOR EXCLUSION. ANY RESIDUE OF THIS CHEMICAL LABELED AS ACUTELY HAZARDOUS AND REMAINING IN A CONTAINER, OR AN INNER LINER R EMOVED FROM A CONTAINER, IS CONSIDERED A HAZARDOUS WASTE IF DISCARDED UNLESS TRIPLE RINSING OR OTHER CLEANING MEASURES ARE TAKEN (40 CFR 261.33E).
entry date: JAN 1992 effective date: 1980

title: RCRA-RESOURCE AND CONSERVATION RECOVERY ACT: DISCARDED COMMERCIAL CHEMICAL PRODUCTS, OFF-SPECIFICATION SPECIES, CONTAINER RESIDUES, AND SPILL RESIDUES THEREOF.
original : FEREAC, Federal Register, 45 , , 78541 , 1980
amendment: CFRUS*, Code of Federal Regulations, 40 , 261 , 33 , 1990

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File: 17.01 LEGAL **rn : 1334044**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : USA type : REG

subject	specification	descriptor
USE		RQR
PACK		RQR

THIS SUBSTANCE IS LISTED AS AN ADJUVANT OF RELEASE AGENTS, WAXES, AND DISPERSANTS.; Summary - THIS SUBSTANCE IS INCLUDED IN A LIST OF RESINOUS AND POLYMERIC COATINGS WHICH MAY BE USED AS THE FOOD CONTACT SURFACE OF ARTICLES IF THE COATING IS APPLIED AS A CONTINUOUS FILM PRODUCED FROM ANY BASIC OLEFIN POLYMER LISTED IN 21 CFR 177.1520 1988 AND FOR MULATED FROM OPTIONAL SUBSTANCES WHICH ARE RECOGNIZED AS SAFE FOR USE IN OR ON FOOD AND FROM SUBSTANCES SUBJECT TO LIMITATIONS AS DESCRIBED HERE.
entry date: NOV 1991 effective date: 1977

title: INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS FOR POLYOLEFIN FILMS
original : FEREAC, Federal Register, 42 , , 14534 , 1977
amendment: CFRUS*, Code of Federal Regulations, 21 , 175 , 320 , 1988

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File: 17.01 LEGAL **rn : 1336032**

systematic name:2-Propanone
common name :acetone
reported name :2-PROPANONE
cas no :67-64-1 rtecs no :AL3150000
area : USA type : REG

subject	specification	descriptor
AIR	EMI	RQR
SOIL	EMI	RQR
AQ	EMI	RQR
MANUF	EMI	RQR

; Summary - FACILITIES THAT EXCEEDED A MANUFACTURING, IMPORTATION, OR PROCESSING THRESHOLD OF 25,000 LBS OR THE USE OF 10,000 LBS FOR THIS CHEMICAL MUST REPORT TO EPA ANY RELEASES OF THE CHEMICAL (OR CATEGORY CHEMICAL) TO AIR, LAND, WATER, POTW, UNDERGROUND INJECTIO N, OR OFF SITE TRANSFER. THIS REGULATION COVERS STANDARD INDUSTRIAL CLASSIFICATION (SIC) CODES 20-39 ONLY).
entry date: OCT 1991 effective date: 1987

title: SUPERFUND AMENDMENTS AND REAUTHORIZATION ACT, TITLE III. EPCRA SECTION 313 LIST OF TOXIC SUBSTANCES
original : CFRUS*, Code of Federal Regulations, 40 , 372 , 65 , 1988
amendment: CFRUS*, Code of Federal Regulations, 40 , 372 , 65 , 1988

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File: 17.01 LEGAL **rn : 1340604**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : USA type : REC

subject	specification	descriptor
AIR	OCC	TLV

Time Weighted Avg (TWA) 750 ppm, 1780 MG/M3, skin; Short Term Exposure Limit (STEL) 1000 ppm, 2380 MG/M3; Summary - THIS THRESHOLD LIMIT VALUE IS INTENDED FOR USE IN THE PRACTICE OF INDUSTRIAL HYGIENE AS A GUIDELINE OR RECOMMENDATION IN THE CONTROL OF POTENTIAL HEALTH HAZARDS.
entry date: DEC 1991 effective date: 1989

title: THRESHOLD LIMIT VALUES
original : ACGIH*, Threshold Limit Values and Biological Exposure Indices, , , 11 , 1989
amendment: ACGIH*, Threshold Limit Values and Biological Exposure Indices, , , 11 , 1991

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File: 17.01 LEGAL **rn : 1402094**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : EEC type : REG

subject	specification	descriptor
FOOD		RQR
FOOD		MXL
FOOD		RSTR

THE SUBSTANCE MAY BE USED FOR THE MANUFACTURE OF REGENERATED CELLULOSE FILM WHICH IS INTENDED TO OR DOES COME INTO CONTACT WITH FOODSTUFFS. IT MAY BY USED AS SOLVENT; MAXIMUM TOTAL QUANTITY OF ALL SOLVENTS: 0.6MG/DM2 ON THE SIDE IN CONTACT WITH FOODSTUFFS.
entry date: OCT 1987 effective date: 01APR1987

title: COUNCIL DIRECTIVE OF 25 APRIL 1983 ON THE APPROXIMATION OF THE LAWS OF THE MEMBER STATES RELATING TO MATERIALS AND ARTICLES MADE OF REGENERATED CELLULOSE FILM INTENDED TO COME INTO CONTACT WITH FOODSTUFFS. (83/229/EEC).
original : OJEC**, Official Journal of the European (Communities)/Union, L123 , , 31 , 1983
amendment: OJEC**, Official Journal of the European (Communities)/Union, L228 , , 32 , 1986

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File: 17.01 LEGAL **rn : 1402327**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : EEC type : REG

subject	specification	descriptor
FOOD	INDST	PRMT

THIS SUBSTANCE, PROVIDED IT SATISFIES THE PURITY CRITERIA LAID DOWN, MAY BE USED AS AN EXTRACTION SOLVENT DURING THE PROCESSING OF RAW MATERIALS, OF FOODSTUFFS, OF FOOD COMPONENTS, OR OF FOOD INGREDIENTS. IT SHOULD BE USED IN COMPLIANCE WITH GOOD MANUFACTURING PRACTICE FOR ALL USES: I.E. ITS USE SHOULD RESULT IN THE PRESENCE OF RESIDUES OR DERIVATIVES IN TECHNICALLY UNAVOIDABLE QUANTITIES PRESENTING NO DANGER TO HUMAN HEALTH.
entry date: 1991 effective date: 13JUN1991

title: COUNCIL DIRECTIVE OF 13 JUNE 1988 ON THE APPROXIMATION OF THE LAWS OF THE MEMBER STATES ON EXTRACTION SOLVENTS USED IN THE PRODUCTION OF FOODSTUFFS AND FOOD INGREDIENTS. (88/344/EEC).
original : OJEC**, Official Journal of the European (Communities)/Union,

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File: 17.01 LEGAL **rn : 1421907**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : EEC type : REG

subject	specification	descriptor
CLASS		CLASS
LABEL		RQR
PACK		RQR

CLASS: F - HIGHLY FLAMMABLE; HIGHLY FLAMMABLE (R 11). LABEL: F - HIGHLY FLAMMABLE; HIGHLY FLAMMABLE (R 11); KEEP CONTAINER IN A WELL-VENTILATED PLACE (S 9); KEEP AWAY FROM SOURCES OF IGNITION - NO SMOKING (S 16); DO NOT BREATH GAS/FUMES/VAPOUR/SPRAY (APPROPRIATE WORDING TO BE SPECIFIED

BY THE MANUFACTURER) (S 23); TAKE PRECAUTIONARY MEASURES AGAINST STATIC DISCHARGES (S 33).
entry date: APR 1992 effective date: 1JUL1992

title: COUNCIL DIRECTIVE 67/548/EEC OF 27 JUNE 1967 ON THE APROXIMATION OF THE LAWS, REGULATIONS AND ADMINISTRATIVE PROVISIONS RELATING TO THE CLASSIFICATION, PACKAGING AND LABELLING OF DANGEROUS SUBSTANCES
original : OJEC**, Official Journal of the European (Communities)/Union, 196 , , 1 , 1967
amendment: OJEC**, Official Journal of the European (Communities)/Union, L 180 , , 79 , 1991

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File: 17.01 LEGAL **rn : 1645330**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : IMO type : REC

subject	specification	descriptor
TRNSP LABEL PACK	MARIN	CLASS

HAZARD CLASS: 3 = INFLAMMABLE LIQUID. PACKING GROUP: II = MEDIUM DANGER (I=GREAT DANGER - III=MINOR DANGER). UN NO. 1090
entry date: JAN 1991

amendment: !IMCOC*, International Maritime Dangerous Goods Code, , , 10004 , 1990

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File: 17.01 LEGAL **rn : 1744374**

systematic name:2-Propanone
common name :acetone
reported name :ACETONE
cas no :67-64-1 rtecs no :AL3150000
area : UN type : REC

subject	specification	descriptor
TRNSP LABEL PACK		CLASS

HAZARD CLASS: 3 = INFLAMMABLE LIQUID. PACKING GROUP: II = MEDIUM DANGER (I=GREAT DANGER - III=MINOR DANGER). UN NO. 1090
entry date: AUG 1990

amendment: !UNTDG*, UN Transport of Dangerous Goods, Recommendation prepared by theCommittee of Experts on the Transport of Dangerous Goods, , , 15 , 1989

2,2'-AZOBIS (2-METHYLPROPIONITRILE)

CAS NO 78-67-1

SIDS Initial Assessment Report
for
9th SIAM

(France, June 29-July 1, 1999)

Chemical Name: 2,2'-Azobis(2-methylpropionitrile)
CAS No: 78-67-1
Sponsor Country: Japan

National SIDS Contact Point in Sponsor Country:
Mr. Kazuhide Ishikawa
Ministry of Foreign Affairs, Japan

HISTORY:

SIDS Testing Plan were reviewed in SIDS Review Process, where the following SIDS Testing Plan was agreed:

no testing ( )
testing (X) Water solubility, Vapour pressure, Octanol/water partition coefficient, Stability in water, Biodegradation

Chronic toxicity to daphnia
Combined repeat dose and reproductive toxicity,
Gene mutation, Chromosomal aberration test in vitro

Deadline for circulation: March 31, 1999
Date of Circulation: March 30, 1999
(To all National SIDS Contact Points and the OECD Secretariat)

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 OF THE SPONSOR COUNTRY

The chemical is currently of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE RECOMMENDATIONS

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.

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.

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.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

FULL SIDS SUMMARY

CAS NO: 78-67-1		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			100 - 103 °C
2.2	Boiling Point			Decomposed
2.3	Density			
2.4	Vapour Pressure		OECD TG 104	0.810 Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	1.10
2.6 A.	Water Solubility		OECD TG 105	350 mg/l at 25 °C
B.	pH			
	pKa			
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			
3.1.2	Stability in Water		OECD TG 111	$T_{1/2}$ = 263 day at pH4 at 25 °C $T_{1/2}$ = 304 day at pH7 at 25 °C $T_{1/2}$ = 210 day at pH9 at 25 °C
3.2	Monitoring Data			In air = not detected In surface water = not detected In soil/sediment = not detected
3.3	Transport and Distribution		Calculated (Fugacity Level III type)	Release: 100% to Water In Air 0.5 % In Water 98.6 % In Sediment 0.5 % In Soil 0.4 %
			(local exposure)	1.6×10^{-9} mg/L (Japan)
3.5	Biodegradation		OECD 301C	Not readily biodegradable 0% in 28 day
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Poecilia reticulata*	OECD TG 203	LD_{50} (96h) = > 10 mg/l LD_{50} (14d) = > 10 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates *Daphnia*	*Daphnia magana*	OECD TG 202	EC_{50} (24hr) = > 10 mg/l EC_{50} (48hr) = > 10 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	ORCD TG 201	EC_{50} (72hr, Growth) = > 9.4 mg/l NOEC = 4.2 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (21d, Repro) = 7.5 mg/l NOEC = 2.2 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			No Data
4.6.2	Toxicity to Terrestrial Plants			No Data
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			No Data

TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Other (unknown)	LD_{50} = 100 mg/kg b.w.
5.1.2	Acute Inhalation Toxicity	Rat	Other (unknown)	LC_{50} = > 12 g/m^3/4 hr
5.1.3	Acute Dermal Toxicity			No data
5.2.1	Skin irritation/corrosion	Rabbit	OECD TG 404 and EC TG	No irritating
5.2.2	Eye irritation/corrosion	Rabbit	OECD TG 405 and EC TG	No irritating
5.3	Skin sensitisation	Guinea pig	OECD TG 406 and EC TG	No sensitizing
5.4	Repeated Dose Toxicity	Rat	OECD Combined	NOAEL = 2 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S. typhimurium* *E. coli* WP2	Japanese TG and OECD TG 471 & 472	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	Chinese hamster CHL cells	Japanese TG and OECD TG 473	- (With metabolic activation) - (Without metabolic activation)
5.6	Genetic Toxicity In Vivo			No data
5.8	Toxicity to Reproduction	Rat	OECD combined	NOAEL = 50 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			No data
5.11	Experience with Human Exposure			No data

[Note] Data beyond SIDS requirements can be added if the items are relevant to the assessment of the chemical, e.g. corrosiveness/irritation, carcinogenicity.

SIDS INITIAL ASSESSMENT REPORT

1. IDENTITY

- OECD Name: 2,2'-Azobis(2-methylpropionitrile)
- Synonym: Azobisisobutyronitrile; Azodiisobutyrodinitrile; 2,2'-Azobis[2-methyl-propanenitrile]; AIBN; alpha,alpha'-Azodiisobutyronitrile; 2,2'-Dicyano-2,2'-azopropane; Porofor-57; 2,2'-Azo-bis(isobutyronitrile); 2,2'-Dimethyl-2,2'-azodipropionitrile
- CAS Number: 78-67-1
- Empirical Formula: $C_8H_{12}N_4$
- Structural Formula:

$(H_3C)_2C(CN)N{=}{=}NC(CN)(CH_3)_2$

- Degree of Purity: 99.3%
- Major Impurity: None
- Essential Additives: None
- Physical-chemical properties
  - Melting Point: 100 – 103 °C
  - Vapour pressure: 0.81 Pa at 25 °C
  - Water solubility: 350 mg/L
  - Log Pow: 1.10

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production and import

The production volume of 2,2'-azobis(2-methylpropionitrile) in Japan is 1,100 tonnes/year in 1995 and 12 tonnes are imported.

2.2 Use pattern

All of 2,2'-azobis(2-methylpropionitrile) produced and imported in Japan is used as a foaming agent for rubber and an initiator of polymerization, and no consumer uses are reported.

2.3 Other information

None

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 General Discussion

2,2'-Azobis(2-methylpropionitrile) is not biodegradable (OECD 301C: 0% after 28d) and stable in water ($T_{1/2}$ = 263,304 and 210 day at pH 4,7,and 9, respectively). Although direct photodegradation

is expected because 2,2'-azobis(2-methylpropionitrile) has absorption band in UV and VIS region, the data of half-lifetime is not available.

2,2'-Azobis(2-methylpropionitrile) is low bioaccumulative based on Log Pow (1.10 at 25 °C).

The potential environmental distribution of 2,2'-azobis(2-methylpropionitrile) obtain from a generic Mackay level III fugacity model is shown in Table 1. Parameters used for this model are shown as Annex to this report. The results show that, if 2,2'-azobis(2-methylpropionitrile) is released into water, it is unlikely to be distributed into other compartment. If 2,2'-azobis(2-methylpropionitrile) is released into air or soil, it is likely to be distributed in water and soil.

Table 1
Environmental distribution of 2,2'-azobis(2-methylpropionitrile)
Using a generic level III fugacity model

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	31.0 %	0.5 %	0.7 %
Water	40.9%	98.6 %	28.6 %
Soil	27.9 %	0.5 %	70.6 %
Sediment	0.2 %	0.4 %	0.1 %

As this chemical is used in closed system as an initiator of polymerization in polymer industry and is not included in consumer products, its release to the environment may occur only from the production site.

3.1.2 Predicted Environmental Concentration

As 2,2'-azobis(2-methylpropionitrile) is produced under the well controlled closed system, amount of release to air phase is negligibly small. The waste of 2,2'-azobis(2-methylpropionitrile) from the production system is released to water phase after treated its own wastewater treatment plant. Therefore, Predicted Environmental Concentration (PEC) will be calculated only for the water environment.

a) Regional exposure

According to report from a Japanese proccesser who import 12 t/y, 1kg/year (measured) of 2,2'-azobis(2-methylpropionitrile) are treated in its own wastewater treatment plant with 99.9% of removal rate (measured) and released with 6.24×10^{8} L/year of effluent into sea. Local Predicted Environmental Concentration (PEC_{local}) is calculated to be 1.6×10^{-9} mg/L as a worst case scenario, employing the following calculation model and dilution factor of 1000(default).

$$\frac{\text{Amount of release } (1 \times 10^{6} \text{ mg/y}) \times (1 - \text{Removal rate } (99.9\%))}{\text{Volume of effluent } (6.24 \times 10^{8} \text{ L/y}) \times \text{Dilution Factor } (1000)}$$

3.2 Effects on the Environments

3.2.1 Effects on aquatic organisms

Acute and chronic toxicity data of 2,2'-azobis(2-methylpropionitrile) to aquatic organisms are summarized below (Table 2). Predicted no effect concentration (PNEC) of this chemical was

determined mainly based on the toxicity data obtained by the Environmental Agency of Japan through a GLP-laboratory.

As the lowest data among test organisms belonging to three trophic levels, 21d NOEC (2.2 mg/l) of *Daphnia magna* is selected. The assessment factor of 100 was adopted to chronic toxicity data to determine PNEC according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects (EXCH/MANUAL /96-4-5.DOC/May 1996), because chronic toxicity data for fish was absent.

From chronic toxicity data (NOEC of 21 d *Daphnia*):

PNEC = 2.2/ 100 = 0.022 mg/l

Thus, PNEC of 2,2'-azobis(2-methylpropionitrile) is 0.022 mg/l.

The toxicity of 2,2'-azobis (2-methylpropionitrile) to test organisms is low. Any symptoms were not observed in the *Orizias latipes* exposed to 9.6 mg/l (measured maximum concentration) in flow-through aquarium for 14-days.

Table 2
Toxicity data of 2,2'-azobis(2-methylpropionitrile) to aquatic organisms at different trophic levels. Relatively high toxicity data were selected from AQUIRE data base.

Species	Endpoint	Conc. (mg/l)	Remarks
Selenastrum capricornutum (algae)	Bms 72 h EC50	> 9.4	a, 1), A
	Bms 72 h NOEC	4.2	c, 1), C
Daphnia magna (Water flea)	Imm 48 h EC50	> 10	a, 1), A
	Rep 21 d EC50	7.5	c, 1)
	Rep 21d NOEC	2.2	c, 1), C
Oryzias latipes (fish, Medaka)	Mor 96 h LC50	>10	a, 1), A
	Mor 14 d LC50	>10	a, 1)

Notes: Bms; biomass, Imm; immobilization, Mor; mortality, Rep; reproduction, A), C); selected as the lowest value respectively among the acute or chronic toxicity data of algae, cladocera (water flea) and fishes to determine PNEC of 2,2'-azobis(2-methylpropionitrile). 1) Toxicity data were obtained by the Environment Agency of Japan based on OECD Test Guidelines and GLP.

3.2.2 Terrestrial effects

No available data

3.2.3 Other effects

No available data

3.3 Initial Assessment for the Environment

Predicted no effect Concentration (PNEC) of 2,2'-azobis(2-methylpropionitrile) for aquatic organisms is calculated based on the lowest acute and/or chronic toxicity data among algae, cladocera (water flea) and fishes and assessment factor of 100.

PNEC = 2.2 (NOEC of *Daphnia*)/ 100 = 0.022 mg/l

The highest PEC from Japanese local exposure scenario is 1.6×10^{-9} mg/l

$$PEC_{local} / PNEC = 1.6 \times 10^{-9} / 0.022 = 7.3 \times 10^{-8} < 1$$

Thus, effects of this chemical on aquatic ecosystems are at low concern at present.

4. HUMAN HEALTH

4.1 Human Exposure

4.1.1 Occupational exposure

2,2'-Azobis(2-methylpropionitrile) is produced in closed systems and used as an initiator for polymer synthesis. The occupational exposure is expected through inhalation and dermal route is assumed negligible because this chemical is solid. As the atmospheric concentration in plant was not measured, the maximum exposure level is estimated according to working schedules as follows. If the worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hour) is assigned to implement this operation without protection, the highest daily intake (EHE) is calculated as 0.015 mg/kg/day as the worst case. Practically, the workers always wear protective gloves and respiratory protective equipment (mask) during the operation.

	Frequency Times/day	Duration hr	Working hr/day	Maximum Concentration mg/m^3	Maximum EHE mg/kg/day
Charging to Reaction Vessel	1	0.17	0.17	5.00	0.015

EHE: Estimated Human Exposure

4.1.2 Consumer exposure

All of 2,2'-azobis(2-methylpropionitrile) produced in Japan is used as an initiator of polymerization, and no consumer uses are reported in Sponsor country.

4.1.3 Indirect exposure via the environment

As 2,2'-azobis(2-methylpropionitrile) is persistent in water and low bioaccumulative, the exposure to the general population via the environment would be possible through drinking water processed from surface water.

The concentration in drinking water should be estimated to be equal to PEC calculated in Section 3.1, i.e. 1.6×10^{-9}mg/l. The daily intake through drinking water is calculated as 5.33×10^{-11} mg/kg/day (2 l/day, 60 kg b.w.).

Using the bioconcentration factor of 1.0 estimated from logPow, the concentration of this chemical in fish can be calculated as follows:

$$PEC_{fish} = (1.6 \times 10^{-9} \text{ mg/l}) \times 1.0 = 1.60 \times 10^{-12} \text{ mg/g-wet}$$

As a daily intake of fish in Japan is estimated to be 90 g for 60 kg body weight person, a daily intake of this chemical will be 2.40 x 10^{-12} mg/kg/day.

4.2 Effects on Human Health

a) Acute toxicity

[SIDS data] The oral LD_{50} value for 2,2'-azobis(2-methylpropionitrile) was 100 mg/kg for rats. General anesthetic, somnolence, and ataxia were observed. In inhalation study, no mortality was observed at a concentration of 12 g/m^3 for 4 hours. Exciting behavior, conjunctive irritation, and weight loss or decreased weight gain were observed (National Technical Information Service[1]).

In another oral study, the LD_{50} value was 700 mg/kg for mice (Merck Index: 1989).

The intraperitoneal LD_{50} value was 25 mg/kg for rats (National Technical Information Service[1]) and mice (National Technical Information Service[2]). General anesthetic, somnolence (general depressed activity), and ataxia were observed in rats.

The subcutaneous LDL_0 values were 30, 40, 50, and 50 mg/kg for rats, mice, rabbits, and guinea pigs, respectively. Convulsions, effect on seizure threshold, and other changes in lungs, thorax, or respiration were observed in all species (*Archiv fuer Toxikologie*: 1957).

b) Irritation

In rabbit dermal study, 2,2'-azobis(2-methylpropionitrile) did not induce skin irritation at a single dose of 500 mg (Elf Atochem: 1996a).

Test in human also showed that this chemical was not a skin irritant (Kanerva *et al.*: 1997). The test was performed with 2 days occlusion and 3 readings (usually on day 2, 3 and 4-6). This chemical (0.1 %) was applied to 173 patients, suspected occupational dermatoses. Skin irritative reaction was observed only in one patient.

There was an eye irritation study, in which application of this chemical at a single dose of 100 mg into the conjunctival sac, induced no irritation approximately 1, 24, 48 and 72 hr after administration (Elf Atochem: 1996b).

Therefore, 2,2'-azobis(2-methylpropanitrile) is considered not to be a skin and eye irritant.

c) Sensitisation

It was showed that 2,2'-azobis(2-methylpropanitrile) was not a skin sensitizer by guinea pig maximization test (Elf Atochem: 1996c). In this study, intradermal injection of this chemical at 0.1 % and topical application at 500 mg were performed as an induction, and topical application of this chemical undiluted at 500 mg as challenge did not induce any response.

Allergic patch test in human also showed that this chemical was not a skin sensitizer (Kanerva *et al.*: 1997). This test was performed with 2 days occlusion and 3 readings (usually on day 2, 3 and 4-6). This chemical was applied at 1.0 % to 173 patients, who were suspected occupational dermatoses. No allergic reaction was observed.

Therefore, 2,2'-azobis(2-methylpropanitrile) is considered not to be a skin sensitizer.

d) Repeated toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test. 2,2'-Azobis(2-methylpropanitrile) was administered by gavage at doses of 2, 10, 50 mg/kg for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

In males, temporary salivation was induced in 10 mg/kg or more groups. Decrease in body weight gain and food consumption was observed at 50 mg/kg. In kidneys, absolute and relative weight was increased in all treatment group and in 10 mg/kg or more groups, respectively. In addition, increases in eosinophilic bodies and basophilic changes of the renal tubular epithelial cells were observed in all treatment groups and granular casts in the lower nephrons were observed in 10 mg/kg and more groups. Liver weights significantly increased by 14 and 66 % for absolute weight (14 and 74 % for relative weight) in 10 and 50 mg/kg group, respectively. Centrilobular hypertrophy of hepatocyte was observed in 10 and 50 mg/kg groups (±: 4 in 13, +: 9 in 13 for 10 mg/kg, ++: 13 in 13 for 50 mg/kg, compared to no changes in 0 and 2 mg/kg groups). In blood analysis conducted only in males, several changes were observed only in 50 mg/kg group.

In females, one female died on postpartum day 3 at 50 mg/kg. Decrease in body weight gain and food consumption was observed in 10 mg/kg and more groups. In kidneys, absolute and relative weight was increased at 50 mg/kg. Liver weights significantly increased by 43 % for absolute weight (51 % for relative weight) in only 50 mg/kg group. However, centrilobular hypertrophy of hepatocytes was observed in 10 and 50 mg/kg groups (±: 6 in 13, +: 1 in 13 for 10 mg/kg, ±: 1 in 13, +: 11 in 13, ++: 1 in 13 for 50 mg/kg, compared to no changes in 0 and 2 mg/kg groups).

As renal pathological changes were observed only in males, accumulation of $_{2u}$-macroglobulin is suspected as a cause of male specific renal toxicity. Therefore, based on pathological changes in liver of both sexes, NOAEL was considered to be 2 mg/kg/day for both sexes.

e) Reproductive/developmental toxicity

Reproductive toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test. 2,2'-Azobis(2-methylpropanitrile) was administered by gavage at doses of 2, 10, 50 mg/kg for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

2,2'-Azobis(2-methylpropanitrile) showed no adverse effects on copulation, fertility, duration of pregnancy, gestation index and parturition at all treated groups. At 50 mg/kg (12 dams), three dams showed the difficulty of nursling and two of them let all their offsprings die within the first 4 days after birth. Although this chemical showed no adverse effects on viability, sex ratio and body weight of newborns at birth, viability and body weight of nurslings on postnatal day 4 at 50 mg/kg were lower than the control levels. These changes were considered to be caused by maternal toxicity. There were no morphological abnormalities in pups at all treated groups. Therefore, NOAEL for reproductive toxicity was considered to be 50 mg/kg/day.

f) Genetic toxicity

Bacterial test
[SIDS data] Gene reverse mutation was negative in *S. typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2 *uvr*A with and without metabolic activation, and TA97 without S9 mix. (MHW, Japan: 1997)

Non-bacterial test *in vitro*
[SIDS data] In chromosomal aberration test using cultured Chinese hamster lung (CHL/IU) cells, the negative result was obtained. (MHW, Japan: 1997)

In SOS chromotest, 2,2'-azobis(2-methylpropanitrile) showed borderline result in *E.coli* PQ37, but negative result in *E. coli* PM21 and GC4798. (Eder *et al.*: 1989)

Based on these results, 2,2'-azobis(2-methylpropanitrile) is considered not to be genotoxic.

4.3 Initial Assessment for Human Health

2,2'-Azobis(2-methylpropionitrile) is considered neither to be irritating to skin and eye nor 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.

Occupational exposure

2,2'-Azobis(2-methylpropanitrile) is imported and used as an initiator for polymer synthesis and workers wear protective gloves and respiratory protective equipment during the operation. Although the occupational exposure route may be an inhalation in limited workers, there is no available data of the atmosphere concentration. Based on the estimated concentration and the possibility of exposure period, the daily intake is calculated as 0.015 mg/kg/day as the worst case. As there is no toxicokinetics data, it is assumed that 100% absorption occurs across the lungs. Occupational risk is presumably low because the margin of safety is 133.

Consumer exposure

No consumer exposure is expected because of use pattern.

Indirect exposure via environment

As for indirect exposure via environment, PEC_{local} of 1.60×10^{-9} mg/l from local exposure scenario was used for the estimation. The daily intakes through drinking water and fish are calculated as 5.33×10^{-11} mg/kg/day and 2.40×10^{-12} mg/kg/day, respectively. Since the margin of safety is very large, such as 3.75×10^{10} for drinking water and 8.33×10^{11} for fish, health risk via environment is presumably low.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

2,2'-Azobis(2-methylpropionitrile) is not biodegradable (OECD 301: 0% after 28d) and stable in water ($T_{1/2}$ = 304 days at pH 7). PEC/PNEC ratio is much less than 1 based on the local exposure scenario in the Sponsor country and PNEC, 0.022 mg/l (NOEC of *Daphnia magna*). It is currently considered of low potential risk for environments and low priority for further work.

2,2'-Azobis(2-methylpropionitrile) is toxic in a repeated dose study (i.e. liver, kidney), such as 2 mg/kg/day of NOAEL. In reproductive/developmental toxicity screening study, this chemical shows only maternal toxicity with the result of fetal toxicity (decrease in mortality and body weight gain). This chemical is neither irritating to the skin and eyes, nor a skin sensitizer. This chemical is not genotoxic. Occupational risk is expected to be low because margin of safety is calculated as 133. The margin of safety via indirect exposure is 3.75×10^{10} for drinking water and 8.33×10^{11} for fish, respectively. Therefore, it is currently considered of low potential human risk and low priority for further work.

5.2 Recommendations

No recommendation

6. REFERENCES

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- National Technical Information Service[1]. (Springfield, VA 22161) OTS0555369
- National Technical Information Service[2]. (Springfield, VA 22161) AD691-490

Appendix 1. Method for Prediction of Environmental Concentration of Pollutant in Surface Water

1. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into river

When decomposition, precipitation and vaporization of pollutant can be ignored, it is used that simplified equation by complete mixing model shown with equation (1) to calculate predicted environmental concentration in the local environment (PEC_{local}) as for release effluent into river.

$$PEC_{local}\ (mg/L) = \frac{Co\ Q + Cs\ Qs}{Q + Qs} \qquad (1)$$

Where

Co: Concentration of pollutant in upper stream of release point (mg/L)
Cs: Concentration of pollutant in effluent (mg/L)
Q: Flow rate of river (m^3/day)
Qs: Flow rate of effluent released into river (m^3/ day)

At the equation (1), when Co can be considered as 0, dilution factor of pollutant in the river (R) can be shown with following equation.

$$R = Cs/C = (Q + Qs) / Qs \qquad (2)$$

As the worst case, it is used to employ a flow rate at dry season as flow rate of river (Q). When flow rate at dry season is indistinct, it is estimated using the following equation in Japan.

$$\text{Flow rate at dry season} = \text{mean flow late} / 2.5 \qquad (3)$$

2. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into sea

For prediction of concentration of pollutant in the sea water with effluent, it is employed generally Joseph-Sendnersymbol 146 \f "Times New Roman" \s 11'}s equation (4). This equation is one of analytic solution led under the following conditions from diffusion equation.

1 It is adopted large area of sea or lake.
2 The flow rate of effluent and concentration of pollutant in the effluent are constant, and distribution of concentration is able to regard as equilibrium state.
3 Effluent is distributed uniformly to vertical direction, and it spreads in a semicircle or segment to horizontal direction.
4 Diffusion coefficient of pollutant at the sea is in proportion to distance from release point of effluent.
5 There is not any effect of tidal current.
6 Decomposition of pollutant can be ignored.

$$C(x) = (C_s - C(r))\left(1 - \exp\left(-\frac{Q_s}{d\,p}\left(\frac{1}{x} - \frac{1}{r}\right)\right)\right) + C(r) \quad (4)$$

Where

C (x): Concentration of pollutant at distance x (m) from release point
Cs: Concentration of pollutant in effluent
C (r): Concentration of pollutant at distance r (m) from release point
Qs: Flow rate of effluent (m^3/day)
: Opening angle of seacoast (rad.)
d: Thickness of diffusion layer (m)
P: Diffusion velocity (m/day) (1.0 0.5 cm/sec)

When C(x) is 0 at r = and density stratification is ignored for simplification, Joseph-Sendnersymbol 146 \f "Times New Roman" \s 11'}s equation (4) is simplified to equation (5)

$$C(x) = C_s\left(1 - \exp\left(-\frac{Q_s}{d\,p\,x}\right)\right) \quad (5)$$

Because of Qs/ d p x << 1 except vicinity of release point, dilution factor in distance x from release point R(x) can be shown with equation (6).

$$R(x) = C_s/C(x) = d\,p\,x/Q_s \quad (6)$$

When it is employed following parameters in equation (6) as default, dilution factor R can be shown with equation (7).

P = 1 cm/sec (860 m/day)
= 3.14
d = 10 m
x = 1000 m

$$R = 2.7\ 10^7/Q_s \quad (7)$$

Qs: volume of effluent (m^3/day)

REVISED OECD HPV FORM 1

SIDS DOSSIER ON THE HPV PHASE 5 CHEMICAL

2,2'-Azobis(2-methylpropionitrile)

CAS No. 78-67-1

Sponsor Country: Japan

DATE: March 31, 1999

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Appendix 1

Note: *; Data elements in the SIDS
†; Data elements specially required for inorganic chemicals

SIDS PROFILE

1.01 A.	**CAS No.**	78-67-1
1.01 C.	**CHEMICAL NAME (OECD Name)**	2,2'-Azobis(2-methylpropionitrile)
1.01 D.	**CAS DESCRIPTOR**	
1.01 G.	**STRUCTURAL FORMULA**	$(H_3C)_2C(CN)N{=}{=}NC(CN)(CH_3)_2$
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	**QUANTITY**	Production: 1,100 tonnes/year Import volume: 12 tonnes/year in Japan
1.7	**USE PATTERN**	Intermediate Intermediate in closed system. Initiator for polymerization.
1.9	**SOURCES AND LEVELS OF EXPOSURE**	1 kg/year Release into river
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)	SIDS testing required: Water solubility, Vapour pressure, Octanol/water partition coefficient, Stability in water, Biodegradation Chronic toxicity to daphnia, Combined repeat dose and reproductive toxicity, Gene mutation, Chromosomal aberration test in vitro	

SIDS SUMMARY

CAS NO: 78-67-1		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	N						N
2.4	Vapour Pressure	N						Y
2.5	Partition Coefficient	N						Y
2.6	Water Solubility	N						Y
	pH and pKa values	N						N
2.12	Oxidation: Reduction potential	N						N
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	N						N
3.1.2	Stability in water	N						Y
3.2	Monitoring data	N						N
3.3	Transport and Distribution	N						N
3.5	Biodegradation	N						Y
OTHER ENV FATE STUDIES RECEIVED								
ECOTOXICITY								
4.1	Acute toxicity to Fish	N						Y
4.2	Acute toxicity to Daphnia	N						Y
4.3	Toxicity to Algae	N						Y
4.5.2	Chronic toxicity to Daphnia	N						Y
4.6.1	Toxicity to Soil dwelling organisms	N						N
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5.1.1	Acute Oral	Y	N	N	Y	N	Y	N
5.1.2	Acute Inhalation	Y	N	N	Y	N	Y	N
5.1.3	Acute Dermal	N						N
5.4	Repeated Dose	N						Y
5.5	Genetic Toxicity *in vitro*							
	. Gene mutation	N						Y
	. Chromosomal aberration	N						Y
5.6	Genetic Toxicity *in vivo*	N						N
5.8	Reproduction Toxicity	N						Y
5.9	Development / Teratogenicity	N						N
5.11	Human experience	N						N
OTHER TOXICITY STUDIES RECEIVED								

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

*A.	**CAS number**	78-67-1
B.	**Name** *(IUPAC name)*	
*C.	**Name** *(OECD name)*	2,2'-Azobis(2-methylpropionitrile)
†D.	**CAS Descriptor**	
E.	**EINECS-Number**	201-132-3
F.	**Molecular Formula**	$C_8H_{12}N_4$
*G.	**Structural Formula**	

$(H_3C)_2C(CN)N{=}{=}NC(CN)(CH_3)_2$

H.	**Substance Group**	
I.	**Substance Remark**	
J.	**Molecular Weight**	164.21

1.02 OECD INFORMATION

A.	**Sponsor Country:**	Japan

B. **Lead Organisation:**

Name of Lead Organisation: Ministry of Health and Welfare (MHW)
Ministry of International Trade and Industry (MITI)
Environmental Agency (EA)
Ministry of Labour (MOL)

Contact person: Mr. Kazuhide Ishikawa
Economic International Bureau
Second International Organization Division
Ministry of Foreign Affairs
.....
2-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100 Japan
Tel: 81-3-3581-0018
Fax: 81-3-3503-3136

C. **Name of responder**

Same as above contact person

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance element [ ]; inorganic [ ]; natural substance [ ]; organic **[X]**; organometallic [ ]; petroleum product [ ]

B. Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [ ]; solid **[X]**

C. Purity

1.2 SYNONYMS

Azobisisobutyronitrile; Azodiisobutyrodinitrile; 2,2'-Azobis[2-methylpropanenitrile]; AIBN; alpha,alpha'-Azodiisobutyronitrile; 2,2'-Dicyano-2,2'-azopropane; Porofor-57; 2,2'-Azo-bis(isobutyronitrile); 2,2'-Dimethyl-2,2'-azodipropionitrile

1.3 IMPURITIES

None

1.4 ADDITIVES

None

*1.5 QUANTITY

Remarks: 1,100 tonnes/year
Reference: MITI, Japan

1.6 LABELLING AND CLASSIFICATION

None

*1.7 USE PATTERN

A. General

	Type of Use:	**Category:**
	main	Intermediate
	industrial	Intermediate in closed system
	use	Initiator for polimerization

Remarks: None
Reference: MITI, Japan

1.8 OCCUPATIONAL EXPOSURE LIMIT

None

* 1.9 SOURCES OF EXPOSURE

In Japan, 2,2'-azobis(2-methylpropionitrile) is produced in 2 companies.

Source:	Media of release: River Quantities per media: 1 kg/year (one company)
Remarks:	
Reference:	MITI, Japan

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value:	100 - 103 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	
GLP:	Yes [ ] No [X] ? [ ]
Remarks:	
Reference:	MITI, Japan

*2.2 BOILING POINT

Value:	decompose
Pressure:	
Decomposition:	Yes [X] No [ ] Ambiguous [ ]
Method:	
GLP:	Yes [ ] No [X] ? [ ]
Remarks:	
Reference:	

*2.4 VAPOUR PRESSURE

Value:	8.1×10^{-1} Pa
Temperature:	25 °C
Method:	calculated [ ]; measured [X] OECD TG 104
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	purity: 99.6 %
Remarks:	
Reference:	MITI, Japan

*2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

Log Pow:	1.10
Temperature:	25 °C
Method:	calculated [ ]; measured [X] OECD TG 107
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	purity: 98 %
Remarks:	
Reference:	MITI, Japan

*2.6 WATER SOLUBILITY

A. Solubility

Value:	350 mg/L
Temperature:	25 °C
Description:	Miscible [ ]; Of very high solubility [ ]; Soluble [ ]; Slightly soluble **[X]**; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	OECD TG 105
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	purity: 99.6 %
Remarks:	
Reference:	MITI, Japan

B. pH Value, pKa Value

No ionizable Functional Group

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

*3.1.2 STABILITY IN WATER

Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment)[ ]
Half life:	263 days at pH 4 at 25 °C 304 days at pH 7 at 25 °C 210 days at pH 9 at 25 °C
Method:	OECD TG 111
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	purity: 99.6 %
Remarks:	
Reference:	MITI, Japan

*3.2 MONITORING DATA (ENVIRONMENTAL)

(a)	Type of Measurement:	Background [ ]; At contaminated site [ ]; Other **[X]**
	Media:	Surface water (river)
	Results:	ND (Detection limits: 0.01 mg/l) in 1 area in Japan as of 1979
	Remarks:	ND: Not detected
	Reference:	Chemicals in the environment, EA, Japan (1980)
(b)	Type of Measurement:	Background [ ]; At contaminated site [ ]; Other **[X]**
	Media:	Surface water (estuary)
	Results:	ND (Detection limits: 0.01 mg/l) in 1 area in Japan as of 1979
	Remarks:	ND: Not detected
	Reference:	Chemicals in the environment, EA, Japan (1980)
(c)	Type of Measurement:	Background [ ]; At contaminated site [ ]; Other **[X]**

Media: Surface water (sea)
Results: ND (Detection limits: 0.01 mg/l) in 3 areas in Japan as of 1979
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1980)

(d) Type of Measurement: Background [ ]; At contaminated site [ ]; Other [X]
Media: Sediment (river)
Results: ND (Detection limits: 0.1 mg/kg-dry) in 1 area in Japan as of 1979
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1980)

(e) Type of Measurement: Background [ ]; At contaminated site [ ]; Other [X]
Media: Sediment (estuary)
Results: ND (Detection limits: 0.1 mg/kg-dry) in 1 area in Japan as of 1979
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1980)

(f) Type of Measurement: Background [ ]; At contaminated site [ ]; Other [X]
Media: Sediment (sea)
Results: ND (Detection limit: 0.1 mg/kg-dry) in 3 areas in Japan as of 1979
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1980)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION

*3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Media: Air-biota [ ]; Air-biota-sediment-soil-water [X]; Soil-biota [ ]; Water-air [ ]; Water-biota [ ]; Water-soil [ ]; Other [ ]
Method: Fugacity level I [ ]; Fugacity level II [ ]; Fugacity level III [X]; Fugacity level IV [ ]; Other (calculation) [ ]; Other (measurement)[ ]
Results:

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	31.0 %	0.5 %	0.7 %
Water	40.9 %	98.6 %	28.6 %
Soil	27.9 %	0.5 %	70.6 %
Sediment	0.2 %	0.4 %	0.1 %

Remarks: Appendix 1
Reference: MITI, Japan

*3.5 BIODEGRADATION

Type:	aerobic **[X]**; anaerobic **[ ]**
Inoculum:	adapted **[ ]**; non-adapted **[X]**;
Concentration of the chemical: related to COD **[ ]**; DOC **[ ]**; test substance **[X]**	
Medium:	water **[X]**; water-sediment **[ ]**; soil **[ ]**; sewage treatment **[ ]**
Degradation:	0 % by BOD after 28 days 3 % by TOC after 28 days 7 % by HPLC after 28 days
Results:	readily biodeg. **[ ]**; inherently biodeg. **[ ]**; under test condition no biodegradation observed **[X]**, other **[ ]**
Method:	OECD TG 301C
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	purity: 99 %
Reference:	MITI, Japan

4. ECOTOXICITY

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a) Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]** open-system **[X]**; closed-system **[ ]**
Species:	*Oryzias latipes* (Himedaka)
Exposure period:	96 h
Results:	$LC_{50\ (96\ h)} > 10$ mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 203 (1992)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.3 %
Remarks:	Groups of ten Himedaka were exposed to the nominal concentrations of 1.0, 1.8, 3.2, 5.6 and 10* mg/l, a solubilizer control (100 mg/l of DMF) and laboratory water control. The LC_{50} (96h) was determined to be over 10 mg/l. 10* mg/l; the highest concentration dispersed completely by the maximum concentration of solubilizer (100 mg/l). Measured concentration was almost same as nominal concentration.
Reference:	Environment Agency of Japan (1996)

(b) Type of test:	static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other *(e.g. field test)* **[ ]** open-system **[X]**; closed-system **[ ]**
Species:	*Poecilia reticulata* (Guppy)
Exposure period:	14 d
Results:	$LC_{50\ (14d)} > 10$ mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 203 (1992)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.3 %
Remarks:	Groups of ten Himedaka were exposed to the nominal concentrations of 1.0, 1.8, 3.2, 5.6 and 10* mg/l, a solubilizer control (100 mg/l of DMF) and laboratory water control. The LC_{50} (14 d) was determined to be over 10 mg/l.

	10* mg/l; the highest concentration dispersed completely by the maximum concentration of solubilizer (100 mg/l). Measured concentrations were almost same as nominal concentrations throughout the test period.
Reference:	Environment Agency of Japan (1996)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

Type of test:	static [ ]; semi-static [X]; flow-through [ ]; other *(e.g. field test)* [ ]; open-system [ ]; closed-system [X]
Species:	*Daphnia Magna.*
Exposure period:	48 h.
Results:	$EC_{50\ (48\ h)} > 10$ mg/l
Analytical monitoring:	Yes [X] No [ ] ? [ ]
Method:	OECD TG 202
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.3 %
Remarks:	20 daphnids (4 replicates by 5 organisms) were exposed to the nominal concentrations of 10* mg/l, solubilizer control (DMF of 100 mg/l) and laboratory water control. 10* mg/l; the highest concentration dispersed completely by the maximum concentration of solubilizer (100 mg/l).
Reference:	Environment Agency of Japan (1995).

Type of test:	static [X]; semi-static [ ]; flow-through [ ]; other *(e.g. field test)* [ ]; open-system [ ]; closed-system [X]
Species:	*Daphnia Magna.*
Exposure period:	48 h.
Results:	$EC_{50\ (48\ h)} > 367$ mg/l
Analytical monitoring:	Yes [X] No [ ] ? [ ]
Method:	C2 of the European Directive 92/69/CEE
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	As prescribed by 1.1 - 1.4, purity: Unknown
Remarks:	Since AZDN is sparingly soluble, the test was carried out with concentrations up to the water solubility. Daphnia were exposed in a static test to a concentration range of 160 to 367 mg/l, forming a geometric progression with a factor of 1.15. The test was performed with 20 daphnia per concentration. The test was performed using closed flasks as test glassware The flasks were entirely filled with test solution and closed with butyl rubber caps covered with PTFE.
Reference:	Service Analyse Environment (France)

*4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

Species:	*Selenastrum capricornutum* ATCC 22662
Endpoint:	Biomass [X]; Growth rate [ ]; Other [ ]
Exposure period:	72 h
Results:	Biomass $EC_{50\ (72h)} > 9.4$ mg/l

	(Endpoint) NOEC = 4.2 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 201 (1984)
	open-system **[X]**; closed-system **[ ]**
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.3 %
Remarks:	Static test. The EC_{50} value for growth rate (% inhibition) was calculated based on 5 measured concentrations (0.46, 0.71, 2.1, 4.2 and 9.4 mg/l). DMF of 100 mg/l was used as a solubilizer.
Reference:	Environment Agency of Japan (1996)

Species:	*Pseudokirchneriella subcapitata (Selenastrum capricornutum)*
Endpoint:	Biomass **[X]**; Growth rate **[ ]**; Other **[ ]**
Exposure period:	72 h
Results:	Biomass $EC_{50\ (72h)}$ 2.9 mg/l
	NOEC = 2.2 mg/l
	Growth rate $EC_{50\ (72h)}$ 6.1 mg/l
	NOEC = 2.2 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 201 (1984)
	open-system **[X]**; closed-system **[ ]**
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: Unknown
Remarks:	
Reference:	Service Analyse Environment (France)

4.4 TOXICITY TO BACTERIA

No data

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

No data

(*) 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[ ]**; closed-system **[X]**
Species:	*Daphnia Magna.*
Endpoint:	Mortality **[ ]**; Reproduction rate **[X]**; Other **[X]**
Exposure period:	21 d
Results:	Reproduction rate: $EC_{50\ (21\ d)}$ = 7.5 mg/l
	(Endpoint) NOEC = 2.2 mg/l
	LOEC = 4.6 mg/l
Analytical monitoring:	Yes [X] No [ ] ? [ ]
Method:	OECD TG 202(1984)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.3 %

Remarks:	40 daphnids (4 replicate of 10 daphnids) were exposed to 5 nominal concentrations (0.46, 1.0, 2.2, 4.6, and 10 mg/l), solvent control (100 mg/l of acetone) control and laboratory water control (dechlorinated tap water, pH: 7.4 to 8.0; DO: 7.5 to 8.0 mg/l). Measured concentrations were within 88 to 98 % of the nominal concentrations throughout the 21-d test period.
Reference:	Environment Agency of Japan (1995).

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data

4.8 BIOTRANSFORMATION AND KINETICS

No data

4.9 ADDITIONAL REMARKS

None

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rats
Value:	100 mg/kg b.w.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	General anesthetic, somnolence, and ataxia
Reference:	National Technical Information Service[1]

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mice
Value:	700 mg/kg b.w.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	Merck Index: 1989

5.1.2 ACUTE INHALATION TOXICITY

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [X]; Other [ ]
Species/strain:	Rats
Exposure time:	4 hr
Value:	> 12 g/m^3
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	Exciting behavior, conjunctive irritation, weight loss or decreased weight gain
Reference:	National Technical Information Service[1]

5.1.3 ACUTE DERMAL TOXICITY

No data

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a) Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rats
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:	
Value:	25 mg/kg
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	General anesthetic, somnolence (general depressed activity), and ataxia
Reference:	National Technical Information Service[1]

(b) Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mice
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:	
Value:	25 mg/kg
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	National Technical Information Service[2]

(c) Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [X]; Other [ ]
Species/strain: Rats
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [ ]; infusion [ ]; s.c. [X]; other [ ]
Exposure time:
Value: 30 mg/kg
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks: Convulsions or effect on seizure threshold, and other changes in lungs, thorax, or respiration
Reference: *Archiv fuer Toxikologie*: 1957

(d) Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [X]; Other [ ]
Species/strain: Mice
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [ ]; infusion [ ]; s.c. [X]; other [ ]
Exposure time:
Value: 40 mg/kg
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks: Convulsions or effect on seizure threshold, and other changes in lungs, thorax, or respiration
Reference: *Archiv fuer Toxikologie*: 1957

(e) Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [X]; Other [ ]
Species/strain: Rabbits
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [ ]; infusion [ ]; s.c. [X]; other [ ]
Exposure time:
Value: 50 mg/kg
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks: Convulsions or effect on seizure threshold, and other changes in lungs, thorax, or respiration
Reference: *Archiv fuer Toxikologie*: 1957

(f) Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [X]; Other [ ]
Species/strain: Guinea pigs
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [ ]; infusion [ ]; s.c. [X]; other [ ]
Exposure time:
Value: 50 mg/kg
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks: Convulsions or effect on seizure threshold, and other changes in lungs, thorax, or respiration
Reference: *Archiv fuer Toxikologie*: 1957

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Species/strain:	New Zealand White rabbits
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating **[X]**
Classification:	Highly corrosive (causes severe burns)[ ]; Corrosive (causes burns)[ ]; Irritating [ ]; Not irritating [ ]
Method:	OECD TG 404 and EC TG 92/69/E.E.C., B_4
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	purity: 99.2 %
Remarks:	A single dose of 500 mg in original form of 2,2'-azobis(2-methylpropanitrile) was applied to the closely-clipped skin of the flank for 4 hours, with semi-occulusive dressing. Cutaneous reaction was evaluated approximately one hour, 24, 48 and 72 hours after removal of the dressing.
Reference:	Elf Atochem: 1996a

Species/strain:	Human
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating **[X]**
Classification:	Highly corrosive (causes severe burns)[ ]; Corrosive (causes burns)[ ]; Irritating [ ]; Not irritating [ ]
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	Test was performed with 2 days occlusion and 3 readings (usually on irritant day 2, 3 and 4-6). 1.0 % in petroleum ether was applied to 173 patients, who were suspected occupational dermatoses.
Reference:	Kanerva *et al.*: 1997

5.2.2 EYE IRRITATION/CORROSION

Species/strain:	New Zealand White rabbits
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating **[X]**
Classification:	Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes [ ]
Method:	OECD TG 405 and EC TG 92/69/E.E.C., B_5
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	purity: 99.2 %
Remarks:	After gently pulling the lower lid away from the eyeball, a single dose of 100 mg in original form of 2,2'-azobis(2-methylpropanitrile) was administered into the conjunctival sac of the left eye. The lower and upper eyelids were held together for about one second to avoid any loss of test substance. The right eye, which remained untreated, served as a control. The eyes were not rinsed and examined approximately one hour, 24, 48 and 72 hours after administration.
Reference:	Elf Atochem: 1996b

5.3 SKIN SENSITISATION

Type:	Maximization test
Species/strain:	Dunkin-Hartley guinea pigs
Results:	Sensitizing [ ]; Not sensitizing **[X]**; Ambiguous [ ]
Classification:	Sensitizing [ ]; Not sensitizing [ ]
Method:	OECD Guideline No. 406 and EC Guideline 92/69/E.E.C., B_6
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	purity: 99.2 %
Remarks:	On day 1, 0.1 % in paraffin oil or the vehicle was injected intradermaly in the dorsal region between the shoulders. On day 7, the same region received a topical application of sodium lauryl sulfate in vaseline in order to induce local irritation. On day 8, topical application of undiluted substance (500 mg) or the vehicle to this same site was performed with an occlusive dressing for 48 hours. After rest period of 12 days, all animals were challenged by a topical application of undiluted substance (500 mg) and the vehicle to the right and the left flank, respectively. This application was held for 24 hours with an occlusive, hypoallergenic dressing. Skin reaction was evaluated approximately 24 and 48 hours after challenge application.
Reference:	Elf Atochem: 1996c

Type:	Allergic and irritant patch test
Species/strain:	Human
Results:	Sensitizing [ ]; Not sensitizing **[X]**; Ambiguous [ ]
Classification:	Sensitizing [ ]; Not sensitizing [ ]
Method:	Other
GLP:	Yes [ ] No **[X]** ? [ ]
Test substance:	purity: unknown
Remarks:	This test was performed with 2 days occlusion and 3 readings (usually on day 2, 3 and 4-6). 1.0 % in petroleum ether was applied to 173 patients, who were suspected occupational dermatoses.
Reference:	Kanerva *et al.*: 1997

*5.4 REPEATED DOSE TOXICITY

Species/strain:	Rats/Crj: CD (SD)
Sex:	Female [ ]; Male [ ]; Male/Female **[X]**; No data [ ]
Route of Administration:	Oral (by gavage)
Exposure period:	Male: 42 days Female: From 14 days before mating to day 3 of lactation
Frequency of treatment:	Daily
Post exposure observation period:	
Dose:	0, 2, 10, 50 mg/kg/day
Control group:	Yes **[X]**; No [ ]; No data [ ]; Corn oil Concurrent no treatment[ ]; Concurrent vehicle**[X]**; Historical [ ]
NOAEL:	Male: 2 mg/kg/day, Female: 2 mg/kg/day
LOAEL:	Male: 10 mg/kg/day, Female: 10 mg/kg/day

Results:	Male:	Temporary salivation was induced at 10 mg/kg or more groups. Decrease in body weight gain and food consumption was observed at 50 mg/kg. In kidneys, absolute and relative weight was increased in all treatment group and in 10 mg/kg or more groups, respectively. In addition, increases in eosinophilic bodies and basophilic changes of the renal tubular epithelial cells were observed in all treatment groups and granular casts in the lower nephrons were observed in 10 mg/kg and more groups. As these pathological changes were observed only in males, accumulation of α_{2u}-macroglobulin is suspected as a cause of male specific renal toxicity. Liver weights significantly increased by 14 and 66 % for absolute weight (14 and 74 % for relative weight) in 10 and 50 mg/kg group, respectively. Centrilobular hypertrophy of hepatocyte was observed in 10 and 50 mg/kg groups (±: 4 in 13, +: 9 in 13 for 10 mg/kg, ++: 13 in 13 for 50 mg/kg, compared to no changes in 0 and 2 mg/kg groups). In blood analysis, there were several changes in 50 mg/kg group, such as an elevation of platelet and white blood cell counts, increases in total protein, albumin, total cholesterol, Ca and inorganic phosphorus, and decreases in the A/G ratio and Cl concentration.
	Female:	One animal died on postpartum day 3 at 50 mg/kg. Decrease in body weight gain and food consumption was observed in 10 mg/kg and more groups. In kidneys, absolute and relative weights were increased at 50 mg/kg. Liver weights significantly increased by 43 % for absolute weight (51 % for relative weight) in only 50 mg/kg group. However, centrilobular hypertrophy of hepatocytes was observed in 10 and 50 mg/kg groups (±: 6 in 13, +: 1 in 13 for 10 mg/kg, ±: 1 in 13, +: 11 in 13, ++: 1 in 13 for 50 mg/kg, compared to no changes in 0 and 2 mg/kg groups).
Method:		OECD Combined Repeat Dose and eproductive/Developmental Toxicity Screening Test
GLP:		Yes **[X]** No **[ ]** ? **[ ]**
Test substance:		purity: 99.9 %
Reference:		MHW, Japan (1997)

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type:	Gene mutation test
System of testing:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA97 (without S9 mix), *Escherichia coli* WP2 *uvr*A
Concentration:	+S9 mix; 0, 313, 625, 1250, 2500, 5000 µg/plate (TA98, TA100, TA1535, TA1537, and WP2 uvrA) -S9 mix; 0, 313, 625, 1250, 2500, 5000 µg/plate (all strains)
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No data [ ]
S9:	Rat liver, induced with phenobarbital and 5,6-benzoflavone
Results:	
Cytotoxicity conc:	With metabolic activation: Not observed

Without metabolic activation: Not observed
Precipitation conc: With metabolic activation: 1250 µg/plate
Without metabolic activation: 2500 µg/plate
Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	**[X]**
Without metabolic activation:	[ ]	[ ]	**[X]**

Method: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Guideline No. 471 and 472
GLP: Yes [X] No [ ] ?[ ]
Test substance: purity: 99.9 %
Remarks: Positive control:
With metabolic activation: 2-Aminoantthracene (five strains)
Without metabolic activation:
Sodium azide (TA 1535)
9-Aminoacridine (TA1537, TA 97)
2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide
(TA100, TA98, WP2)
Reference: MHW, Japan (1997)

Type: SOS chromotest
System of testing: *Escherichia coli* PQ37, PM21, GC4798
Concentration: Not indicated
Metabolic activation: With [ ]; Without [X]; With and Without [ ]; No data [ ]
Results: 2,2'-Azobis(2-methylpropanitrile) showed borderline result in PQ37, but negative result in PM21, GC4798.
Cytotoxicity conc: With metabolic activation:
Without metabolic activation:
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[ ]
Without metabolic activation:	[ ]	**[X]**	[ ]

Method: Other
GLP: Yes [ ] No [X] ?[ ]
Test substance: purity: 98 %
Remarks:
Reference: Eder *et al.*: 1989

B. NON-BACTERIAL IN VITRO TEST

Type: Chromosomal aberration test
System of testing: Chinese hamster lung (CHL/IU) cells
Concentration: +S9 mix (short-term treatment): 0, 0.40, 0.80, 1.6 mg/ml
-S9 mix (short-term treatment): 0, 0.40, 0.80, 1.6 mg/ml
-S9 mix (continuous treatment): 0, 0.40, 0.80, 1.6 mg/ml
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone.
Results:
Cytotoxicity conc: Not observed
Precipitation conc:

Genotoxic effects:

	clastogenicity			polyploidy		
	+	?	-	+	?	-
With metabolic activation:	[ ]	[ ]	[X]	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]	[ ]	[ ]	[X]

Method: Guide for Screening Mutagenicity Testing of Chemicals (Japan), and OECD TG No. 473

GLP: Yes [X] No [ ] ? [ ]

Test substance: purity: 99.9%

Remarks: Exposure period: short-term treatment: 6 hr
continuous treatment: 24, or 48 hr
Positive control: -S9: Mitomycin, +S9: Cyclophosphamide

Reference: MHW, Japan (1997)

* 5.6 GENETIC TOXICITY IN VIVO

No data

5.7 CARCINOGENICITY

No data

*5.8 TOXICITY TO REPRODUCTION

Type: Fertility [ ]; One-generation study [ ]; Two-generation study [ ]; Other [X]

Species/strain: Rats/Crj: CD (SD)

Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]

Route of Administration: Oral (by gavage)

Exposure period: Male: From 14 days before mating to 14 days after mating
Female: From 14 days before mating to day 3 of lactation

Frequency of treatment: Daily

Post exposure observation period:

Premating exposure period: 14 days

Duration of the test:

Dose: 0, 2, 10, 50 mg/kg/day

Control group: Yes [X]; No [ ]; No data [ ]; Corn oil
Concurrent no treatment[ ]; Concurrent vehicle[X]; Historical [ ]

NOAEL Parental: 10 mg/kg/day

NOAEL F1 Offspring: 50 mg/kg/day

NOAEL F2 Offspring:

Results:

General parental toxicity:

There were no adverse effects of 2,2'-azobis(2-methylpropanitrile) on copulation and fertility, duration of pregnancy, gestation index and parturition at all treated group. Three of 12 dams at 50 mg/kg showed the difficulty of nursling and two of them let all their offsprings die within the first 4 days after birth.

Toxicity to offspring:

This compound showed no adverse effects on viability, sex ratio and body weight gain of pups. However, viability of newborns

	at birth and body weight of nurslings on postnatal day 4 was lower than the control levels at 50 mg/kg/day. These changes were considered to be caused by maternal toxicity. There were no morphological abnormalities in pups at all treated groups.
Method:	OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MHW, Japan (1997)

*5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

No data

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

No data

B. Toxicodynamics, toxicokinetics

No data

* 5.11 EXPERIENCE WITH HUMAN EXPOSURE

No data

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Appendix 1.

scenario 1

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	1,000	7.1.E-06	7.1.E+04	31.0	1.8E+02	7.1.E+02
water	0	4.7.E-03	9.4.E+04	40.9	7.5E+00	9.4.E+01
soil	0	4.0.E-02	6.4.E+04	27.9	5.1E+00	
sediment		4.3.E-03	4.3.E+02	0.2	3.4E-02	8.5.E-03
		total amount	2.3.E+05			

scenario 2

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	4.6.E-07	4.6.E+03	0.5	1.2.E+01	4.6.E+01
water	1000	4.4.E-02	8.7.E+05	98.6	7.0.E+01	8.7.E+02
soil	0	2.6.E-03	4.2.E+03	0.5	3.4.E-01	
sediment		3.9.E-02	3.9.E+03	0.4	3.2.E-01	7.9.E-02
		total amount	8.8.E+05			

scenario 3

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	1.6.E-06	1.6.E+04	0.7	4.1.E+01	1.6.E+02
water	0	3.1.E-02	6.2.E+05	28.6	5.0.E+01	6.2.E+02
soil	1000	9.6.E-01	1.5.E+06	70.6	1.2.E+02	
sediment		2.8.E-02	2.8.E+03	0.1	2.3.E-01	5.7.E-02
		total amount	2.2.E+06			

scenario 4

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	600	4.6.E-06	4.6.E+04	7.4	1.2.E+02	4.6.E+02
water	300	1.9.E-02	3.8.E+05	61.2	3.1.E+01	3.8.E+02
soil	100	1.2.E-01	1.9.E+05	31.2	1.6.E+01	
sediment		1.7.E-02	1.7.E+03	0.3	1.4.E-01	3.4.E-02
		total amount	6.2.E+05			

Physico-chemical parameter

molecular weight		164.21	Measured
melting point		101.5	Measured
vapor pressure [Pa]		8.1E+01	Measured
water solubility [g/m^3]		350	Measured
log Kow		1.1	Measured
half life [h]	in air	272	Estimated
	in water	8640	Estimated
	in soil	8640	Estimated
	in sediment	8640	Estimated

Temp. []	25

Environmental parameter

		volume	depth	area	organic	lipid content	density	residence
		[m^3]	[m]	[m^2]	carbon []	[]	[kg/m^3]	time [h]
bulk air	air	1.0E+13					1.2	100
	particles	2.0E+03						
	total	1.0E+13	1000	1E+10				
bulk water	water	2.0E+10					1000	1000
	particles	1.0E+06			0.04		1500	
	fish	2.0E+05				0.05	1000	
	total	2.0E+10	10	2E+09				
bulk soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8.0E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
bulk sediment	water	8.0E+07					1000	
	solid	2.0E+07			0.06		2400	50000
	total	1.0E+08	0.05	2E+09				

Intermedia Transport Parameters

m/h

air side air-water MTC	5	soil air boundary layer MTC	5
water side air water MTC	0.05	sediment-water MTC	1E-04
rain rate	1E-04	sediment deposition	5E-07
aerosol deposition	6E-10	sediment resuspension	2E-07
soil air phase diffusion MTC	0.02	soil water runoff	5E-05
soil water phase diffusion MTC	1E-05	soil solid runoff	1E-08

EXTRACT FROM IRPTC LEGAL FILES

File: 17.01 LEGAL **rn : 1645478**

systematic name:Propanenitrile, 2,2'-azobis½2-methyl-
common name :Azodiisobutyronitrile
reported name :AZODIISOBUTYRONITRILE
cas no :78-67-1
area : IMO type : REC

subject	specification	descriptor
TRNSP LABEL PACK	MARIN	CLASS

HAZARD CLASS: 4.1 = INFLAMMABLE SOLID. PACKING GROUP: II = MEDIUM DANGER (I=GREAT DANGER - III=MINOR DANGER). SUBSIDIARY RISK LABEL: EXPLOSIVE UN NO. 2952
entry date: JAN 1991

amendment: !IMCOC*, International Maritime Dangerous Goods Code, , , 10004 , 1990

****

File: 17.01 LEGAL **rn : 1745186**

systematic name:Propanenitrile, 2,2'-azobis½2-methyl-
common name :Azodiisobutyronitrile
reported name :AZODIISOBUTYRONITRILE
cas no :78-67-1
area : UN type : REC

subject	specification	descriptor
TRNSP LABEL PACK		CLASS

HAZARD CLASS: 4.1 = INFLAMMABLE SOLID. PACKING GROUP: II = MEDIUM DANGER (I=GREAT DANGER - III=MINOR DANGER). UN NO. 2952
entry date: AUG 1990

amendment: !UNTDG*, UN Transport of Dangerous Goods, Recommendation prepared by theCommittee of Experts on the Transport of Dangerous Goods, , , 15 , 1989

HEXAMETHYLENE GLYCOL

CAS NO. 629-11-8

SIDS INITIAL ASSESSMENT PROFILE

CAS Nr.	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 0.19 g/l (site specific) and 29 g/l (generic) were estimated. With a PNECaqua of 500 g/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.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

No further work is recommended.

SIDS PROFILE SUMMARY

CAS-NO.: 629-11-8			PROTOCOL	RESULTS
PHYSICAL CHEMICAL				
2.1	Melting Point		NA	40-42 °C
2.2	Boiling Point		NA	243 °C (at101.3 kPa)
2.3	Density		DIN 51 757	960 kg/m^3
2.4	Vapour Pressure		NA	< 0.01 hPa at20°C
2.5	Partition Coefficient (Log Pow)		OECD 107	0
2.6 A	Water solubility			miscible at 20°C
2.12	Oxidation : Reduction potential			mV
ENVIRONMENTAL FATE / BIODEGRADATION				
3.1.1	Photodegradation		calc. (Atkinson)	In air $T_{1/2}$ = 28.8 hour
3.3	Transport and Distribution		calculated (fugacity level 1 type)	In air % In water 99 % In sediment % In soil % In biota %
3.5	Biodegradation		OECD 301 C	readily biodegradable
ECOTOXICOLOGY				
4.1	acute/prolonged toxicity to fish	Leuciscus idus	DIN 38 412 / 15	LC_{50} (96hr) = 460-1000 mg/l
4.2	acute/prolonged toxicity to aquatic invertebrates (daphnia)	Daphnia magna	84 / 449 / EEC, C.2	EC_{50} (48hr) = > 500mg/l
4.3	toxicity to aquatic plants e. g. algae	Scenedesmus subspicatus	DIN 38 412 / 9	EC_{50} (72hr) = 2200mg/l EC_{10} (72hr) = 810mg/ll
TOXICOLOGY				
5.1.1	acute oral toxicity	rat	NA	LD_{50} = 3000 mg/kg
5.1.2	acute inhalation toxicity			LC_{50} = mg/m^3
5.1.3	acute dermal toxicity	rabbit	NA	LD_{50} > 10000mg/kg
5.4	repeated dose toxicity	rat	OECD 407	NOAEL = 400mg/kg
5.5	genetic toxicity in vitro			

A.	bacterial test (gen mutation)	Ames	OECD 471	- (with metabolic activation) - (without metabolic activation)
	non-bacterial test (gene mutation)	CHO-HPRT	OECD 476	- (with metabolic activation) - (without metabolic activation)
B.	mammalian cytogenetic in vitro test (chromosomal aberration)	CHO-V79	OECD 473	- (with metabolic activation) - (without metabolic activation)
5.6	genetic toxicity in vivo			
5.8	toxicity to reproduction	rat	OECD 421	NOAEL = 400 mg/Kg (rep. tox. parental, male) NOAEL = 1000mg/Kg (rep. tox. parental, female)
5.9	developmental toxicity / teratogenicity	rat	OECD 421	NOEL = 1000mg/Kg (pregnancy/litter) NOEL = 1000mg/Kg (foetal data)
5.11	experience with human exposure			

SIDS Initial Assessment Report

1. Identity

Name:	Hexane-1,6-diol
CAS-No.:	629-11-8
Empirical formula:	$C_6H_{14}O_2$
Structural formula:	$HO-(CH_2)_6-OH$
Synonyms:	Hexanediol Hexanediol 1,6-Dihydroxyhexane 1,6-Hexanediol Hexamethylene glycol Hexamethylenediol Hexan-1,6-diol
Degree of purity:	> 96%

2. General Information on Exposure

The production level of Hexane-1,6-diol in Germany was 10,000-50,000 t in 1991. There is no information about export and import volumes.

The production capacity in Japan and USA was 8,500 t resp. 6,000 t in 1987. There are no data available from other countries.

All the produced Hexane-1,6-diol 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.

During production and processing in Germany, about 0.8 kg/t production volume were emitted into the waste water by one German producer. Exhaust gases are burnt in an incinerator.

Supposing a residual concentration of monomeres in the polyesters, an unknown amount of Hexane-1,6-diol is entering the environment during the life of the polymeres.

3. Environment

3.1 Environmental Exposure

3.1.1 General Discussion

Hexane-1,6-diol is miscible with water at 20 °C and has a vapour pressure of <0.01 hPa at 20°C. Its measured log Pow of 0.0 indicates that there is no considerable potential for bio- and geoaccumulation.

Based on the physico-chemical properties, the preferred environmental compartment of Hexane-1,6-diol is the hydrosphere (Mackay I: 99%).

Hexane-1,6-diol is biologically readily degradable. According to the model SIMPLETREAT (cf. Ref.1), in wwpt's a removal rate of 91% is predicted.

In water solution, hydrolysis or photolysis are not likely to occur.

The calculated half-life due to photochemical-oxidative degradation in the atmosphere by OH-radicals is about 1.2 days.

3.1.2 Predicted Environmental Concentration

a. Point emissions

For production and processing of Hexane-1,6-diol, we would consider the following scenario:: Based on a maximum production volume of 50,000 t/a and an emission rate of 0.8 kg/t during production and processing a total amount of 40 t/a is emitted into the waste water by one German producer. With an elimination factor of 91 % in the sewage treatment plant, 3.6 t/a are emitted into the river Rhine. The flow-rate (10%ile) is 734 m^3/s and therefore the predicted environmental concentration is calculated to:

$$PEC = \frac{3.6\ t/a}{734\ m^3/s} = 0.19\ \mu g/l$$

In addition the PEC_{local} is calculated using a generic exposure model. Based on a maximum production volume of 50,000 t/a and an emission rate of 0.3 % during production and 0.7 % during processing (Emission Scenario Documents in (1)), a total amount of 500 t/a is emitted into the waste water. With an elimination factor of 91% in the treatment plant, 45 t/a are emitted into the environment. A flow-rate of the receiving river of 60 m^3/s is assumed as default value (Emission Scenario Document in (1)).

The predicted environmental concentration is

$$PEC = \frac{45\ t/a}{60\ m^3/s} = 29\ \mu g/l$$

b. Diffuse emissions

An unknown amount of Hexane-1,6-diol residual monomere from polyesters is entering into atmosphere and hydrosphere. Because of the fast degradability in both compartments and the diffuse release, significant concentrations in the environment are not to be expected.

3.2 Effects on the Environment

3.2.1 Aquatic effects

Available data

The following ecotoxicological effect concentrations, corresponding to the aquatic environment, are available:

a) fish

Leuciscus idus LC_{50} = 460-1000 mg/l (96h)
(test substance: Hexane-1,6-diol crude 65%)

Leuciscus idus LC_{50} = 4600-10000 mg/l (96h)
(test substance: Hexane-1,6-diol flakes)

Note: The different results are probably caused by impurities in the technical product.

b) invertebrates

Daphnia magna EC_{50} > 500 mg/l (24 and 48h)
(effect: immobilisation)

c) algae

Scenedesmus subspicatus EC_{50} = 2200 mg/l (72h)
EC_{10} = 810 mg/l (72h)
(effect: growth inhibition, biomass)

d) bacteria

Pseudomonas putida EC_{50} > 10000 mg/l (17h)
EC_{10} = 8400 mg/l (17h)
(effect: cell multiplication inhibition)

Pseudomonas putida EC_{10} = 5200 mg/l (18 h)
(effect: cell multiplication inhibition)

activated sludge (industrial) EC_0 = 1000 mg/l (30 min)
EC_{10} > 1000 mg/l (30 min)
(effect: inhibition of oxygen consumption)

Photobacterium phosphoreum EC_{50} = 205 mg/l (30 min)
(effect: inhibition of light emission)

Determination of $PNEC_{aqua}$

There are data from short-term tests with three trophic levels available. An assessment factor of 1000 is applied to the lowest effect value of 500 mg/l derived from tests with *Leuciscus idus* and *Daphnia magna*.

Therefore: $PNEC_{aqua}$ = 500 mg/l / 1000 = 500 µg/l

3.2.2 Terrestrial organisms

There are no data available on terrestrial organisms.

3.3 Initial Assessment for the Environment

With the PECs of 0.19 µg/l and. 29 µg/l (site-specific resp. generic model) and a $PNEC_{aqua}$ of 500 µg/l PEC/PNEC ratios of $3.8 \cdot 10^{-4}$ and $5.8 \cdot 10^{-2}$ can be calculated. Therefore, at present no risk to the aquatic environment is to be expected.

A significant exposure to the terrestrial compartment could not be identified. Further work is presently not necessary for a risk assessment for this compartment.

4. Human Health

4.1. Human Exposure

Hexanediol is an intermediate in chemical industry for the synthesis of polyesters and polyesterol-type polyurethanes, which are used for paints, laquers and varnishes. Production and further processing is performed in closed systems. It is assumed that hexanediol is completely converted to the end products. Measurements of residual hexanediol concentrations in reaction products are not available. On the other hand hexanediol is readily biodegradable and has no considerable potential for bio- or geoaccumulation. Thus it can be concluded that exposure for consumers and also for humans via the environment is neglegible as laid out in previous chapters. Workers can be exposed during filling or routine analysis at production sites.

4.1.1 Workers

Workers can be exposed during filling or routine analytical sampling. The maximum product temperature is 80°C. No work place analysis has been performed.

A "worst case assessment" has been made using the model "EASE". Assuming a product temperature of 80°C a concentration range of 100 -200 ppm hexanediol has been calculated using LEV (local exhaust ventilation). During routine production without product emission concentrations between 0 and 0.1 ppm have been calculated. The high value of 200 ppm is representing a theoretical exposure during the sampling procedure without protective measures other than local exhaust ventilation. Due to the required use of personal protection measures this high exposure can be ruled out. For workplace assessment the predicted upper value of 0,1 ppm during routine production can be used as 'worst case'.

4.1.2 Consumers

Hexanediol is an intermediate in chemical industry for the synthesis of polyesters and polyesterol-type polyurethanes, which are used for paints, laquers and varnishes. It is assumed that hexanediol is completely converted to the end products. On the other hand hexanediol is readily biodegradable and has no considerable potential for bio- or geoaccumulation. Thus it can be concluded that exposure for consumers is neglegible low as laid out in previous chapters.

4.1.3 Population exposed via the environement

Based on the information given in chapter 4.3.1 it can also be concluded that exposure for humans via the environment is negligible.

4.2 Effects on Humans

Although the technical synthesis of hexanediol has already been published 1932 [21], no adverse effects on humans have been reported in the literature. Therefore, also information from animal and in vitro studies is presented.

a) mode of action of the chemical, toxicokinetics and metabolism

There are no detailed studies with respect to toxicokinetics or metabolism. However, based on the structure and shown after oral application to rabbits (26), oxidation of both alcohol-groups resulting in the formation of adipic acid was observed. The toxic profile of this dicarbonic acid has been well examined [2, 27].

No signs of cytotoxicity or intermediary filaments in a human skin fibroblast culture were noted after hexanediol exposure of 16 mM over 14 days and 8 mM over 60 days. [23]

A series of homologous n-alkanols and n-alkanediols was tested for inhibition of K+ ion flux through a Ca2+ -activated channel in rat glioma cells. The 50 % inhibitory concentration (IC50) is 3.5 times more potent for hexanediol than for n-hexanol. This was interpreted as a direct effect on protein involved in the inhibitory action rather than only lipid solubility criteria [22].

b) acute toxicity

- acute oral/inhalation/dermal toxicity

The acute oral toxicity was tested in rats with comparable LD_{50} values of 3,000 mg/kg b.w. [3] or 3,730 mg/kg b.w. [4,5] Hexanediol was not lethal to 3 rabbits given 3,000 mg/kg b.w. by gavage [6]. Two cats dosed once with 300 mg/kg b.w. by gavage survived, while 2 out of 4 animals receiving 1,000 mg/kg b.w. died. No mortality was observed when six rats were exposed to an atmosphere that had been saturated at 100 degrees centigrade with the vapor of the substance [3]. This holds also for eight rats exposed at room temperature for 8 hours to the volatile part of the compound [4]. No mortality ocurred when 5 rabbits/sex received 2,500 mg/kgb.w. for eight hours dermally under occlusive conditions [7]. Another author reported an LD_{50} > 10,000 mg/kg after dermal application of rabbits [4,5]. Comparable LD_{50} values (about 2,300 and 1,738 mg/kg b.w.) were noted for mice after intraperitoneal application[3 and 8,9].

Conclusion:
The available data are sufficient for Initial Hazard Assessment. The data indicate that Hexanediol is not acute toxic and has not to be classified according to EU-criteria.

- irritation

An 80% aqueous preparation of hexanediol was not irritating to rabbit skin after up to 20h occlusive exposure [3]. In another study the irritation index according to Smyth-Carpenter reached 2 out of 10 points, which is considered to be not irritant [4]. Eye irritation was tested in rabbits according to the method of Draize. Initial findings were slight chemosis and slight corneal opacity. The findings were completely reversible within 8 days after application [3]. In another eye irritation study

according to the method of Smyth-Carpenter the compound reached grade 3 on a 10 point scale indicating an irritant effect based on this grading scheme [4].

Conclusion:
The available data are sufficient for Initial Hazard Assessment. Hexanediol is considered as not irritant to the skin and only slightly irritant to the eyes. According to EU-criteria it has not to be classified as irritant.

- sensitization

In a Guinea pig maximization test according to the method of Magnusson and Kligman (OECD 406) Hexanediol was not sensitizing [10]. The intradermal induction was performed with 5%, while the dermal induction (48 hours occlusive exposure) was performed with a concentration of 50%. The challenge concentration was 25% (24 hours occlusive exposure). Water was used as vehicle in this study. There was no indication that Hexanediol is a skin sensitizer.

Conclusion:
No skin sensitizing potential.

c) repeated dose toxicity

Male and female Wistar rats received 0, 100, 400 and 1,000 mg/kg b.w. Hexanediol by gavage for 28 days in compliance with OECD test method 407 to assess the effect of hexanediol with respect to repeated toxicity and for 28 days (males) / 42 days (females) in comliance with OECD test method 421. There were no clinical, clinico-chemical, hematological parameters adversely affected in these studies. In addition no test substance-related gross- or histopathological alterations were noted in these studies. Slight changes in body weight and body weight gain at 1000 mg/kg b.w./d were observed always only in one sex: fermales (OECD 407) and males (OECD 421). This effect is assessed as a borderline effect of questionable toxicological relevance because of the following reasons: only one sex (either males or females) is affected; there is no correlation to foods consumption, no changes in hematology, clinical chemistry and histopathology were found. The NOAEL is 400 mg/kg b.w. for male and female rats [13, 20]. Other repeated dose toxicity studies were performed with non relevant routes of administration (intraperitoneal [14,15], subcutaneous [16]) or animal species not routinely considered as relevant for the assessment of repeated dose toxicity [6]. Compared to the above mentioned OECD 407 study, the studies lack an appropriate study design due to limited scope of examination such as low number of animals, limited scope of examination including histopathology [6, 14, 15, 16].

Conclusion:
In valid OECD studies, tested up to the highest recommended dose of 1,000 mg/kg b.w. hexanediol revealed no effects of toxicological relevance beside a borderline effect on body weight either in males (OECD 421) or in females (OECD 407). NOAEL = 400 mg/kg b.w..

d) reproduction/developmental toxicity

Male and female Wistar rats received 0, 100, 400 and 1,000 mg/kg body weight Hexanediol by gavage for 4 (males) to 6 (females) weeks in compliance with OECD test method 421 to screen the effect of hexanediol on reproduction and developmental toxicity. The premating exposure period was at least 14 days and the study was terminated 4 days post partum of the F1 generation pups. Marginal retarded body weight development in males at 1,000 mg/kg b.w. was the only effects noted in this study. This dose level represent the highest concentration required for this type of

study. There were no signs indicating impairment of reproductive function of F0 rats and no signs of developmental toxicity in their offspring. The NOAEL for parental toxicity is 400 mg/kg b.w. (males) and 1,000 mg/kg b.w. (females). The NOAEL for reproductive function and development toxicity is 1,000 mg/kg b.w.[20].

Conclusion:
In a valid OECD 421 study no indication of toxic effect on reproductive function or developmental toxicity were observed.

e) genetic toxicity

Hexandiol was not mutagenic in the Ames test (OECD 471) when Salmonella typhimurium strains (TA 98, TA 100, TA 1535 and TA 1537) were exposed up to 5,000 µg/plate with and without metabolic activation 17]. In vitro point mutation was also studied in mammalian cells (Chinese hamster V79 HPRT locus, OECD 476) with no indication of a mutagenic response either in the presence or absence of metabolic activation [19]. This holds also for chromosome aberration according to OECD 473 performed with the same cell line with and without S9 mix [18]. In the absence of positive mutagenicity data in vitro no in vivo mutagenicity studies have been performed.

These data indicate that Hexanediol has no mutagenic potential in the above described in vitro assays. No in vivo mutagenicity studies have been performed.

Conclusion:
Neither a mutagenic nor a clastogenic potential could be detected in in vitro tests with Hexanediol. No in vivo mutagenicity studies have been performed.

f) any other human health related information that is available

1,6-Hexanediol and 2,5 Hexanediol have been tested for neurotoxic effects. Rats were receiving 0,5% Hexanediol (500 mg/kg b.w.) via the drinking water over a period of 12 weeks. In contrast to 2,5-hexanedione no signs of neurotoxicity or histopathological alteration of nervous tissue was observed with 1,6-hexanediol [11, 12].

Hexanediol did not inhibit the glyceroaldehyde-3-phosphatase dehydrogenase activity of the nervous system in vitro as did, for example the neurotoxic hexacarbon compound 2,5-hexanedione [25].

After local application to the nervous tissue hexanediol caused no and 2,5-hexanedione caused changes of the neurofilaments and swelling of Schwann´s cells [24]. This correlated with the above described in vivo neurotoxicity studies.

Other information relevant for the risk assessment with human health is not available.

4.3 Initial Assessment for Human Health

As shown in chapter 4.2 hexanediol has a very low toxic potential: no local or organ-specific effects were detected. The toxic potency is also low: the lowest NOAEL has been derived in the OECD Test 421 the effect observed (reduced body weight development in adult male rats) is representing a systemic effect not related to reproductive/developmental toxicity. Compared to the 28 day gavage study in the same rat species (OECD 407), the effect was somewhat more pronounced and statistical significant ($P<0.05$) in the OECD 421 test. At study termination bodyweight only of male rats was

5% lower when compared to the untreated control indicating a toxicological effect of borderline significance. 400 mg/kg is taken as a NOAEL for repeated application.

4.3.1 Workers

Assuming 100% resorption, an inhaled air volume of 10 m^3/8 h working day and estimated (worst-case) concentration of 0.1 ppm, the EHE for a 70 kg worker will be 5 mg hexanediol/working day corresponding to 0,07 mg/kg/d.

Comparing this estimated dose with the NOAEL, a very high margin of safety of

$$\frac{\text{NOAEL}}{\text{EHE}} = \frac{400 \text{ mg/kg/d}}{0{,}07 \text{ mg/kg/d}} = 5{,}714$$

is estimated. Even under "worst-condition-assumptions" a risk cannot be identified. Hexanediol is considered as of low potential for risk to man.

4.3.2 Consumers

Following the assessment of the use of the substance and the exposure scenario, there is no reason to assume relevant consumer exposure. Taking into account the inherent toxicity of the substance, there is no reason for concern; the substance is considered of low potential risk and low priority for further work.

4.3.3 Population exposed via the environment

According to the ready biodegradability in the environment a very low potential for risk to man is assessed.

5. Conclusions and Recommendations

5.1 Conclusions

Environemnt:
The risk assessment for the aquatic compartment showed that PEC/PNEC < 1. On the whole, Hexane-1,6-diol is of low concern to the environment.

Human health:
Taking into account the inherent toxicity of the substance, there is no reason for concern; the substance is considered of low potential risk and low priority for further work.

5.2 Recommendations

No further tests are needed.

6. References

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4 -HYDROXYBENZOIC ACID

CAS NO. 99-96-7

SIDS Initial Assessment Report
for
9th SIAM

(France, June 29-July 1, 1999)

Chemical Name: 4-Hydroxybenzoic acid
CAS No: 99-96-7
Sponsor Country: Japan

National SIDS Contact Point in Sponsor Country:
Mr. Kazuhide Ishikawa
Ministry of Foreign Affairs, Japan

HISTORY:

SIDS Testing Plan were reviewed in SIDS Review Process, where the following SIDS Testing Plan was agreed:

no testing ( )
testing (X) Water solubility, Vapour pressure, Octanol/water partition coefficient, Stability in water, Biodegradation

Chronic toxicity to daphnia
Combined repeat dose and reproductive toxicity,
Gene mutation, Chromosomal aberration test in vitro

Deadline for circulation: March 31, 1999
Date of Circulation: March 30, 1999
(To all National SIDS Contact Points and the OECD Secretariat)

SIDS INITIAL ASSESSMENT PROFILE

CAS NO.	99-96-7
CHEMICAL NAME	4-Hydroxybenzoic acid
Structural formula	

RECOMMENDATIONS OF THE SPONSOR COUNTRY

The chemical is currently of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE RECOMMENDATIONS

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.

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 toxcity 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.

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.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

FULL SIDS SUMMARY

CAS NO: 99-96-7		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			216.2 °C
2.2	Boiling Point			Decomposed
2.3	Density			
2.4	Vapour Pressure		OECD TG 104	3.9×10^{-3} Pa at 100 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	1.37
2.6 A.	Water Solubility		OECD TG 105	6 g/l at 25 °C
B.	pH			
	pKa			
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			
3.1.2	Stability in Water		OECD TG 111	Stable at pH4,7 and 9 $pK_1 = 4.582$ $pK_2 = 9.23$
3.2	Monitoring Data			
3.3	Transport and Distribution		Calculated (Fugacity Level III type)	Release: 100% to Water In Air 0.0 % In Water 99.5 % In Sediment 0.0 % In Soil 0.5 %
			(local exposure)	9.7×10^{-4} mg/L (Japan)
3.5	Biodegradation		OECD 301C	Readily biodegradable 100% in 28 days
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (48hr) = > 100 mg/l LC_{50} (72hr) = 92.8 mg/l LC_{50} (96hr) = 92.8 mg/l LC_{50} (14d) = 66.5 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates *Daphnia*	*Daphnia magna*	OECD TG 202	EC_{50} (48hr): 135.7 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50} (72hr) = 68.5 mg/l NOEC = 32 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (21d, Repro)= > 100 mg/l NOEC = > 100 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			None

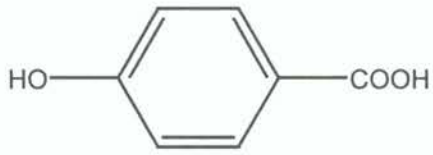
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			None
	TOXICOLOGY			
5.1.1	Acute Oral Toxicity	Rat	Other (unknown)	LD_{50} = 6,000 mg/kg
5.1.2	Acute Inhalation Toxicity			No data
5.1.3	Acute Dermal Toxicity			No data
5.2.1	Skin Irritation/Corrosion	Rabbit	Other (unknown)	Slightly irritating
5.2.2	Eye Irritation/Corrosion	Rabbit	Other (unknown)	Moderate irritating
5.3	Skin Sensitisation	Guinea pig	Guinea pig maximization test	Mildly sensitising
5.4	Repeated Dose Toxicity	Rat	OECD Combined	NOAEL = 1,000 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S. typhimurium* *E. coli* WP2	Japanese TG and OECD TG 471 & 472	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	Chinese hamster CHL cells	Japanese TG and OECD TG 473	- (With metabolic activation) - (Without metabolic activation)
5.6	Genetic Toxicity In Vivo			No data
5.8	Toxicity to Reproduction	Rat	OECD combined	NOAEL = 1,000 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			No available data
5.11	Experience with Human Exposure			No available data

[Note] Data beyond SIDS requirements can be added if the items are relevant to the assessment of the chemical, e.g. corrosiveness/irritation, carcinogenicity.

SIDS INITIAL ASSESSMENT REPORT

1. IDENTITY

- OECD Name: 4-Hydroxybenzoic acid
- Synonym: 4-Hydroxybenzenecarboxylic acid
- CAS Number: 99-96-7
- Empirical Formula: $C_7H_6O_3$
- Structural Formula:



- Degree of Purity: 99.7%
- Major Impurity: None
- Essential Additives: None
- Physical-chemical properties
  - Melting Point: 216.2 °C
  - Vapour pressure: 3.9×10^{-3} Pa at 100 °C
  - Water solubility: 6,000 mg/L
  - Log Pow: 1.37

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production and import

The production volume of 4-hydroxybenzoic acid in Japan is 10,000 tonnes/year in 1995.

2.2 Use pattern

All of 4-hydroxybenzoic acid produced in Japan are used as a monomer unit of polymer and as an intermediate of pesticide and antiseptics, and no consumer use is reported.

2.3 Other information

None

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 General Discussion

4-Hydroxybenzoic acid is readily biodegradable (OECD 301C: 100 % after 28d). Although direct photodegradation is expected because 4-hydroxybenzoic acid has absorption band in UV and VIS region, the data of half-lifetime is not available.

4-Hydroxybenzoic acid is low bioaccumulative based on Log Pow (1.37 at 25 °C).

The potential environmental distributions of 4-hydroxybenzoic acid obtained from a generic Mackay level III fugacity model is shown in Table 1. Parameters used for this model are shown as Annex to this report. The results show that, if 4-hydroxybenzoic acid is released into water, it is unlikely to be distributed into other compartments. If 4-hydroxybenzoic acid is released into air or soil, it is likely to be distributed in other compartments.

Table 1
Environmental distribution of 4-hydroxybenzoic acid
Using a generic level III fugacity model.

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.0 %	0.0 %	0.0 %
Water	28.5 %	99.5 %	23.3 %
Soil	71.4 %	0.0 %	76.6 %
Sediment	0.1 %	0.5 %	0.1 %

As this chemical is used in closed system as a monomer unit of polymer or an intermediate of pesticide, and is not included in consumer products, its release to the environment may occur only from the production site.

3.1.2 Predicted Environmental Concentration

As 4-hydroxybenzoic acid is produced under the well-controlled closed system, amount of release to air phase is negligibly small. The waste of 4-hydroxybenzoic acid from the production system is released to water phase after treated its own wastewater treatment plant. Therefore, Predicted Environmental Concentration (PEC) will be calculated only for the water environment.

a. Regional exposure

According to report from a Japanese manufacturer, 142 tonnes/year (measured) of 4-hydroxybenzoic acid are treated in its own wastewater treatment plant with 97% of removal rate (Plant 1:80%, Plant 2:85%) and released with 4.4×10^9 L/year of effluent into sea. Local Predicted Environmental Concentration (PEC_{local}) is calculated to be 9.7×10^{-4} mg/L as a worst case scenario, employing the following calculation model and dilution factor of 1000 (default).

$$\frac{\text{Amount of release } (1.42 \times 10^{11} \text{ mg/y}) \times (1 - \text{Removal rate } (97\ \%))}{\text{Volume of effluent } (4.4 \times 10^9 \text{ L/y}) \times \text{Dilution Factor } (1000)}$$

A. Effects on the Environments

3.2.1 Effects on aquatic organisms

Acute and chronic toxicity data of 4-hydroxybenzoic acid to test organisms are summarized below (Table 2). Toxicity of this chemical to aquatic organisms seems relatively low, because

NOEC values of *Selenastrum* and *Oryzias latipes* are 32.0 mg/l and 66.5 mg/l, respectively. PNEC of this chemical was determined mainly based on the toxicity data obtained by the Environment Agency of Japan through a GLP-laboratory. Concentrations of the chemical were kept at the levels of 84 to 105 % of the nominal concentrations in all toxicity tests. Several data by different organizations were available in the AQUIRE and IUCLID. As the lowest acute and chronic toxicity data, 14d LC_{50} of fish and NOEC of algae were adopted, respectively (Table 2).

The assessment factors of 100 were used to both acute and chronic toxicity data to determine PNEC, according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects (EXCH/MANUAL/96-4-5.DOC/May 1996), because chronic toxicity data for fish was absent.

From acute toxicity data (14d LC_{50} of fish):

PNEC = 66.5/100 = 0.665 mg/l

From chronic toxicity data (72h NOEC of algae):

PNEC = 32.0/100 = 0.32 mg/l

Thus, PNEC of 4-hydroxybenzoic acid is 0.32 mg/l.

Table 2

Acute and chronic toxicity data of 4-hydroxybenzoic acid to aquatic organisms at different trophic levels. The data were obtained by the Environmental Agency of Japan based on the OECD Test Guide Lines and GLP.

Species	Endpoint	Conc. (mg/l)	Remarks
Selenastrum capricornutum (algae)	Bms 72 h EC50	68.5	A, 1)
	Bms 72 h NOEC	32.0	C, 1), C
Chlorella pyrenoidosa (algae)	Bms 96 h EC50	42.8	a, 2), A
Daphnia magna (Water flea)	Imm 48 h EC50	135.7	a, 1), A
	Rep 21 d EC50	> 100	c, 1)
	Rep 21 d NOEC	> 100	c, 1), C
Daphnia magna	Imm 48 h EC50	173.0	a, 3)
Oryzias latipes (fish, Medaka)	Mor 48h LC50	> 100	a, 1)
	Mor 72h LC50	92.8	a, 1)
	Mor 96h LC50	92.8	a, 1)
	Mor 14d LC50	66.5	a, 1), A
Oncorhynchus mykiss (Rainbow trout)	Mor 96h LC50	> 99.4	a, 4)

Notes: Bms; biomass, Mor; mortality, Rep; reproduction

A), C); the lowest values among the acute or chronic toxicity data of algae, cladocera (water flea) and fishes to determine PNEC of 4-hydroxybenzoic acid.

References in Table 2: (1) Toxicity tests were conducted by the Environment Agency of Japan based on OECD Test GuideLines and GLP; (2) Larson, L.J. (1991); (3) Kuhn, R., Pattard, M., Pernak, K., and Winter, A. (1989); (4) Hodson, P.V., and Kaiser, K.L. (1984)

3.2.2 Terrestrial effects

No data available

3.2.3 Other effects

No data available

3.3 Initial Assessment for the Environment

Predicted No Effect Concentration (PNEC) of this chemical has been calculated as 0.32 mg/l.

PEC from Japanese local exposure scenario is 9.7×10^{-4} mg/l.

Thus, PEC_{local} / PNEC = 9.7×10^{-4}/ 0.32 = 0.003 < 1

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

4. HUMAN HEALTH

4.1 Human Exposure

4.1.1 Occupational exposure

4-Hydroxybenzoic acid is produced in closed systems and used as an intermediate for agricultural chemical synthesis and antiseptics. The occupational exposures are expected through inhalation and the dermal route is assumed negligible because this chemical is solid. As the atmospheric concentration in plant was not measured, the maximum exposure levels are estimated according to working schedules as follows. If a single worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hr) is assigned to implement these two bag filling operations without protection, the highest daily intake (combined EHE) is calculated as 0.067 mg/kg/day as the worst cases. Practically, workers always wear protective gloves and respiratory protective equipment (mask) during the operation.

	Frequency Times/day	Duration hr	Working hr/day	Concentration mg/m^3	EHE mg/kg/day	Combined EHE mg/kg/day
Bag Filling	0.44	2	0.88	2.99	0.04700	
Bag Filling	0.058	6.6	0.38	2.99	0.02000	0.067

EHE: Estimated Human Exposure

4.1.2 Consumer exposure

As all of 4-hydroxybenzoic acid produced in Japan are used as a monomer unit of polymer and as an intermediate of pesticide, and no consumer use is reported in Sponsor country, consumer exposure is not expected.

4.1.3 Indirect exposure via the environment

Although 4-hydroxybenzoic acid is readily biodegradable and low bioaccumulative, the exposure to the general population via the environment would be possible through drinking water processed from surface water and through fish which may accumulate this chemical.

The concentration in drinking water should be estimated to be equal to PEC calculated in Section 3.1, i.e. 9.7 x 10^{-4} mg/l. The daily intake through drinking water is calculated as 3.23 x 10^{-5} mg/kg/day (2 l/day, 60 kg b.w.).

Using the bioconcentration factor of 5.0 estimated from log Pow (1.37), the concentration of this chemical in fish can be calculated as follows:

$$PEC_{fish} = (9.70 \times 10^{-4} \text{ mg/l}) \times 5.0 = 4.85 \times 10^{-6} \text{ mg/g-wet}$$

As a daily intake of fish in Japan is estimated to be 90 g for 60 kg body weight person, a daily intake of this chemical will be 7.28 x 10^{-6} mg/kg/day.

4.2 Effects on Human Health

a) Acute toxicity

[SIDS data] The oral LD_{50} value for 4-hydroxybenzoic acid was 6,000 mg/kg for rats (Ueno Pharm. Inc.).

In another oral study, the LD_{50} value was 2,200 mg/kg for mice (Drug Standards: 1952).

The intraperitoneal LD_{50} value was 340 and 210 mg/kg for rats (Gigiena i Sanitariya: 1986) and mice (J Am Pharm Assoc, Sci Ed: 1956), respectively. Muscle weakness was observed in rats and flaccid paralysis without anesthesia (usually neuromuscular blockage), somnolence (general depressed activity), and ataxia were observed in mice.

The subcutaneous LD_{50} was 1,050 mg/kg for mice (Arch Intl Pharmacodyn Ther: 1960).

b) Irritation

4-Hydroxybenzoic acid was reported to be slightly irritating to skin and moderate to eyes in Bayer Report (1980a,b).

This chemical (500 mg) was applied to the clipped skin with occlusive dressing for 24 hours. Erythema and edema were observed but these changes were very weak. Erythema was reversible within 8 days but edema was not.

As for eye irritation, this chemical (100 µg) was applied to conjunctivae under the right eyelid. Corneal opacity, conjunctival redness, and chemosis were observed. These signs of irritation were not reversible within 8 days.

Based on these observations, this chemical is considered to be slightly irritating to skin and moderate to eyes.

c) Sensitisation

4-Hydroxybenzoic acid was reported as a mild sensitizer by guinea pig maximization test (Scholes *et al.*; 1992). In this test, 10 animals (4 animals in control group) were induced intradermally at 1.0 % and topically at 20 % six to eight days later. After 12-14 days, all animals were challenged by 20

%. The sensitization potential was 20 % (the percentage of animals exhibiting a reaction significantly greater than control animals).

On the other hand, the local lymph node assay in mice showed that this chemical was not a sensitizer (Scholes *et al.*; 1992). In this assay, 4 animals were inducted by daily topical application of 2.5 – 15.0 % for three consecutive days. Five days after the initiation of exposure, [^{3}H] methyl thymidine was injected and the labeling in lymph node cells was measured. The ratio of labeling incorporation by tested lymph node cells to that recorded for control lymph node cells, (T/C) ratio was 0.6 – 1.5 (more than 3.0 is positive).

d) Repeated toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test. 4-Hydroxybenzoic acid was administered by gavage at doses of 40, 200 and 1,000 mg/kg for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

All animals survived at all treated groups. 4-Hydroxybenzoic acid induced rale and temporary salivation (sometimes accompanied by rhinorrhea) at 1,000 mg/kg and slightly at 200 mg/kg. These changes were suggesting the irritation of this chemical to respiratory tract. There were no adverse effects on body weight change and food consumption. At necropsy, no histological and morphological changes were observed. In hematological and blood chemical findings of males, decrease in the percentage of lymphocytes and the blood glucose at 200 mg/kg or more groups and decrease in total protein and increase in A/G ratio, GPT and GOT at 1,000 mg/kg were observed. These changes were significant, but not considered adverse effects. Therefore, NOAEL for systemic toxicity was considered to be 1,000 mg/kg/day.

e) Reproductive/developmental toxicity

Reproductive toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeated dose and reproductive/developmental toxicity screening test. 4-Hydroxybenzoic acid was administered by gavage at doses of 40, 200 and 1,000 mg/kg for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

4-Hydroxybenzoic acid showed no adverse effects on copulation, fertility, maintenance of pregnancy, parturition and lactation, as well as viability, sex ratio, body weights and morphological appearance of pups at all treated groups. The NOAEL of reproductive toxicity for parents and offsprings was considered to be 1,000 mg/kg/day.

Developmental toxicity

Single oral toxicity study (day 11 of gestation) was performed in Sprague-Dawley rats at doses of 333, 667, 1,000 mg/kg. 4-Hydroxybenzoic acid showed no maternal toxicity, including death and change in body weight gain at 24 and 72 hours after treatment. In addition, no developmental toxicity was observed, including change in litter size, pup weight, and total litter weight at 1 and 6 days after birth, and overt malformation. Therefore, NOAEL was considered to be 1,000 mg/kg. (Kavlock *et al.*: 1990)

Some other developmental toxicity studies by a single administration were performed. No teratogenic effect was observed after subcutaneous application to rats at day 9 of gestation or

intramuscular application to mice at day 9 or 12 of gestation (Details were not clear, Larsson and Bostrom: 1965, Koshakji and Scheulert: 1973).

However, any above experiments does not fully support no developmental toxicity of 4-hydroxybenzoic acid, because the exposure conditions were not suitable as the developmental toxicity study.

There was a data on developmental toxicity of ethylparaben (102-47-8). This chemical was shown to hydrolyse to 4-hydroxybenzoic acid rapidly in liver and kidney tissue taken from dogs (Jones *et al.*: 1956) and almost completely after intravenous injection or injected directly into the small intestine in rats (Kiwada et al: 1979 & 1980). In this study, a diet containing 0.1, 1 or 10 % ethylparaben (around 60, 540 and 2800 mg/kg/day) was given to rats on days 8 – 15 of pregnancy. In the 10 % group, some fetuses showed low body weight, and there were some instances of malformations of bones and viscera. However, these changes were considered due to malnutrition of dams. Neonatal growth curves showed no abnormal trends. No signs of teratogenicity were observed in fetuses. (Moriyama *et al*: 1975)

f) Genetic toxicity

Bacterial test

[SIDS data] Gene reverse mutation was negative in *S. Typhimurium* TA100, TA98, TA1535, TA1537 and *E.coli* WP2 *uvr*A with and without metabolic activation (MHW, Japan: 1997).

Non-bacterial test *in vitro*

[SIDS data] Chromosomal aberration test was conducted at concentrations of 0, 0.18, 0.35, 0.70 mg/ml with and without metabolic activation in cultured Chinese hamster lung (CHL/IU) cells. 4-Hydroxybenzoic acid induced structural chromosomal aberrations at 0.70 mg/ml with short-term treatment with metabolic activation and with continuous treatment. Polyploidy was also induced at 0.70 mg/ml with 48 hr continuous treatment, and at 0.70 and 0.18 mg/ml with short-term treatment with metabolic activation. Since this chemical decreased pH in the medium, a confirmation test was conducted under pH-adjusted conditions. As a result, no chromosomal aberrations were observed. As the further study, micronucleus in those cells under the same exposure condition was analysed. Although sufficient increase in micronucleus (Type 2: typical micronucleus) was observed, occurrence was low (1.9 %) and other micronucleus was not observed. Therefore, it was suggested that chromosomal aberrations induced by this chemical were not caused by the direct effects on DNA. (MHW. Japan: 1997)

Based on these results, 4-hydroxybenzoic acid was considered not to be genotoxic.

g) Specific toxicity

It is reported that various phenyl and phenolic acids inhibit the incorporation of mevalonate into cholesterol by homogenates of rat liver and of rat brain. In order to find the specificity and mechanism of this inhibition, a study on various phenyl and phenolic acids was conducted with homogenate of rat liver. As a result, 4-hydroxybenzoic acid competed with the substrate mevalonate 5-pyrophosphate, and inhibited mevalonate pyrophosphate decarboxylase. And this chemical also inhibited mevalonate phosphate kinase. (Shama Bhat and Ramasarma: 1979) However, since no change in cholesterol level was observed in all toxicity studies, this result is considered not to be important for toxicity of this chemical.

Estrogenic effect of 4-hydroxybenzoic acid was examined in vaginal cornification and uterotrrophic assay (Lemini *et al.*: 1997). Immature intact and adult ovariectomized female mice (CD1) were treated subcutaneously daily for 3 days with vehicle (corn oil, 0.3 ml/100 g), E2 (1 μg/100 g), and 4-hydroxybenzoic acid (0.5, 5, 50, and 500 μg/100 g). Four days after treatment, a dose-dependent response on vaginal cornification and uterotrophic activity was observed in both immature intact and adult ovariectomized mice treated with this chemical. The relative uterotrophic potency of this chemical (500 μg/100 g) to estradiol (1 μg m/100 g) was 0.0011 in immature and 0.0018 in ovarectomized animals.

h) Toxicokinetics

Toxicokinetics study was performed in Fischer 344 female rats (29 days old) to examine the disposition of 4-hydroxybenzoic acid 120 hr after i.p. (2.5 μg, approx. 1 μCi) and dermal (5 μg, 3.9 $\mu g/cm^2$, approx. 2 μCi) administration (Hughes and Hall: 1997). Urinary excretion was the predominant means of elimination and occurred primarily within 24 hr after i.p. and dermal administration. The 120 hr cumulative excretion after i.p. administration was 86.5 % in urine and 3.4 % in faeces, and 10.2 % was detected in the carcasses of treated animals. The dermal absorption was very low (2 %). The major portion of the dose not absorbed dermally in 24 hr was washed from the skin. The 120 hr cumulative excretion after dermal administration was 1.9 % in urine and 0.04 % in faeces. 2 % and 0.28 % was detected in the treated skin and the carcasses of treated animals, respectively. In this study, the skin irritation did not occur because of very small amount application to skin.

i) Experience with human exposure

Occupational exposure to airborne epichlorohydrin (0.9-1.5 mg/m^3), toluene (1.3-2.13 mg/m^3), and diphenylolpropane, 4-hydroxybenzoic acid, N-glycidyl-m-aminobenzoic acid, and isophthalic acid (2-5 mg/m^3) at the manufacture of epoxy resins induced contact and allergic dermatitis and sensitization to bacterial and chemical allergens. However, any further detailed information is not given. (Chernykh and Savchenko: 1988)

4.3 Initial Assessment for 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. As these changes of blood chemistry are considered not to be adverse, NOAEL for systemic toxicity is 1,000 mg/kg/day. Reproductive toxicity was not observed (NOAEL = 1,000 mg/kg/day). 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 *in vivo*.

Occupational exposure

4-Hydroxybenzoic acid is used in a closed system at industries. Although the occupational exposure route is expected as an inhalation in limited workers, there is no available data of the atmosphere concentration. Based on the predicted high concentration and the possibility of exposure period, the daily intake is calculated as 0.067 mg/kg/day as the worst cases. Occupational risk is presumably

low because the margin of safety is 1.49×10^4. Although this chemical is considered as an irritant for the skin and eyes, and a skin sensitizer, the risk is probably low because workers wear protective gloves and respiratory protective equipment (mask) during the operation.

Consumer exposure
No consumer exposure is expected because of use pattern.

Indirect exposure via environment
As for indirect exposure via environment, PEC_{local} of 9.70×10^{-4} mg/l from local exposure scenario was used for the estimation. The daily intakes through drinking water and fish are calculated as 3.23×10^{-5} mg/kg/day and 7.28×10^{-6} mg/kg/day, respectively. Since the margin of safety is very large, such as 3.09×10^7 for drinking water and 1.37×10^8 for fish, health risk is presumably low.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

4-Hydroxybenzoic acid is readily biodegradable (OECD 301C: 100 % after 28-d) and low bioaccumulative judging from a relative low Pow value (1.37 at 25 °C). Toxicity of this chemical seems relatively low to aquatic organisms because all toxicity data to test organisms belonging to three trophic levels are higher than 32 mg/l. 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 for the environment and low priority for further work.

4-Hydroxybenzoic acid showed no systemic and reproductive toxicity in an OECD combined repeat dose and reproductive/developmental toxicity study. This chemical is not genotoxic and considered to be slightly irritating to skin and moderate to eyes, and a mild skin sensitizer. The margin of safety for occupational and indirect exposure is calculated as 1.49×10^4 and 3.09×10^7 or 1.37×10^8 (through drinking water or fish), respectively. Therefore, it is currently considered of low potential human risk and low priority for further work.

5.2 Recommendations

No recommendation

6. REFERENCES

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Appendix 1

Method for Prediction of Environmental Concentration of Pollutant in Surface Water

1. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into river

When decomposition, precipitation and vaporization of pollutant can be ignored, it is used that simplified equation by complete mixing model shown with equation (1) to calculate predicted environmental concentration in the local environment (PEC_{local}) as for release effluent into river.

$$PEC_{local}\ (mg/L) = \frac{Co\ Q + Cs\ Qs}{Q + Qs} \qquad (1)$$

Where

Co: Concentration of pollutant in upper stream of release point (mg/L)
Cs: Concentration of pollutant in effluent (mg/L)
Q: Flow rate of river (m^3/day)
Qs: Flow rate of effluent released into river (m^3/ day)

At the equation (1), when Co can be considered as 0, dilution factor of pollutant in the river (R) can be shown with following equation.

$$R = Cs/C = (Q + Qs) / Qs \qquad (2)$$

As the worst case, it is used to employ a flow rate at dry season as flow rate of river (Q). When flow rate at dry season is indistinct, it is estimated using the following equation in Japan.

$$\text{Flow rate at dry season} = \text{mean flow late} / 2.5 \qquad (3)$$

2. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into sea

For prediction of concentration of pollutant in the sea water with effluent, it is employed generally Joseph-Sendnersymbol 146 \f "Times New Roman" \s 11'}s equation (4). This equation is one of analytic solution led under the following conditions from diffusion equation.

1 It is adopted large area of sea or lake.
2 The flow rate of effluent and concentration of pollutant in the effluent are constant, and distribution of concentration is able to regard as equilibrium state.
3 Effluent is distributed uniformly to vertical direction, and it spreads in a semicircle or segment to horizontal direction.
4 Diffusion coefficient of pollutant at the sea is in proportion to distance from release point of effluent.
5 There is not any effect of tidal current.
6 Decomposition of pollutant can be ignored.

$$C(x) = (C_s - C(r))\left(1 - \exp\left(-\frac{Q_s}{d\,p}\left(\frac{1}{x} - \frac{1}{r}\right)\right)\right) + C(r) \qquad (4)$$

Where

C (x): Concentration of pollutant at distance x (m) from release point
Cs: Concentration of pollutant in effluent
C (r): Concentration of pollutant at distance r (m) from release point
Qs: Flow rate of effluent (m^3/day)
: Opening angle of seacoast (rad.)
d: Thickness of diffusion layer (m)
P: Diffusion velocity (m/day) (1.0 0.5 cm/sec)

When C(x) is 0 at r = and density stratification is ignored for simplification, Joseph-Sendnersymbol 146 \f "Times New Roman" \s 11'}s equation (4) is simplified to equation (5)

$$C(x) - Cs\left(1 - \exp\left(-\frac{Qs}{d\,p\,x}\right)\right) \qquad (5)$$

Because of Qs/ d p x << 1 except vicinity of release point, dilution factor in distance x from release point R(x) can be shown with equation (6).

$$R(x) = Cs/C(x) = d\,p\,x/Qs \qquad (6)$$

When it is employed following parameters in equation (6) as default, dilution factor R can be shown with equation (7).

P = 1 cm/sec (860 m/day)
= 3.14
d = 10 m
x = 1000 m

$$R = 2.7\ 10^7/Qs \qquad (7)$$

Qs: volume of effluent (m^3/day)

REVISED OECD HPV FORM 1

SIDS DOSSIER ON THE HPV PHASE 5 CHEMICAL

4-Hydroxybenzoic acid

CAS No. 99-96-7

Sponsor Country: Japan

DATE: March 15, 1999

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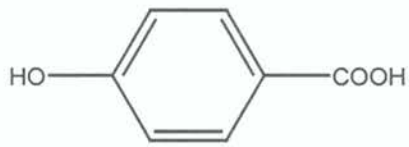
Appendix

Note: *; Data Elements In The Sids
†; Data Elements Specially Required For Inorganic Chemicals

SIDS PROFILE

1.01 A.	**CAS No.**	99-96-7
1.01 C.	**CHEMICAL NAME (OECD Name)**	4-Hydroxybenzoic acid
1.01 D.	**CAS DESCRIPTOR**	
1.01 G.	**STRUCTURAL FORMULA**	
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	**QUANTITY**	10,000 tonnes/year in Japan
1.7	**USE PATTERN**	Intermediate for pesticides and preservatives in closed system.
1.9	**SOURCES AND LEVELS OF EXPOSURE**	142 tonnes/year Release into Bay
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)	SIDS testing required: Water solubility, Vapour pressure, Octanol/water partition coefficient, Stability in water, Biodegradation Combined repeat dose and reproductive toxicity, Gene mutation, Chromosomal aberration test in vitro	

SIDS SUMMARY

CAS NO: 99-96-7		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	N						N
2.4	Vapour Pressure	N						Y
2.5	Partition Coefficient	N						Y
2.6	Water Solubility	N						Y
	pH and pKa values	N						N
2.12	Oxidation: Reduction potential	N						N
	OTHER P/C STUDIES RECEIVED							
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	N						N
3.1.2	Stability in water	N						Y
3.2	Monitoring data	N						N
3.3	Transport and Distribution	N						N
3.5	Biodegradation	N						Y
	OTHER ENV FATE STUDIES RECEIVED							
ECOTOXICITY								
4.1	Acute toxicity to Fish	Y	N	N	Y	N	N	Y
4.2	Acute toxicity to Daphnia	Y	N	N	Y	N	N	Y
4.3	Toxicity to Algae	Y	N	N	Y	N	N	Y
4.5.2	Chronic toxicity to Daphnia	N						Y
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	N						N
4.6.3	Toxicity to Birds	N						N
	OTHER ECOTOXICITY STUDIES RECEIVED							
TOXICITY								
5.1.1	Acute Oral	Y	N	N	Y	N	Y	N
5.1.2	Acute Inhalation	N						N
5.1.3	Acute Dermal	N						N
5.4	Repeated Dose	N						Y
5.5	Genetic Toxicity *in vitro*							
	. Gene mutation	N						Y
	. Chromosomal aberration	N						Y
5.6	Genetic Toxicity *in vivo*	N						N
5.8	Reproduction Toxicity	N						Y
5.9	Development / Teratogenicity	Y	N	N	N	N	Y	N
5.11	Human experience	Y	N	N	N	N	Y	N
	OTHER TOXICITY STUDIES RECEIVED							

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

***A. CAS number** 99-96-7

B. Name *(IUPAC name)*

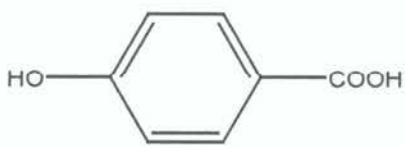
***C. Name** *(OECD name)* 4-Hydroxybenzoic acid

†D. CAS Descriptor

E. EINECS-Number 202-804-9

F. Molecular Formula $C_7H_6O_3$

***G. Structural Formula**



H. Substance Group

I. Substance Remark

J. Molecular Weight 138.13

1.02 OECD INFORMATION

A. Sponsor Country: Japan

B. Lead Organisation:

Name of Lead Organisation: Ministry of Health and Welfare (MHW)
Ministry of International Trade and Industry (MITI)
Environmental Agency (EA)
Ministry of Labour (MOL)

Contact person: Mr. Kazuhide Ishikawa
Economic International Bureau
Second International Organisation Division
Ministry of Foreign Affairs

Address:

Street: 2-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100 Japan
Tel: 81-3-3581-0018
Fax: 81-3-3503-3136

C. Name of responder

Name: Same as above contact person

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic **[X]**; organometallic [ ]; petroleum product [ ]

B. Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [ ]; solid **[X]**

C. Purity 99.7%

1.2 SYNONYMS

4-Hydroxybenzenecarboxylic acid

1.3 IMPURITIES

None

1.4 ADDITIVES

None

*1.5 QUANTITY

Remarks: 4,044 tonnes/year
Reference: MITI, Japan

1.6 LABELLING AND CLASSIFICATION

None

*1.7 USE PATTERN

A. General

	Type of Use:	**Category:**
	main	Intermediate
	industrial	Intermediate in closed system
	use	Intermediate for pesticides and preservatives

Remarks: None
Reference: MITI, Japan

1.8 OCCUPATIONAL EXPOSURE LIMIT

None

* 1.9 SOURCES OF EXPOSURE

In Japan, 4-hydroxybenzoic acid is produced in 1 company.

Source:	Media of release: Bay Quantities per media: 142 tonnes/year
Remarks:	
Reference:	MITI, Japan

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value:	216.2 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	
GLP:	Yes [ ] No [X] ? [ ]
Remarks:	
Reference:	Company data

*2.2 BOILING POINT

Value:	Decompose
Pressure:	
Decomposition:	Yes [X] No [ ] Ambiguous [ ]
Method:	
GLP:	Yes [ ] No [X] ? [ ]
Remarks:	
Reference:	Company data

*2.4 VAPOUR PRESSURE

Value:	$< 3.9 \times 10^{-3}$ Pa
Temperature:	100 °C
Method:	calculated [ ]; measured [X] OECD TG 104
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan

*2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

Log Pow:	1.37
Temperature:	25 °C
Method:	calculated [ ]; measured [X] OECD TG 107
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan.

*2.6 WATER SOLUBILITY

A. Solubility

Value:	6.0 g/L
Temperature:	25 °C
Description:	Miscible [ ]; Of very high solubility [ ]; Soluble [ ]; Slightly soluble[X]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	OECD TG 105
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan.

B. pH Value, pKa Value

Value:	pK1 = 4.582 pK2 = 9.23
Reference:	Lang's Handbook of Chemistry (13th Edition)

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

*3.1.2 STABILITY IN WATER

Type:	Abiotic (hydrolysis) [X]; biotic (sediment)[ ]
Half life:	Stable at pH 4, 7, 9 at 25 °C
Method:	OECD TG 111
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan

*3.2 MONITORING DATA (ENVIRONMENTAL)

No studies located

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION

*3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Media:	Air-biota [ ]; Air-biota-sediment-soil-water [X]; Soil-biota [ ]; Water-air [ ]; Water-biota [ ]; Water-soil [ ]; Other [ ]
Method:	Fugacity level I [ ]; Fugacity level II [ ]; Fugacity level III [X]; Fugacity level IV [ ]; Other (calculation) [ ]; Other (measurement)[ ]

Results:

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.0 %	0.0 %	0.0 %
Water	28.5 %	99.5 %	23.3 %
Soil	71.4 %	0.0 %	76.6 %
Sediment	0.1 %	0.5 %	0.1 %

Remarks: Appendix 1
Reference: MITI, Japan

*3.5 BIODEGRADATION

Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**;
Concentration of the chemical: related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X]**; water-sediment **[ ]**; soil **[ ]**; sewage treatment **[ ]**
Degradation: 90 % by BOD after 14 days
100 % by TOC after 14 days
100 % by GC after 14 days
Results: readily biodeg. **[X]**; inherently biodeg. **[ ]**; under test condition no biodegradation observed **[ ]**, other **[ ]**
Method: OECD TG 301C
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: purity: 99.9 %
Reference: MITI, Japan

4. ECOTOXICITY

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a) Type of test: static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other *(e.g. field test)* **[ ]** open-system **[X]**; closed-system **[ ]**
Species: *Oryzias latipes* (Himedaka)
Exposure period: 96 h
Results: LC_{50} (96 h) = 92.8 mg/l
Analytical monitoring: Yes **[X]** No **[ ]** ? **[ ]**
Method: OECD TG 203 (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4, purity: > 95 %
Remarks: Groups of ten Himedaka were exposed to the nominal concentrations of 30.9, 55.6 and 100 mg/l, and laboratory water control. No solubilizer was used. Concentrations of the chemical were kept within ± 20% changes from the nominal concentrations throughout the test period.
Reference: Environment Agency of Japan (1995)

(b) Type of test:	static [ ]; semi-static [ ]; flow-through **[X]**; other *(e.g. field test)* [ ] open-system **[X]**; closed-system [ ]
Species:	*Poecilia reticulata* (Guppy)
Exposure period:	14 d
Results:	$LC_{50\ (14d)}$ = 66.5 mg/l
Analytical monitoring:	Yes **[X]** No [ ] ? [ ]
Method:	No data
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	As prescribed by 1.1 - 1.4, purity: > 95 %
Remarks:	Groups of ten Himedaka were exposed to the nominal concentrations of 9.5, 17.1, 30.9, 55.6 and 100 mg/l, and laboratory water control. No solubilizer was used. Concentrations of the chemical were kept within ± 20% changes from the nominal concentrations throughout the test period. Toxicity data was calculated based on nominal concentrations.
Reference:	Environment Agency of Japan (1995)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

Type of test:	static [ ]; semi-static **[X]**; flow-through [ ]; other *(e.g. field test)* [ ]; open-system **[X]**; closed-system [ ]
Species:	*Daphnia Magna.*
Exposure period:	48 h
Results:	$EC_{50\ (48\ h)}$ = 135.7 mg/l
Analytical monitoring:	Yes **[X]** No [ ] ? [ ]
Method:	OECD TG 202
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	As prescribed by 1.1 - 1.4, purity: > 95 %
Remarks:	20 daphnids (4 replicates of 5 organisms) were exposed to nominal concentrations of 26, 42, 67, 107, 172 and 275 mg/l, and laboratory water control (M4-medium). The measured concentrations were within 95.0 to 99.7% of the nominal concentrations throughout the test period. No solubilizer was used.
Reference:	Environment Agency of Japan (1995)

*4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

Species:	*Selenastrum capricornutum* ATCC 22662
Endpoint:	Biomass **[X]**; Growth rate [ ]; Other [ ]
Exposure period:	72 h
Results:	Biomass $EC_{50\ (72h)}$ = 68.5 mg/l *(Endpoint)* NOEC = 32 mg/l
Analytical monitoring:	Yes [**X**] No [ ] ? [ ]
Method:	OECD TG 201 (1984) open-system **[X]**; closed-system [ ]
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	As prescribed by 1.1 - 1.4, purity: > 95 %

Remarks:	Static test. The EC_{50} value for growth rate (% inhibition) was calculated based on 5 nominal concentrations (20, 32, 51, 82, 131 and 210 mg/l). No solubilizer was used. Measured concentrations were within 98.5 to 101.3 of the nominal concentrations after 3 days test period.
Reference:	Environment Agency of Japan (1995)

4.4 TOXICITY TO BACTERIA

No data

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

No data

(*) 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test:	static [ ]; semi-static **[X]**; flow-through [ ]; other *(e.g. field test)* [ ]; open-system **[X]**; closed-system [ ]
Species:	*Daphnia Magna.*
Endpoint:	Mortality [ ]; Reproduction rate **[X]**; Other **[X]**
Exposure period:	21 d
Results:	Reproduction rate: $EC_{50\ (21\ d)}$: > 100 mg/l *(Endpoint)* NOEC: > 100 mg/l
Analytical monitoring:	Yes **[X]** No [ ] ? [ ]
Method:	OECD TG 202(1984)
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	As prescribed by 1.1 - 1.4, purity: > 95 %
Remarks:	40 daphnids (4 replicates of 10 daphnids) were exposed to the nominal concentrations of 100 mg/l and laboratory water control (M4-medium). No solubilizer used.
Reference:	Environment Agency of Japan (1995)

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data

4.8 BIOTRANSFORMATION AND KINETICS

No data

4.9 ADDITIONAL REMARKS

None

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)	Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
	Species/strain:	Rats
	Value:	6,000 mg/kg b.w.
	Method:	Other
	GLP:	Yes [ ] No [X] ? [ ]
	Test substance:	purity: unknown
	Remarks:	
	Reference:	Ueno Pharm Inc

(b)	Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
	Species/strain:	Mice
	Value:	2,200 mg/kg b.w.
	Method:	Other
	GLP:	Yes [ ] No [X] ? [ ]
	Test substance:	purity: unknown
	Remarks:	
	Reference:	Drug Standards: 1952

5.1.2 ACUTE INHALATION TOXICITY

No data

5.1.3 ACUTE DERMAL TOXICITY

No data

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a)	Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
	Species/strain:	Rats
	Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
	Exposure time:	
	Value:	340 mg/kg

Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	Muscle weakness
Reference:	Gigiena i Sanitariya: 1986

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mice
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:	
Value:	210 mg/kg
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	Flaccid paralysis without anesthesia (usually neuromuscular blockage), somnolence (general depressed activity), and ataxia
Reference:	J Am Pharm Assoc, Sci Ed: 1956

(c)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mice
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [ ]; infusion [ ]; s.c. [X]; other [ ]
Exposure time:	
Value:	1,050 mg/kg
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	Arch Intl Pharmacodyn Ther: 1960

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Species/strain:	New Zealand white rabbits
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**; Not irritating **[ ]**
Classification:	*(If possible, according to EC Directive 67/548/EEC)* Highly corrosive (causes severe burns)**[ ]**; Corrosive (causes burns)**[ ]**; Irritating **[ ]**; Not irritating **[ ]**
Method:	Other (according Code of Federal Regulation (CFR))
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	purity: unknown
Remarks:	4-Hydroxybenzoic acid (500 mg) was applied to the clipped skin with occulusive dressing for 24 hours. Cutaneous reaction was evaluated approximately 24, 48 and 72 hours, and 8 days after the test beginning. Erythema and edema were observed but these changes were very weak. Erythema was reversible within 8 days but edema was not.
Reference:	Bayer Report: 1980a

5.2.2 EYE IRRITATION/CORROSION

Species/strain:	New Zealand white rabbits
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating **[X]**; Slightly irritating [ ]; Not irritating [ ]
Classification:	*(if possible, according to EC Directive 67/548/EEC)* Irritating[ ]; Not irritating [ ]; Risk of serious damage to eyes [ ]
Method:	Other (according Code of Federal Regulation (CFR))
GLP:	Yes [ ] No [ ] ? **[X]**
Test substance:	purity: unknown
Remarks:	4-Hydroxybenzoic acid (100 µg) was applied to conjunctivae under the right eyelid. The eye was closed for 1 second and not washed. As control, left eye remained. Eye reaction was evaluated approximately 24, 48, and 72 hours, and 8 days after the test beginning. Corneal opacity, conjunctival redness, and chemosis were observed. These signs of irritation were not reversible within 8 days.
Reference:	Bayer Report: 1980b

5.3 SKIN SENSITISATION

(a)

Type:	Guinea pig maximization test
Species/strain:	Guinea pigs/Dunkin Hartley strain
Results:	Sensitizing [X]; Not sensitizing [ ]; Ambiguous [ ]
Classification:	Sensitizing [ ]; Not sensitizing [ ]
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	10 animals (4 animals in control group) were inducted intradermally at 1.0 % and topically at 20 % six to eight days later. After 12-14 days, all animals were challenged at 20 %. Mild response was induced. The sensitization potential was 20 % (the percentage of animals exhibiting a reaction significantly greater than control animals).
Reference:	Scholes *et al.*: 1992

(b)

Type:	Local lymph node assay
Species/strain:	Mice/CBA/Ca strain/female
Results:	Sensitizing [ ]; Not sensitizing [X]; Ambiguous [ ]
Classification:	Sensitizing [ ]; Not sensitizing [ ]
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	Four animals were inducted by daily topical application of 2.5 – 15.0 % for three consecutive days. Five days after the initiation of exposure, [^{3}H] methyl thymidine was injected and the labeling in lymph node cells was measured.

	The ratio of labeling incorporation by test lymph node cells to that recorded for control lymph node cells, (T/C) ratio was 0.6 – 1.5 (more than 3.0 is positive).
Reference:	Scholes *et al.*: 1992

*5.4 REPEATED DOSE TOXICITY

Species/strain:	Rats/Crj: CD (SD)
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration:	Oral (by gavage)
Exposure period:	Male: 42 days Female: From 14 days before mating to day 3 of lactation
Frequency of treatment:	Daily
Post exposure observation period:	
Dose:	0, 40, 200, 1,000 mg/kg/day
Control group:	Yes [X]; No [ ]; No data [ ]; 0.5 % CMC-Na Concurrent no treatment];Concurrent vehicle[X]; Historical[ ]
NOAEL:	Male: 1,000 mg/kg/day, Female: 1,000 mg/kg/day
LOAEL:	All animals survived at all treated groups. 4-Hydroxybenzoic acid induced rale and temporary salivation (sometimes accompanied by rhinorrhea) at 1,000 mg/kg and slightly at 200 mg/kg. These changes were suggesting the irritation of this chemical to respiratory tract. There were no adverse effects on body weight change and food consumption. At necropsy, no histological and morphological changes were observed. In hematological and blood chemical findings of males, decrease in the percentage of lymphocytes and the blood glucose at 200 mg/kg or more groups and decrease in total protein and increase in A/G ratio, GPT and GOT at 1,000 mg/kg were observed. These changes were significant, but not considered adverse effects. Therefore, NOAEL for systemic toxicity was considered to be 1,000 mg/kg/day.
Method:	OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	purity: 99.7 %
Reference:	MHW, Japan: 1997

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type:	Gene mutation test
System of testing:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *Escherichia coli* WP2 *uvr*A
Concentration:	+S9 mix; 0, 78.1, 156, 313, 625, 1250, 2500, 5000 μg/plate (TA1537) 0, 313, 625, 1250, 2500, 5000 μg/plate (TA100, TA1535, TA98 and WP2) -S9 mix; 0, 78.1, 156, 313, 625, 1250, 2500, 5000 μg/plate (TA98 and TA1537)

0, 313, 625, 1250, 2500, 5000 µg/plate (TA100, TA1535, and WP2)

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]

S9; Rat liver, induced with phenobarbital and 5,6-benzoflavone,

Results:

Cytotoxicity conc: With metabolic activation: not observed
Without metabolic activation: 5000 µg/plate (observed only in TA100, TA98, TA1537)

Precipitation conc: 5000 µg/plate

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Guideline No. 471 and 472

GLP: Yes [X] No [ ] ? [ ]

Test substance: purity: 99.7 %

Remarks: Positive control:
With metabolic activation: 2-Aminoantthracene (five strains)
Without metabolic activation:
Sodium azide (TA 1535)
9-Aminoacridine (TA1537)
2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide
(TA100, TA98, WP2)

Reference: MHW, Japan: 1997

B. NON-BACTERIAL IN VITRO TEST

Type: Chromosomal aberration test

System of testing: Chinese hamster lung (CHL/IU) cells

Concentration: +S9 mix (short-term treatment): 0, 0.18, 0.35, 0.70 mg/ml
-S9 mix (short-term treatment): 0, 0.18, 0.35, 0.70 mg/ml
-S9 mix (continuous treatment): 0, 0.18, 0.35, 0.70 mg/ml

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]

S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone.

Results: Structural chromosomal aberrations were observed at 0.70 mg/ml with short-term treatment with metabolic activation and with continuous treatment. Polyploidy was also induced at 0.70 mg/ml with 48 hr continuous treatment, and at 0.70 and 0.18 mg/ml with short-term treatment with metabolic activation. Since 4-hydroxybenzoic acid decreased pH in the medium, a confirmation test was conducted under pH-adjusted conditions. As a result, no chromosomal aberrations were observed.

Cytotoxicity conc: 0.70 mg/ml (observed only with short-term treatment with metabolic activation)

Precipitation conc:

Genotoxic effects:

	clastogenicity			polyploidy		
	+	?	-	+	?	-
With metabolic activation:	[ ]	[ ]	[X]	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]	[ ]	[ ]	[X]

Method: Guide for Screening Mutagenicity Testing of Chemicals (Japan), and OECD TG No.473.

GLP: Yes [X] No [ ] ? [ ]
Test substance: purity: 99.7%
Remarks: Exposure period: short-term treatment: 6 hr
continuous treatment: 24 or 48 hr
Positive control: -S9: Mitomycin, +S9: Cyclophosphamide
Reference: MHW, Japan: 1997

* 5.6 GENETIC TOXICITY IN VIVO

No data

5.7 CARCINOGENICITY

No data

*5.8 TOXICITY TO REPRODUCTION

Type: Fertility[ ]; One-generation study[ ]; Two-generation study [ ]; Other [X]
Species/strain: Rats/Crj: CD (SD)
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Oral (by gavage)
Exposure period: Male: From 14 days before mating to 14 days after mating
Female: From 14 days before mating to day 3 of lactation
Frequency of treatment: Daily
Post exposure observation period:
Premating exposure period: 14 days
Duration of the test:
Dose: 0, 40, 200, 1,000 mg/kg/day
Control group: Yes [X]; No [ ]; No data [ ]; 0.5 % CMC-Na
Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
NOAEL Parental: 1,000 mg/kg/day
NOAEL F1 Offspring: 1,000 mg/kg/day
NOAEL F2 Offspring:
Results:
General parental toxicity:
4-Hydroxybenzoic acid showed no adverse effects on copulation, fertility, maintenance of pregnancy, parturition and lactation at all treated groups.
Toxicity to offspring:
4-Hydroxybenzoic acid showed no adverse effects on viability, sex ratio, body weights and morphological appearance of pups at all treated groups.
Method: OECD Combined Repeat Dose and Reproductive/ Developmental Toxicity Screening Test
GLP: Yes [X] No [ ] ? [ ]
Test substance: purity: 99.7 %
Remarks:
Reference: MHW, Japan: 1997

*5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Species/strain: Rats/Sprague-Dawley
Sex: Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration: Oral (a single dose)
Duration of the test: Until weaning
Exposure period: Day 11 of gestation
Frequency of treatment:
Doses: 0, 333, 667, 1,000 mg/kg
Control group: Yes [X]; No [ ]; No data [ ]; consisting of water, Tween 20, propylene glycol, and ethanol in a ratio of 4: 4: 1: 1
Concurrent no treatment[ ]; Concurrent vehicle[X];Historical[ ]
NOAEL Maternal Toxicity: 1,000 mg/kg
NOAEL teratogenicity: 1,000 mg/kg
Results:
Maternal general toxicity:
No significant change was observed in the mortality and body weight at 24 and 72 hr, compared to vehicle control.
Pregnancy/litter data:
There was no significant change in the number of pregnancy, the number of implantation scars in the uterus, the number of perinatal loss of offspring (calculated as the difference between the number of implantation sites and the litter size on 6 day after birth), and litter size, total litter weight and litter biomass at 1 and 6 days, compared to vehicle control.
Foetal data: No significant change in pup weight and overt malformation were observed.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: Kavlock *et al.*: 1990

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

Type: Inhibitory effect on hepatic enzyme
Results: 4-Hydroxybenzoc acid competed with the substrate mevalonate 5-pyrophosphate, and inhibited mevalonate pyrophosphate decarboxylase. And this chemical also inhibited mevalonate phosphate kinase.
Remarks: Male albino rats were killed and the liver were quickly removed, chilled and homogenised in 0.25 M sucrose. The homogenate was centrifuged at 38,000 x g for 40 min and the resultant supernatant was used as the source of enzyme.
As the substrate, (R)-[1-^{14}C] mevalonate 5-phosphate and (R)-[1-^{14}C] mevalonate 5-pyrophosphate was used.
Reference: Shama Bhat & Ramasarma: 1979

Type: Estrogenic assay (vaginal cornification and uterotrophic assay)

Results: A dose-dependent response on vaginal cornification and uterotrophic activity was observed in both immature intact and adult ovariectomized mice treated with 4-hydroxybenzoic acid. The relative uterotrophic potency of this chemical (500 µg/100 g) to estradiol (1 µg /100 g) was 0.0011 and 0.0018 in immature and ovariectomized animals, respectively.

Remarks: Immature intact and adult ovariectomized female mice (CD1) were treated subcutaneously daily for 3 days with vehicle (corn oil, 0.3 ml/100 g), estradiol (1 µg /100 g), and 4-hydroxybenzoic acid (0.5, 5, 50, and 500 µg/100 g). Four days after treatment, estrogenic effect was analyzed.

Reference: Lemini *et al.*: 1997

B. Toxicodynamics, toxicokinetics

Type: Toxicokinetics

Results: Urinary excretion was the predominant means of elimination and occurred primarily within 24 hr after dermal and i.p. administration. The 120 hr cumulative excretion after i.p. administration was 86.5 % in urine and 3.4 % in faeces, and 10.2 % was detected in the carcasses of treated animals. The dermal absorption was very low (2 %). The major portion of the dose not absorbed dermally in 24 hr was washed from the skin. The 120 hr cumulative excretion after dermal administration was 1.9 % in urine and 0.04 % in faeces. 2 % and 0.28 % was detected in the treated skin and the carcasses of treated animals, respectively.

Remarks: Female Fischer 344 rats (29 days old) were dosed with 4-hydroxybenzoic acid by i.p. (2.5 µg, approx. 1 µCi) and dermal (5 µg, 3.9 µg/cm^2, approx. 2 µCi) route. In the dermally treated animals, treated area was washed 24 hr after dosing. Urine and faces were collected at 4, 8, 12, 24, 48, 72, 96 and 120 hr, weighted after collection and stored at –70 until analysed. The animals were killed by CO_2 asphyxiation at 120 hr after treatment. A sample of treated and untreated skin was removed from the dermally treated animals. The skin and samples of the whole-animal homogenate were weighted, combusted and analysed for radioactivity.

References: Hughes & Hall: 1997

* 5.11 EXPERIENCE WITH HUMAN EXPOSURE

Results: Occupational exposure to airborne epichlorohydrin, 0.9-1.5 mg/m^3; toluene, 1.3-2.13 mg/m^3; and diphenylolpropane, p-hydroxybenzoic acid, N-glycidyl-m-aminobenzoic acid, and isophthalic acid, 2-5 mg/m^3 at the manufacture of epoxy resins induced contact and allergic dermatitis and sensitization to bacterial and chemical allergens.

Remarks:

Reference: Chernykh & Savchenko: 1988

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Appendix 1

scenario 1

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	1,000	3.6.E-08	3.6.E+02	0.0	9.2E-01	3.6.E+00
water	0	3.9.E-02	7.8.E+05	28.5	6.2E+01	7.8.E+02
soil	0	1.2.E+00	1.9.E+06	71.4	1.6E+02	
sediment		4.0.E-02	4.0.E+03	0.1	3.2E-01	7.9.E-02
		total amount	2.7.E+06			

scenario 2

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	6.1.E-13	6.1.E-03	0.0	1.5.E-05	6.1.E-05
water	1000	4.6.E-02	9.3.E+05	99.5	7.4.E+01	9.3.E+02
soil	0	2.0.E-05	3.3.E+01	0.0	2.6.E-03	
sediment		4.7.E-02	4.7.E+03	0.5	3.8.E-01	9.5.E-02
		total amount	9.3.E+05			

scenario 3

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	1.0.E-10	1.0.E+00	0.0	2.6.E-03	1.0.E-02
water	0	3.7.E-02	7.4.E+05	23.3	6.0.E+01	7.4.E+02
soil	1000	1.5.E+00	2.4.E+06	76.6	2.0.E+02	
sediment		3.8.E-02	3.8.E+03	0.1	3.0.E-01	7.6.E-02
		total amount	3.2.E+06			

scenario 4

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	600	2.2.E-08	2.2.E+02	0.0	5.5.E-01	2.2.E+00
water	300	4.1.E-02	8.2.E+05	36.6	6.6.E+01	8.2.E+02
soil	100	8.8.E-01	1.4.E+06	63.2	1.1.E+02	
sediment		4.2.E-02	4.2.E+03	0.2	3.4.E-01	8.4.E-02
		total amount	2.2.E+06			

Physico-chemical parameter

molecular weight		138.13	Measured
melting point		216.2	Measured
vapor pressure [Pa]		3.90E-03	Measured
water solubility [g/m^3]		6000	Measured
log Kow		1.37	Measured
half life [h]	in air	272	Estimated
	in water	8640	Estimated
	in soil	8640	Estimated
	in sediment	8640	Estimated

Temp. []	25

Environmental parameter

		volume	depth	area	organic	lipid content	density	residence
		[m^3]	[m]	[m^2]	carbon []	[]	[kg/m^3]	time [h]
bulk air	air	1.0E+13					1.2	100
	particles	2.0E+03						
	total	1.0E+13	1000	1E+10				
bulk water	water	2.0E+10					1000	1000
	particles	1.0E+06			0.04		1500	
	fish	2.0E+05				0.05	1000	
	total	2.0E+10	10	2E+09				
bulk soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8.0E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
bulk sediment	water	8.0E+07					1000	
	solid	2.0E+07			0.06		2400	50000
	total	1.0E+08	0.05	2E+09				

Intermedia Transport Parameters m/h

air side air-water MTC	5	soil air boundary layer MTC	5
water side air water MTC	0.05	sediment-water MTC	1E-04
rain rate	1E-04	sediment deposition	5E-07
aerosol deposition	6E-10	sediment resuspension	2E-07
soil air phase diffusion MTC	0.02	soil water runoff	5E-05
soil water phase diffusion MTC	1E-05	soil solid runoff	1E-08

EXTRACT FROM IRPTC LEGAL FILES

File: 17.01 LEGAL **rn : 25998**

systematic name:Benzoic acid, 4-hydroxy-
common name :p-hydroxybenzoic acid
reported name :4-HYDROXYBENZOIC ACID
cas no :99-96-7
area : EEC type : REG

subject	specification	descriptor
GOODS		PRMT
GOODS		MXL

PRESERVATIVE ALLOWED IN COSMETIC PRODUCTS. MEMBER STATES SHALL PROHIBIT THE MARKETING OFCOSMETIC PRODUCTS CONTAINING THE PRESERVATIVEBEYOND THE LIMITS AND OUTSIDE THE CONDITIONS LAID DOWN UNLESS OTHER CONCENTRATIONS ARE USED FOR SPECIFIC PURPOSES APPARENT FROM THE PRESENTATION OF THE PRODUCT. (COUNCIL DIRECTIVE 76/768/EEC - OJEC L262,169,1976 AS LAST AMENDED BY THE REFERENCE GIVEN)
entry date: SEP 1987 effective date: 1JAN1988

amendment: OJEC**, Official Journal of the European (Communities)/Union, L56 , , 20 , 1987

****

File: 17.01 LEGAL **rn : 401002**

systematic name:Benzoic acid, 4-hydroxy-
common name :p-hydroxybenzoic acid
reported name :p-hydroxybenzoic acid
cas no :99-96-7
area : CSK type : REG

subject	specification	descriptor
FOOD		MPC

LIMIT OF ADDITIVE PRESENT DUE TO PRODUCTION, PACKING, TRANSPORT AND STORAGE OF FOOD PRODUCTS: 0.4G/KG.
entry date: DEC 1991 effective date: 1JUL1986

title: DIRECTIVE NO. 50/1978 ON FOREIGN SUBSTANCES IN FOODSTUFFS
original : HPMZC*, HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 43 , , , 1978
amendment: HPMZC*, HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 61 , , , 1986

ISOCYANURIC ACID

CAS NO 108-80-5

SIDS Initial Assessment Report
for
9th SIAM

(France, June 29-July 1, 1999)

Chemical Name: Isocyanuric acid
CAS No: 108-80-5
Sponsor Country: Japan

National SIDS Contact Point in Sponsor Country:
Mr. Kazuhide Ishikawa
Ministry of Foreign Affairs, Japan

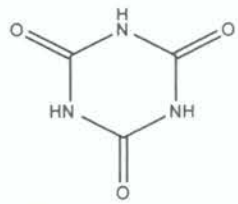
HISTORY:

SIDS Testing Plan were reviewed in SIDS Review Process, where the following SIDS Testing Plan was agreed:

no testing ( )
testing (X) Water solubility, Vapour pressure, Octanol/water partition coefficient, Stability in water Biodegradation
Chronic toxicity to daphnia
Combined repeat dose and reproductive toxicity,
Chromosomal aberration test in vitro

Deadline for circulation: March 31, 1999
Date of Circulation: March 30, 1999
(To all National SIDS Contact Points and the OECD Secretariat)

SIDS INITIAL ASSESSMENT PROFILE

CAS NO.	108-80-5
CHEMICAL NAME	Isocyanuric acid
Structural formula	

RECOMMENDATIONS OF THE SPONSOR COUNTRY

The chemical is currently of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE RECOMMENDATIONS

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.

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.

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.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

FULL SIDS SUMMARY

CAS NO: 108-80-5		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			330 °C
2.2	Boiling Point			Decomposed
2.3	Density			
2.4	Vapour Pressure		OECD TG 104	< 5.0×10^{-3} Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	< 0.3
2.6 A.	Water Solubility		OECD TG 105	2.7 g/L at 25 °C
B.	pH			
	pKa			
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4,7 and 9 $pK_1 = 6.88$, $pK_2 = 11.40$, $pK_3 = 13.5$
3.2	Monitoring Data			In surface water = not detected In soil/sediment = not detected
3.3	Transport and Distribution		Calculated (Fugacity Level III type)	Release: 100% to Water In Air 0.0 % In Water 99.6% In Sediment 0.0 % In Soil 0.4 %
			(local exposure)	0.19 mg/L (Japan)
3.5	Biodegradation		OECD 301C	Not readily biodegradable 0% in 28 day
3.7	Bioaccumulation		OECD 305C	BCF: < 0.5
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50}(96hr) > 100 mg/l LC_{50}(14 d) > 100 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates *Daphnia*	*Daphnia magna*	OECD TG 202	EC_{50}(48hr): 1000 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50}(72hr) = 620 mg/l NOEC= 62.5 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50}(21d, Repro)= 65.9 mg/l NOEC= 32.0 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			None
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			None

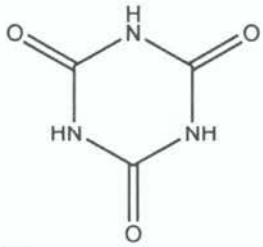
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Other (unknown)	LD_{50} = 7700 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	Other (unknown)	Minimum toxic concentration = 612 mg/m^3
5.1.3	Acute Dermal Toxicity	Rabbit	Other (unknown)	LD_{50} = > 7940 mg/kg
5.2.1	Skin Irritation/Corrosion	Rabbit	FHSA test	Not irritating
5.2.2	Eye Irritation/Corrosion	Rabbit	FHSA test	Slightly irritating
5.4	Repeated Dose Toxicity	Rat	OECD Combined	NOAEL = 150 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S. typhimurium*	Other (unknown)	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	Chinese hamster CHL cells	Japanese TG and OECD TG 473	- (With metabolic activation) - (Without metabolic activation)
5.6	Genetic Toxicity In Vivo (Chromosomal aberrations)	Rat	Other	-
5.7	Carcinogenicity	Rat	Other	Not carcinogenic
5.8	Toxicity to Reproduction	Rat	OECD combined	NOAEL = 600 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity	Rabbit	Other	NOAEL = 200 mg/kg/day
5.11	Experience with Human Exposure		Other (Toxicokinetics)	

[Note] Data beyond SIDS requirements can be added if the items are relevant to the assessment of the chemical, e.g. corrosiveness/irritation, carcinogenicity.

SIDS INITIAL ASSESSMENT REPORT

1. IDENTITY

- OECD Name: Isocyanuric acid
- Synonym: sym-Triazine-2,4,6-triol; sym-Triazinetriol; normal Cyanuric acid; 2,4,6-Trihydroxy-1,3,5-triazine; Trihydroxycyanidine; Tricyanic acid; Isocyanuric acid; Pseudocyanuric acid; 1,3,5-Triazine-2,4,6(1H,3H,5H)-trione; 1,3,5-Triazine-2,4,6-triol; 1,3,5-Triazinetriol; 1,3,5-Triazinetrione; Tricarbimide; Trihydroxy-1,3,5-triazine
- CAS Number: 108-80-5
- Empirical Formula: $C_3H_3N_3O_3$
- Structural Formula:



- Degree of Purity: 99.7 %
- Major Impurity: None
- Essential Additives: None
- Physical-chemical properties
  - Melting Point: 330 °C
  - Vapour pressure: < 5.0 x 10^{-3} Pa at 25 °C
  - Water solubility: 2.7 g/L
  - Log Pow: < 0.3

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production and import

The production volume of isocyanuric acid in Japan is 20,000 tonnes/year in 1995.

2.2 Use pattern

All of isocyanuric acid produced in Japan is used as intermediate of chemical products, and no consumer use is reported.

2.3 Other information

None

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 General Discussion

Isocyanuric acid is not readily biodegradable (OECD 301C: 0 % after 14d) and stable in water. Direct photodegradation is not expected because isocyanuric acid has not absorption band in UV and VIS region.

Isocyanuric acid is low bioaccumulative (BCF < 0.5, Carp).

The potential environmental distributions of isocyanuric acid obtain from a generic Mackay level III fugacity model is shown in Table 1. Parameters used for this model are shown as Annex to this report. The results show that, if isocyanuric acid is released into water, it is unlikely to be distributed into other compartments. If isocyanuric acid is released into air and soil, it is likely to be distributed in other compartments.

Table 1
Environmental distribution of isocyanuric acid
Using a generic level III fugacity model.

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.1 %	0.0 %	0.0 %
Water	46.5 %	99.6 %	40.5 %
Soil	53.3 %	0.0 %	59.3 %
Sediment	0.2 %	0.4 %	0.2 %

As this chemical is used in closed system as an intermediate of chemical products and is not included in consumer products, its release to the environment may occur only from the production cite.

3.1.2 Predicted Environmental Concentration

As isocyanuric acid is produced under the well-controlled closed system, amount of release to air phase is negligibly small. The waste of isocyanuric acid from the production system is released to water phase after treated its own wastewater treatment plant. Therefore, Predicted Environmental Concentration (PEC) will be calculated only for the water environment.

a. Regional exposure

According to report from a Japanese manufacturer, 407.7 tonnes/year (measured) of isocyanuric acid are released with 2.19 x 10^{10} L/year of effluent into river. Local Predicted Environmental Concentration (PEC_{local}) is calculated to be 0.186 mg/L as a worst case scenario, employing the following calculation model and dilution factor of 100.

$$\frac{\text{Amount of release } (4.08 \times 10^{11} \text{ mg/y})}{\text{Volume of effluent } (2.19 \times 10^{10} \text{ L/y}) \times \text{Dilution Factor } (100)}$$

3.2 Effects on the Environments

3.2.1 Effects on aquatic organisms

Acute and chronic toxicity data of isocyanuric acid to aquatic organisms are summarized below (Table 2). Toxicity of this chemical to aquatic organisms seems low because all toxicity data are higher than 32 mg/l (NOEC of reproduction of *Daphnia magna*). Predicted No Effect Concentration (PNEC) of this chemical was determined based mainly on the toxicity data obtained by the Environment Agency of Japan through a GLP-laboratory. Toxicity data by different organizations were few. As the lowest acute and chronic toxicity data, 96 h LC_{50} of *Oryzias latipes* and 21 d NOEC (reproduction) of *D. magna* were used, respectively (Table 2). All toxicity in Table 2 were calculated based on the nominal concentration as the measured concentrations were kept within 95 to 102 % of the nominal concentrations.

The assessment factors of 100 were used to both acute and chronic toxicity data to determine PNEC, according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects (EXCH/MANUAL/96-4-5.DOC/May 1996), because chronic toxicity data for fish was absent.

From chronic toxicity data (21 d NOEC of *Daphnia*):

PNEC = 32/100 = 0.32 mg/l

Thus, PNEC of isocyanuric acid is 0.32 mg/l.

Table 2

Acute and chronic toxicity data of isocyanuric acid to aquatic organisms at different trophic levels. The data were obtained by the Environmental Agency of Japan based on the OECD Test Guide Lines.

Species	Endpoint	Conc. (mg/l)	Remarks
Selenastrum capricornutum (algae)	Bms 72 h EC50 Bms. 72 h NOEC	620.0 62.5	a, 1) c, 1),
Daphnia magna (Water flea)	Imm 48 h EC50 Rep 21 d EC50 Rep 21 d NOEC	1000 65.9 32.0	a, 1), c, 1) c, 1), C
Oryzias latipes (fish, Medaka)	Mor 96 h LC50 Mor 14 d LC50	> 100 > 100	a, 1), A a, 1)

Notes: Bms; biomass, Mor; mortality, Rep; reproduction, NR; not recorded.
A), C); the lowest values among the acute or chronic toxicity data of algae, Cladocera (water flea) and fishes to determine PNEC of isocyanuric acid.

1) Toxicity data were obtained by the Environment Agency of Japan based on OECD Test Guidelines and GLP.

3.2.2 Terrestrial effects

No data available

3.2.3 Other effects

No data available

3.3 Initial Assessment for the Environment

Predicted No Effect Concentration (PNEC) of this chemical has been calculated as 0.32 mg/l.

PEC from Japanese local exposure scenario is 0.186 mg/l.

PEC_{local} / PNEC = 0.186/0. 32 = 0.58 < 1

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

4. HUMAN HEALTH

4.1 Human Exposure

4.1.1 Occupational exposure

Isocyanuric acid is produced in a closed system and used as an intermediate for organic chemicals. The occupational exposure is expected through inhalation and the dermal route is assumed negligible because this chemical is solid. As the atmospheric concentration in plant was not measured, the maximum exposure level is estimated according to working schedules as follows. If a single worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hr) is assigned to implement this operation without protection, the highest daily intake (EHE) is calculated as 0.23 mg/kg/day as the worst case. Practically, workers always wear protective gloves and respiratory protective equipment (mask) during the operation.

	Frequency Times/day	Duration hr	Working hr/day	Maximum Concentration mg/m^3	Maximum EHE mg/kg/day
Bag Filling	80	0.08	6.5	2	0.23

EHE: Estimated Human Exposure

4.1.2 Consumer exposure

Chloroisocyanurates such as sodium dichloroisocyanurate, potassium dichloroisocyanurate, sodium dichloroisocyanurate hydrate, potassium dichloroisocyanurate hydrate and trichloroisocyanuric acid have been used in sterilizing water tank, swimming pool, bathing water, and kitchen. In water, chloroisocyanurates are hydrolized to isocyanuric acid and hypochloric acid, that is the active agent (Golaszewski & Seux: 1994). The antimicrobial activity of sodium dichloroisocyanurate was evaluated against Gram negative bacteria such as *E. coli* or *Salmonella typhimurium* and against some fungi (D'Auria, *et al.*: 1989).

It is considered that the potential for exposure to pool chemicals through swallowing water and/or dermal absorption is quite high. Allen et al. (1982) reported cumulative recovery of isocyanuric acid in the urine of swimmers, 20 hr after swimming, averaging 9.8 mg. As the worst case, high performance athletes in training are known to spend up to 4 hr/day in the pool for 300 day/year and are estimated to swallow up to 60 ml/hr of pool water (Datta: 1979). In Japan, trichloroisocyanurate is mainly used in swimming pool and the average concentration of isocyanuric acid is estimated as

50 to 100 μg/ml. Based on this information, oral daily intake of isocyanuric acid for 60 kg b.w. person is calculated as 0.17 to 0.33 mg/kg/day. Continuous-dose automated *in vitro* dermal absorption studies conducted with isocyanuric acid demonstrated minimal absorption through rat, hairless guinea pig, human, and Test skin (Moody: 1993). Total cumulative absorption of isocyanuric acid by 24 h in Test skin and human skin was 0.02 $\mu g/cm^2$ in both cases. As 1.5 m^2 of body surface is estimated for 60 kg b.w. person, the daily intake through skin is calculated as 5 μg/kg/day as the maximum value.

4.1.3 Indirect exposure via the environment

As isocyanuric acid is persistent in water and low bioaccumulative, the exposure to the general population via the environment would be possible through drinking water processed from surface water and through fish which may accumulate this chemical.

The concentration in drinking water should be estimated to be equal to PEC calculated in Section 3.1, i.e. 0.186 mg/l. The daily intake through drinking water is calculated as 6.20×10^{-3} mg/kg/day (2 l/day, 60 kg b.w.).

Using the maximum bioconcentration factor of 0.5 obtained by tests, the concentration of this chemical in fish can be calculated as follows:

$$PEC_{fish} = 0.186 \text{ mg/l} \times 0.5 = 9.03 \times 10^{-5} \text{ mg/g-wet}$$

As a daily intake of fish in Japan is estimated to be 90 g for 60 kg body weight person, a daily intake of this chemical will be 1.40×10^{-4} mg/kg/day.

4.2 Effects on Human Health

a) Acute toxicity

[SIDS data] Oral LD_{50} for isocyanuric acid was 7,700 mg/kg b.w. for rats. In inhalation study, the minimum toxic concentration was reported to be 612 mg/m^3 in rats. (Babayan and Aleksandryan: 1985) Dermal LD_{50} for isocyanuric acid was higher than 7940 mg/kg b.w. for rabbits (Toxikologische Bewertung: 1993).

Other acute toxicity information including sodium isocyanurate are given in Table. In addition, it is also reported that a single oral dosage of isocyanuric acid up to 10 g/kg was tolerated by rats and daily dosage of 20 g/kg was tolerated by rabbits for periods up to 4 days (Hodge et al.: 1965). Based on these data, isocyanuric acid is considered to be low toxic when administered as a single dose.

Routes	Strain	Type	Values	
Isocyanic acid				
Oral	Rats	LD_{50}	7,700 mg/kg	SIDS data, Ref.1
	Mice	LD_{50}	3,400 mg/kg	Ref.1
	Rabbits	LDL_0	> 10 g/kg	Ref.2
Inhalation	Rats	Other*	612 mg/m^3	SIDS data, Ref.1
Dermal	Rabbits	LD_{50}	> 7,940 mg/kg	SIDS data, Ref.3

Intravenous	Rats	LD_{50}	> 100 mg/kg	Ref.4
	Mice	LD_{50}	> 500 mg/kg	Ref.4
Sodium isocyanurate				
Oral	Rats	LD_{50}	> 7,500 mg/kg	Ref.4
Intravenous	Cats	LD_{50}	2,144 mg/kg	Ref.5

Ref.1: Babayan & Aleksandryan: 1985, Ref.2: Toxicity Information: 1972, Ref.3: Toxikologische Bewertung: 1993, Ref.4: *Gigiena i Sanitariya*: 1962, Ref.5: *J Pharmacol Exp Ther*: 1951, *: Minimum toxic concentration

b) Irritation

Federal Hazardous Substances Act (FHSA) tests of isocyanuric acid were performed in rabbits. As a result, isocyanuric acid slightly irritated to eyes but not to the skin (Hammond *et al.*: 1986). As for eye irritation, there are two other data. Moderate eye irritation followed administration into the rabbit eyes for 24 hr at 20 or 500 mg (Toxicity Information: 1972, Marhold: 1972). This chemical is not listed in IUCLID labelling and classification.

Based on these data, this chemical is considered as a slightly irritant to eyes, but not to the skin.

c) Sensitisation

There is no available data.

d) Repeated toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test. Isocyanuric acid was administered by gavage at doses of 10, 40, 150 and 600 mg/kg/day for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

Isocyanuric acid induced toxic effects at 600 mg/kg in both sexes. Excretion of reddish urine was evident. In addition, depression of body weight gain was observed in males. Urinalyses of males revealed appearance of crystals, which is considered this chemical precipitated from urine, and increases of erythrocytes and leukocytes. In hematological examination of males, significant decreases in erythrocyte counts, hemoglobin concentrations and hematocrit values were observed. In blood chemical examination of males, increases in urea nitrogen and creatinine, and a decrease of sodium were revealed. In histopathological examination, dilatation of the renal tubules, necrosis or hyperplasia of the tubular epithelium, increased basophilic tubules, neutrophilic infiltration, mineralization and fibrosis in the kidney, hyperplasia of the mucosal epithelium in the urinary bladder and vacuolization of the zona fasciculata in the adrenals were observed in both sexes. In addition, the incidence of atrophic thymus also showed a tendency for increase in females. Absolute and relative kidney weights and relative adrenal weights were increased in both sexes. As no toxic sign was observed at doses of 150 mg/kg and the less, NOAEL was considered to be 150 mg/kg/day in both sexes.

Oral toxicity study of sodium isocyanurate for 90 days was performed in B6C3F1 mice at doses of 896, 1,792 and 5,375 ppm in drinking water. Sodium hippurate was used as a second control in order

to have the sodium burden as the top concentration. Although an increase in water consumption in both sexes and absolute and relative weights of ovaries in females were observed, these changes were considered due to the high sodium intake. Therefore, NOAEL was considered to be 5,375 ppm (male: 1,994 mg/kg/day, female: 2,200mg/kg/day). (Hazleton: 1982)

Hodge *et al.* (1965) conducted oral toxicity study in rats and beagle dogs, and skin and eye application study in rabbits.

In first study, rats of the Rochester strain were maintained for 20 weeks on diets containing 0.8 %, and 8 % sodium isocyanurate. As a result, 14/20 males and 4/20 females died at 8 %, but no died at 0.8 %. Considerable decrease in body weight gain was observed at 8 %. Urine samples taken prior to the start of feeding and again near termination of the study showed normal concentrations of protein and sugar. In hematological examination no change was observed. There were no changes in organ weights (thyroid, liver, brain, lungs, heart, etc.), except kidney weight, which increased at 8 % in females. In histologic study, dilatation of distal collecting tubules and ducts of Bellini, with focal areas of epithelial proliferation were observed at 8 % in both sexes. Therefore, NOAEL was considered to be 0.8 % (56 mg/kg/day).

In second study, groups of 3 dogs were maintained in diets of 0.8 % sodium isocyanurate for 6 months and 8 % for 2 years. In 0.8 % dogs, there were no changes in body weight gain, organ weight, and sugar and protein in urine. In addition, hematological and histological changes were not observed. In 8 % group, 2 dogs died after 16 and 21 months on the regimen. No change or slight increase in body weights was observed. Periodic urinalyses gave normal trace values for sugar and protein. In hematologic study, only a survival dog showed changes, which are low red blood cell counts, hemoglobin values, and hematocrits. There was no change in organ weights (thyroid, liver, brain, lungs, heart, etc.), except decrease in kidney weight of 2 dogs surviving more than 20 months. In these dogs, there was gross evidence of kidney fibrosis. Sections revealed numerous linear streaks of gray fibrous tissue extending from the papillary tip to the cortical surface. Microscopically, similar changes were observed in the kidneys of all three dogs. The collecting tubules were more uniformly and severely involved, but all portions of the nephron were compressed by fibrosis. There were slight focal dilatation and epithelial proliferation in the ducts of Bellini. In survival dog, focal areas of thyroid atrophy were found with lymphocytic infiltration, but without evidence of hyperplasia. Therefore, NOAEL for 6 months study was considered to be 0.8 % (291 mg/kg/day) and LOAEL for 2 years study to be 8 % (2,912 mg/kg/day).

In skin application study, 5 ml of 0.8 % or 8 % aqueous suspension were administered to the skin of albino rabbits 5 days/week for about 3 months, respectively. Urinalyses (sugar and protein) and hematological study showed no changes. There were no irritation or other adverse effects on the skin. In histological findings of liver and skin from treated and untreated area, no change was observed at the termination of the study. In the kidneys of the rabbits treated with the 8 % sodium isocyanurate suspension, slight dilation of the ducts of Bellini and mild tubular changes were found. Therefore, NOAEL was considered to be 0.8 %.

In eye application studies, 0.1 ml of 0.8 % or 8 % aqueous suspension were administered to eye of albino rabbits 5 days/week for about 3 months, respectively. Increase in body weight was observed during the period of the study in all treated groups. No eye injury and irritation was caused. Therefore, NOAEL was considered to be 8 %.

e) Reproductive/developmental toxicity

Reproductive toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeated dose and reproductive/developmental toxicity screening test. Isocyanuric acid was administered by gavage at doses of 10, 40, 150 and 600 mg/kg/day for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

The parental animals exhibited no alteration in reproductive parameters including the copulation index, fertility index, gestation length, numbers of corpora lutea or implantation, implantation index, gestation index, delivery index, and behavior at delivery and lactation. There were no significant differences in offspring parameters including number of offspring or live offspring, the sex ratio, live birth index, viability index and body weight. No external or visceral abnormalities related to the test substance were detected in any of the offspring. Therefore, NOAEL for parents and offsprings was considered to be 600 mg/kg/day.

Three-generation study was conducted. Sodium isocyanurate was given by drinking water at concentrations of 400, 1,200 and 5,375 ppm to CD rats. Treatment was initiated at 36 days of age and continued for a minimum of 100 days before mating. Weanlings from the F1 and F2 litters were randomly selected as the next parents and continued on treatment for the additional 120 days. Selected litters and F3 offsprings were sacrificed 4 weeks after weaning, and organ weight measurements and microscopic examination of tissues were carried out. (Wheeler *et al.*: 1985)

No compound-related changes were observed in mortality, body weights, food consumption, gestation length, litter size, pup survival to weaning, sex ratio, and pup weight. In pathological and histological findings, epithelial hyperplasia with chronic cystitis was observed only in a few of high-dose treated males in F2 offsprings, which were attributed to chronic irritation by the calculi in the urinary bladder. However, this change is considered not to be due to reproductive toxicity of this chemical. In other treated groups, there were no changes. Therefore, NOAEL for reproductive toxicity was considered to be 5,375 ppm (approx. 370 mg/kg/day for male and 630 mg/kg/day for female).

Male CD-1 mice were treated intraperitoneally at doses of sodium isocyanurate (125 and 250 mg/kg/day). As positive control, methyl methane sulfonate was used at dose of 50 mg/kg/day. Males were mated with non-treated females. Although early resorptions were observed in females mated with males treated with methyl methane sulfonate, any chemical-related effects were not observed in females, mated with sodium isocyanurate treated males. Therefore, NOAEL was considered to be 250 mg/kg/day. (FMC Corporation: 1972)

Developmental toxicity

[SIDS data] Pregnant Dutch belted rabbits were given sodium isocyanurate at doses of 50, 200 and 500 mg/kg/day by gavage during days 6-18 of gestation. (FMC Corporation, unpublished observations)

Although slight decrease in body weight was observed in mid- and high-dose dams during the treatment period, compensatory weight gains occurred after termination of treatment on day 18. There were no compound related mortality or other adverse reactions in all treated dams. The mean number of live fetus/dam and sex ratio was essentially comparable for all groups. Fetal body weights and crown/rump lengths were reduced slightly in high-dose groups, compared to control. These changes may have resulted from the slight manifestations of maternal toxicity that occurred during treatment. There was no evidence of external or internal malformations or skeletal anomalies. Therefore, NOAEL for developmental toxicity was considered to be 200 mg/kg/day.

Sodium isocyanurate was administered at doses of 200, 1,000, and 5,000 mg/kg/day by oral gavage to pregnant CD rats during days 6-15 of gestation. Sodium control groups received sodium hippurate at dose of 1,118 and 5,590 mg/kg/day. (Industry ad hoc Committee for Isocyanurates: 1982)

There was no mortality in all treated groups. Although decrease in body weight and crown/rum length, increase in post-implantation loss, incidence incomplete ossification were observed in sodium control group, no treatment related effect on maternal appearance, behaviour and body weight gain, and no teratogenic effect were observed in all groups treated with sodium isocyanurate. Therefore, NOAEL for developmental toxicity was considered to be 5,000 mg/kg/day.

f) Genetic toxicity

Bacterial test
[SIDS data] Isocyanuric acid was not mutagenic to *S. typhimurium* TA1535, TA1537, TA98, TA100 with or without metabolic activation (Hayworth *et al.*: 1983).

Isocyanuric acid did not induce the bacteriophage Lambda in *Escherichia coli* K12 en VA UVRB (NORSOLOR/APC: 1977).

Non-bacterial test *in vitro*
[SIDS data] In chromosomal aberration test *in vitro*, clastogenicity or polyploidy in CHL/IU cells was not induced in the absence or presence of an exogenous metabolic activation system (MHW, Japan: 1997).

In lymphoma assay, this chemical also showed negative result at up to a concentration of 2000 μg/ml in the TK locus of L5178Y mouse lymphoma cells (Industry ad hoc Committee for Isocyanurates: 1981a). This chemical did not induce sister chromatid exchange in CHO cells (Industry ad hoc committee for Isocyanurates: 1981b), and this negative result was confirmed on human lymphoid cell line (LAZ-007) by Sobti *et al.* (1981), although the concentration was very low (2μg/ml).

in vivo Test
[SIDS data] In chromosomal aberration test *in vivo*, rats were killed 24 and 48 hr after administration of sodium isocyanurate by gavage at single dosages up to 5000 mg/kg, and bone marrow cells were collected and examined. As a result, this chemical did not induce chromosomal aberrations in rat bone marrow cells (Hammond *et al*: 1985).

g) Carcinogenicity

CD rats were administered sodium isocyanurate in drinking water at concentrations of 400, 1,200, 2,400 or 5,375 ppm for 2 years. Estimated daily doses were indicated only for 2,400 and 5,375 ppm (male: 154 and 371 mg/kg/day, female: 266 and 634 mg/kg/day, respectively). For a second control, sodium hippurate was administered as the same amount of sodium as the highest dose. Treatment-related mortality was observed in some males of the highest dose group, which died during the first 12 months of the study. This mortality was due to the development of calculi in the urinary tract. In some males that died on test and in some that were sacrificed at 12 months, there were pathologic changes, including hyperplasia, bleeding, and inflamed ureters, and renal tubular nephrosis. Although slight tubular nephrosis was also observed in a few females of the highest dose group during the first 12 months, these animals did not exhibit bladder calculi. Inflammatory

lesions in the heart were also apparent in some of the highest dose males that died early. There was no evidence of a test article related carcinogenic effect. (Cascieri *et al.*: 1985)

B6C3F1 mice were administered sodium isocyanurate in drinking water at concentrations of 100, 400, 1,200 and 5,375 ppm for 2 years. Apparently swollen enlarged abdomen was observed at the highest dose groups, related to increase in water consumption. There were no effects on survival, clinical pathology (except for urinary sodium), organ weight, gross and histopathology. There was no evidence of a test article related carcinogenesis. (Industry Ad hoc Committee for Isocyanurates: 1986)

h) Toxicodynamics/toxicokinetics

Toxicokinetics study of sodium isocyanurate was performed in rats and dogs, using [^{14}C] sodium isocyanurate. Administration was performed at 5 mg/kg by oral or intravenous route and at 500 mg/kg by oral route. At 5 mg/kg, this chemical was completely absorbed and largely eliminated in urine, while at 500 mg/kg, this chemical was incompletely absorbed and largely eliminated in feces. The elimination half-life was 30 to 60 min in rats and 1.5 to 2 hr in dogs after oral or intravenous administration. In dogs, sodium isocyanurate distributed into an apparent volume of distribution of 0.7 L/kg, which is somewhat greater than total body water volume. Rats and dogs were also administered unlabeled sodium isocyanurate orally at 5 mg/kg/day followed by the single exposure of 5 mg/kg radiolabeled sodium isocyanurate on day 15. In rats, the remainder of radioactivity in most tissues was below the level of detection 7 days after treatment for repeated dose administration and for all sampling times for both single and repeated dose administration in dogs. As results of repeated dose study, it was shown that isocyanurate did not bioaccumulate in tissues. There was no evidence that isocyanurate was biodegraded, as only unchanged isocyanurate was found in excreta. (Barbee *et al.*: 1983)

Toxicokinetics study by dermal route was performed, in which species was not indicated. After dermal application, the ^{14}C-labelled substance is not detectable in the blood and < 0.01 % of the administered dose is found in the urine. This result showed that isocyanuric acid was absorbed only in very small quantities. (Toxikologische Bewertung: 1993)

i) Experience with human exposure

Toxicokinetics of isocyanuric acid was investigated in 5 volunteers, who soaked in a swimming pool for 120 minutes. As a result, the cumulative excretion of isocyanuric acid was 0.03-2.8 mg, equivalent to 3.0-3.6 ml of pool water and the elimination half-life is calculated as 3 hr. On the other hand, recovery of ingested isocyanuric acid was 98 % in urine. There was no correlation between toxicokinetics and gamma glutamyl transpeptidase activity. (Allen *et al.*: 1982)

4.3 Initial Assessment for 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.

Occupational exposure

Isocyanuric acid is used in a closed system at industries and workers wear protective gloves and respiratory protective equipment during the operation. Although the occupational exposure route is expected as an inhalation in limited workers, there is no available data of the atmosphere concentration. Based on the predicted high concentration and the possibility of exposure period, the daily intake is calculated as 0.23 mg/kg/day as the worst case. Occupational risk is presumably low because the margin of safety is 652.

Consumer exposure

Isocyanuric acid is used in the form of chlorides in sterilizing water tank, swimming pool, bathing water, and kitchen. In Japan, trichloroisocyanurate is mainly used in swimming pool and the average concentration of isocyanuric acid is estimated as 50 to 100 μg/ml. The exposure of high performance athletes in training is expected through a swallow and skin absorption. The combined daily intake is calculated as 0.34 mg/kg/day as the worst case. Consumer risk is presumably low because the margin of safety is 441.

Indirect exposure via environment

As for indirect exposure via environment, PEC_{local} of 0.186 mg/l from local exposure scenario was used for the estimation. The daily intakes through drinking water and fish were calculated as 6.20×10^{-3} mg/kg/day and 1.40×10^{-4} mg/kg/day, respectively. Since the margin of safety is very large, such as 2.42×10^{4} for drinking water and 1.08×10^{6} for fish, health risk via environment is presumably low.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Isocyanuric acid is not readily biodegradable (OECD 301C: 0 % after 14-d) and stable in water. Bioaccumulation factor of this chemical is low (BCF < 0.5, Carp). PEC/PNEC ratio (0.186/0.32 = 0.58) is less than 1 based on the local exposure scenario in the Sponsor country. It is currently considered of low potential risk to environments and low priority for further work. However, relatively high PEC/PNEC value suggests necessity for assessment of this chemical to the river ecosystem contaminated with this chemical.

Isocyanuric acid is moderately toxic in a repeated dose study (i.e. kidney) but not toxic in reproductive toxicity study. In a developmental toxicity study, this chemical is toxic to dams, which resulted in slight fetal toxicity (reduction of body weights and crown/rump lengths). This chemical is neither genotoxic nor carcinogenic but slightly irritating to eyes. Occupational and consumer risks are expected to be low because the margin of safety is 652 and 441, respectively. As the margin of safety via indirect exposure is more than 10,000, it is currently considered of low potential human risk and low priority for further work.

5.2 Recommendations

Environment:	Relatively high PEC (0.18 mg/l) and PEC/PNEC ratio (0.58) in the river receiving the effluents from the production site.
Human health:	No recommendation

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Appendix 1

Method for Prediction of Environmental Concentration of Pollutant in Surface Water

1. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into river

When decomposition, precipitation and vaporization of pollutant can be ignored, it is used that simplified equation by complete mixing model shown with equation (1) to calculate predicted environmental concentration in the local environment (PEC_{local}) as for release effluent into river.

$$PEC_{local}\ (mg/L) = \frac{Co\ Q + Cs\ Qs}{Q + Qs} \quad (1)$$

Where

Co: Concentration of pollutant in upper stream of release point (mg/L)
Cs: Concentration of pollutant in effluent (mg/L)
Q: Flow rate of river (m^3/day)
Qs: Flow rate of effluent released into river (m^3/ day)

At the equation (1), when Co can be considered as 0, dilution factor of pollutant in the river (R) can be shown with following equation.

$$R = Cs/C = (Q + Qs) / Qs \quad (2)$$

As the worst case, it is used to employ a flow rate at dry season as flow rate of river (Q). When flow rate at dry season is indistinct, it is estimated using the following equation in Japan.

$$\text{Flow rate at dry season} = \text{mean flow late} / 2.5 \quad (3)$$

2. Predicted environmental concentration in the local environment (PEC_{local}) with effluent release into sea

For prediction of concentration of pollutant in the sea water with effluent, it is employed generally Joseph-Sendnersymbol 146 \f "Times New Roman" \s 11'}s equation (4). This equation is one of analytic solution led under the following conditions from diffusion equation.

1 It is adopted large area of sea or lake.
2 The flow rate of effluent and concentration of pollutant in the effluent are constant, and distribution of concentration is able to regard as equilibrium state.
3 Effluent is distributed uniformly to vertical direction, and it spreads in a semicircle or segment to horizontal direction.
4 Diffusion coefficient of pollutant at the sea is in proportion to distance from release point of effluent.
5 There is not any effect of tidal current.
6 Decomposition of pollutant can be ignored.

$$C(x) = (C_s - C(r))\left(1 - \exp\left(-\frac{Q_s}{d\,p}\left(\frac{1}{x} - \frac{1}{r}\right)\right)\right) + C(r) \qquad (4)$$

Where

C (x): Concentration of pollutant at distance x (m) from release point
Cs: Concentration of pollutant in effluent
C (r): Concentration of pollutant at distance r (m) from release point
Qs: Flow rate of effluent (m^3/day)
: Opening angle of seacoast (rad.)
d: Thickness of diffusion layer (m)
P: Diffusion velocity (m/day) (1.0 0.5 cm/sec)

When C(x) is 0 at r = and density stratification is ignored for simplification, Joseph-Sendnersymbol 146 \f "Times New Roman" \s 11'}s equation (4) is simplified to equation (5)

$$C(x) = C_s\left(1 - \exp\left(-\frac{Q_s}{d\,p\,x}\right)\right) \qquad (5)$$

Because of Qs/ d p x << 1 except vicinity of release point, dilution factor in distance x from release point R(x) can be shown with equation (6).

$$R(x) = C_s/C(x) = d\,p\,x/Q_s \qquad (6)$$

When it is employed following parameters in equation (6) as default, dilution factor R can be shown with equation (7).

P = 1 cm/sec (860 m/day)
= 3.14
d = 10 m
x = 1000 m

$$R = 2.7\ 10^7/Q_s \qquad (7)$$

Qs: volume of effluent (m^3/day)

REVISED OECD HPV FORM 1

SIDS DOSSIER ON THE HPV PHASE 5 CHEMICAL

Isocyanuric acid

CAS No. 108-80-5

Sponsor Country: Japan

DATE: March 15, 1999

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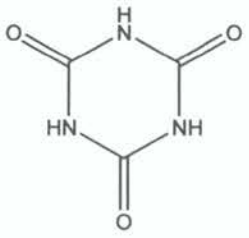
Appendix-1

Note: *; Data Elements In The Sids
†; Data Elements Specially Required For Inorganic Chemicals

SIDS PROFILE

1.01 A.	**CAS No.**	108-80-5
1.01 C.	**CHEMICAL NAME (OECD Name)**	Isocyanuric acid
1.01 D.	**CAS DESCRIPTOR**	
1.01 G.	**STRUCTURAL FORMULA**	
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	**QUANTITY**	20,000 tonnes/year in Japan
1.7	**USE PATTERN**	Intermediate in closed system.
1.9	**SOURCES AND LEVELS OF EXPOSURE**	407.7 tonnes/year Release into river
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)	SIDS testing required: Water solubility, Vapour pressure, Octanol/water partition coefficient, Stability in water, Biodegradation, Chronic toxicity to daphnia, Combined repeat dose and reproductive toxicity, Chromosomal aberration test in vitro	

SIDS SUMMARY

CAS NO: 108-80-5		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	N						N
2.4	Vapour Pressure	N						Y
2.5	Partition Coefficient	N						Y
2.6	Water Solubility	N						Y
	pH and pKa values	N						N
2.12	Oxidation: Reduction potential	N						N
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	N						N
3.1.2	Stability in water	N						Y
3.2	Monitoring data	N						N
3.3	Transport and Distribution	N						N
3.5	Biodegradation	N						Y
OTHER ENV FATE STUDIES RECEIVED								
ECOTOXICITY								
4.1	Acute toxicity to Fish	Y	N	N	Y	N	N	Y
4.2	Acute toxicity to Daphnia	Y	N	N	Y	N	N	Y
4.3	Toxicity to Algae	N						Y
4.5.2	Chronic toxicity to Daphnia	N						Y
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	. Chromosomal aberration	N						Y
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5.9	Development / Teratogenicity	Y	N	Y	Y	N	Y	N
5.11	Human experience	Y	N	N	Y	N	Y	N
OTHER TOXICITY STUDIES RECEIVED		Y	N	N	Y	N	Y	N

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

***A. CAS number** 108-80-5

B. Name *(IUPAC name)*

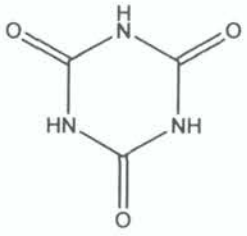
***C. Name** *(OECD name)* Isocyanuric acid

†D. CAS Descriptor

E. EINECS-Number 203-618-0

F. Molecular Formula $C_3H_3N_3O_3$

***G. Structural Formula**



H. Substance Group

I. Substance Remark

J. Molecular Weight 129.08

1.02 OECD INFORMATION

A. Sponsor Country: Japan

B. Lead Organisation:

Name of Lead Organisation: Ministry of Health and Welfare (MHW)
Ministry of International Trade and Industry (MITI)
Environmental Agency (EA)
Ministry of Labour (MOL)

Contact person: Mr. Kazuhide Ishikawa
Second International Organization Division
Economic International Bureau
Ministry of Foreign Affairs

Address:

Street: 2-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100 Japan
Tel: 81-3-3581-0018
Fax: 81-3-3503-3136

C. Name of responder

Same as above contact person

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

element [ ]; inorganic[ ]; natural substanc [ ]; organic[X]; organometallic [ ]; petroleum product [ ]

B. Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [ ]; solid [X]

C. Purity 99.7 %

1.2 SYNONYMS

sym-Triazine-2,4,6-triol; sym-Triazinetriol; normal Cyanuric acid; 2,4,6-Trihydroxy-1,3,5-triazine; Trihydroxycyanidine; Tricyanic acid; Pseudocyanuric acid; 1,3,5-Triazine-2,4,6(1H,3H,5H)-trione; 1,3,5-Triazine-2,4,6-triol; 1,3,5-Triazinetriol; 1,3,5-Triazinetrione; Tricarbimide; Trihydroxy-1,3,5-triazine

1.3 IMPURITIES

None

1.4 ADDITIVES

None

*1.5 QUANTITY

Remarks: 20,000 tonnes/year
Reference: MITI, Japan

1.6 LABELLING AND CLASSIFICATION

None

*1.7 USE PATTERN

A. General

Type of Use:	Category:
main	Intermediate
industrial	Intermediate in closed system
use	Intermediate for various chemicals

Remarks: None
Reference: MITI, Japan

1.8 OCCUPATIONAL EXPOSURE LIMIT

None

* 1.9 SOURCES OF EXPOSURE

In Japan, isocyanuric acid is produced in 2 companies.

Source:	Media of release:	River
	Quantities per media:	407.7 tonnes/year
Remarks:		
Reference:	MITI, Japan	

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value:	330 °C
Decomposition:	Yes **[X]** No [ ] Ambiguous [ ]
Sublimation:	Yes [ ] No **[X]** Ambiguous [ ]
Method:	
GLP:	Yes [ ] No **[X]** ? [ ]
Remarks:	
Reference:	Organic Chemical Dictionary

*2.2 BOILING POINT

Value:	not measurable
Pressure:	
Decomposition:	Yes [ ] No **[X]** Ambiguous [ ]
Method:	
GLP:	Yes [ ] No **[X]** ? [ ]
Remarks:	
Reference:	MITI, Japan

*2.4 VAPOUR PRESSURE

Value:	$< 5.0 \times 10^{-3}$ Pa
Temperature:	25 °C
Method:	calculated [ ]; measured **[X]**
	OECD TG 104
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan

*2.5 PARTITION COEFFICIENT $\log_{10} P_{ow}$

Log Pow:	< 0.3
Temperature:	25 °C

Method:	calculated [ ]; measured **[X]** OECD TG 107 HPLC method
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan

***2.6 WATER SOLUBILITY**

A. Solubility

Value:	2.7 g/l
Temperature:	25 °C
Description:	Miscible [ ]; Of very high solubility **[X]**; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	OECD TG 105
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan

B. pH Value, pKa Value

Value:	$pK_1 = 6.88$ $pK_2 = 11.40$ $pK_3 = 13.50$
Reference:	Merck Index

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

***3.1.2 STABILITY IN WATER**

Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment)[ ]
Half life:	Stable in pH 4, 7, 9 at 25 °C
Method:	OECD TG 111
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	purity: 99.9 %
Remarks:	
Reference:	MITI, Japan

***3.2 MONITORING DATA (ENVIRONMENTAL)**

(a)

Type of Measurement:	Background [ ]; At contaminated site [ ]; Other **[X]**
Media:	Surface water (lake)
Results:	ND (Detection limits: 0.002 mg/l) in 3 areas in Japan as of 1983

Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1984)

(b)
Type of Measurement: Background [ ]; At contaminated site [ ]; Other **[X]**
Media: Surface water (estuary)
Results: ND (Detection limits: 0.004 mg/l) in 1 area in Japan as of 1983
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1984)

(c)
Type of Measurement: Background [ ]; At contaminated site [ ]; Other **[X]**
Media: Surface water (sea)
Results: ND (Detection limits: 0.002 - 0.004 mg/l) in 6 areas in Japan as of 1983
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1984)

(d)
Type of Measurement: Background [ ]; At contaminated site [ ]; Other **[X]**
Media: Sediment (lake)
Results: ND (Detection limits: 0.12 - 0.24 mg/kg-dry) in 3 areas in Japan as of 1983
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1984)

(e)
Type of Measurement: Background [ ]; At contaminated site [ ]; Other **[X]**
Media: Sediment (estuary)
Results: ND (Detection limit: 0.09 mg/kg-dry) in 1 area in Japan as of 1983
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1984)

(f)
Type of Measurement: Background [ ]; At contaminated site [ ]; Other **[X]**
Media: Sediment (sea)
Results: ND (Detection limit: 0.025 - 0.15 mg/kg-dry) in 6 areas in Japan as of 1983
Remarks: ND: Not detected
Reference: Chemicals in the environment, EA, Japan (1984)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION

*3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Media: Air-biota [ ]; Air-biota-sediment-soil-water **[X]**; Soil-biota [ ]; Water-air [ ]; Water-biota [ ]; Water-soil [ ]; Other [ ]

Method: Fugacity level I [ ]; Fugacity level II [ ]; Fugacity level III **[X]**; Fugacity level IV [ ]; Other (calculation) [ ]; Other (measurement)[ ]

Results:

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.1 %	0.0 %	0.0 %
Water	46.5 %	99.6 %	40.5 %
Soil	53.3 %	0.0 %	59.3 %
Sediment	0.2 %	0.4 %	0.2 %

Remarks: Appendix 1
Reference: MITI. Japan

*3.5 BIODEGRADATION

Type: aerobic **[X]**; anaerobic [ ]
Inoculum: adapted [ ]; non-adapted **[X]**;
Concentration of the chemical: related to COD [ ]; DOC [ ]; test substance **[X]**
Medium: water **[X]**; water-sediment [ ]; soil [ ]; sewage treatment [ ]
Degradation: 0 % by BOD after 14 days
7.8 % by TOC after 14 days
5.3 % by HPLC after 14 days
Results: readily biodeg. [ ]; inherently biodeg. [ ]; under test condition no biodegradation observed **[X]**, other [ ]
Method: OECD TG 301C
GLP: Yes **[X]** No [ ] ? [ ]
Test substance: purity: 99.9 %
Reference: MITI, Japan

3.7 BIOACCUMULATION

Species: Carp (*Cyprinus carpio*)
Exposure period: 6 weeks
Temperature: 25 °C
Concentration: (1) 10 mg/L
(2) 1 mg/L
BCF: (1) < 0.1
(2) < 0.5
Method: OECD TG 305C
Type of test: calculated [ ]; measured **[X]**
static[ ]; semi-static[ ]; flow-through**[X]**; other*(e.g. field test)*[ ]
GLP: Yes **[X]** No [ ] ? [ ]
Test substance: purity: 99.9 %
Remarks:
Reference: MITI, Japan

4. ECOTOXICITY

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	static [ ]; semi-static **[X]**; flow-through [ ]; other *(e.g. field test)* [ ] open-system **[X]**; closed-system [ ]
Species:	*Oryzias latipes* (Himedaka)
Exposure period:	96 h
Results:	$LC_{50\ (96h)} > 100$ mg/l
Analytical monitoring:	Yes **[X]** No [ ] ? [ ]
Method:	OECD TG 203 (1992)
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.7 %
Remarks:	Groups of 10 Himedaka were exposed to the nominal concentrations of 6.25, 12.5, 25, 50 and 100 mg/l and laboratory water control. Solubilizer was not used. Concentrations of the test substance were kept close to the nominal concentrations (99.5 to 103 %).
Reference:	Environment Agency of Japan (1996)

(b)

Type of test:	static [ ]; semi-static[ ]; flow-through **[X]**; other *(e.g. field test)* [ ] open-system **[X]**; closed-system [ ]
Species:	*Oryzias latipes* (Himedaka)
Exposure period:	14 d
Results:	$LC_{50\ (14d)} > 100$ mg/l
Analytical monitoring:	Yes **[X]** No [ ] ? [ ]
Method:	OECD TG 203 (1992)
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.7 %
Remarks:	Groups of 10 Himedaka were exposed to the nominal concentrations of 10, 32 and 100 mg/l and laboratory water control. Solubilizer was not used. Concentrations of the test substance were kept close to the nominal concentrations throughout the 14-d test (99 to 102 %).
Reference:	Environment Agency of Japan (1996)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. Daphnia

Type of test:	static **[X]**; semi-static [ ]; flow-through [ ]; other*(e.g. field test)*[ ]; open-system **[X]**; closed-system [ ]
Species:	*Daphnia magna*.
Exposure period:	48 h
Results:	$EC_{50\ (48h)} = 1000$ mg/l
Analytical monitoring:	Yes **[X]** No [ ] ? [ ]
Method:	OECD TG 202
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.7 %

Remarks:	20 daphnids (4 replicates; 5 organisms per replicate) were exposed to measured concentrations of 100, 180, 320, 580 and 1000 mg/l and laboratory water control. Solubilizer was not used. Concentrations of the test substance were kept close to the nominal concentrations throughout the 48-h test (99.2 to 103.0 %).
Reference:	Environment Agency of Japan (1996)

*4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

Species:	*Selenastrum capricornutum* ATCC 22662
Endpoint:	Biomass **[X]**; Growth rate **[ ]**; Other **[ ]**
Exposure period:	72 h
Results:	Biomass $EC_{50\ (72h)}$ = 620 mg/l *(Endpoint)* NOEC = 62.5 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 201 (1984) open-system **[ ]**; closed-system **[X]**
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.7 %
Remarks:	Static test. The EC_{50} value for biomass was calculated based on the measured concentrations of the nominal concentrations 62.5, 125, 250, 500 and 1000 mg/l. No solubilizer was used. Concentrations of the test substance were kept close to the nominal concentrations throughout the 72-h test (98 to 105 %).
Reference:	Environment Agency of Japan (1996)

4.4 TOXICITY TO BACTERIA

No data

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

(*)4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[X]**; closed-system **[ ]**
Species:	*Daphnia magna*
Endpoint:	Mortality **[ ]**; Reproduction rate **[X]**; Other **[X]**
Exposure period:	21 d
Results:	Reproduction rate: $EC_{50\ (21\ d)}$ = 65.9 mg/l *(Endpoint)* NOEC = 32.0 mg/l
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 202(1984)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4, purity: 99.7 %
Remarks:	40 daphnids (4 replicate; 10 daphnids per replicate) were exposed to the nominal concentrations of 1.0, 3.2, 10, 32 and 100 mg/l and laboratory water control (dechlorinated tap water).

Concentrations of the test substance were kept close to the nominal concentrations throughout the 21-d test (95 to 103 %). The test water was renewaled every 2 or 3 days.

Reference: Environment Agency of Japan (1996)

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data

4.8 BIOTRANSFORMATION AND KINETICS

No data

4.9 ADDITIONAL REMARKS

None

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rats/albino
Value:	7,700 mg/kg b.w.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	Babayan & Aleksandryan: 1985

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rats
Value:	> 7,500 mg/kg b.w.

Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Sodium isocyanurate, purity: unknown
Remarks:	
Reference:	*Gigiena i Sanitariya*: 1962

(c)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mice
Value:	3,400 mg/kg b.w.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	Babayan & Aleksandryan: 1985

(d)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [X]; Other [ ]
Species/strain:	Rabbits
Value:	> 10 g/kg b.w.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	Toxicity Information: 1972

5.1.2 ACUTE INHALATION TOXICITY

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; Other [X]
Species/strain:	Rats
Exposure time:	not indicated
Value:	612 mg/m^3
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	As an aerosol, purity: unknown
Remarks:	Minimum toxic concentration
Reference:	Babayan & Aleksandryan: 1985

5.1.3 ACUTE DERMAL TOXICITY

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rabbits
Value:	> 7,940 mg/kg b.w.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	Toxikologische Bewertung: 1993

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rats

Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:	
Value:	> 100 mg/kg b.w.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	*Gigiena i Sanitariya*: 1962

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mice
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:	
Value:	> 500 mg/kg b.w.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	*Gigiena i Sanitariya*: 1962

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Cats
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:	
Value:	2,144 mg/kg b.w.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Sodium isocyanurate, purity: unknown
Remarks:	
Reference:	*J. Pharmacol. Exp. Ther.*: 1951

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Species/strain:	Rabbits
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [X]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (causes burns)[ ]; Irritating [ ]; Not irritating [ ]
Method:	Federal Hazardous Substances Act (FHSA) tests
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	Hammond *et al.*: 1986

5.2.2 EYE IRRITATION/CORROSION

(a) Species/strain: Rabbits

	Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [X]; Not irritating [ ]
	Classification:	Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes [ ]
	Method:	Federal Hazardous Substances Act (FHSA) tests
	GLP:	Yes [ ] No [X] ? [ ]
	Test substance:	purity: unknown
	Remarks:	
	Reference:	Hammond *et al.*: 1986
(b)	Species/strain:	Rabbits
	Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [X]; Slightly irritating [ ]; Not irritating [ ]
	Classification:	Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes [ ]
	Method:	Rinsed with water
	GLP:	Yes [ ] No [X] ? [ ]
	Test substance:	purity: unknown
	Remarks:	Administration into the eye at 20 mg/24 hr
	Reference:	Toxicity Information: 1972
(c)	Species/strain:	Rabbits
	Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [X]; Slightly irritating [ ]; Not irritating [ ]
	Classification:	Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes [ ]
	Method:	Standard Draize test
	GLP:	Yes [ ] No [X] ? [ ]
	Test substance:	purity: unknown
	Remarks:	Administration into the eye at 500 mg/24 hr
	Reference:	Marhold: 1972

5.3 SKIN SENSITISATION

No data

*5.4 REPEATED DOSE TOXICITY

(a)	Species/strain:	Rats/Crj: CD (SD)
	Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
	Route of Administration:	Oral (by gavage)
	Exposure period:	Male: 44 days Female: From 14 days before mating to day 3 of lactation
	Frequency of treatment:	Daily
	Post exposure observation period:	
	Dose:	0, 10, 40, 150, 600 mg/kg/day
	Control group:	Yes [X]; No [ ]; No data [ ]; Sesame oil Concurrent no treatment[ ]; Concurrent vehicle[X];Historical[ ]
	NOAEL:	150 mg/kg/day
	LOAEL:	600 mg/kg/day

	Results:	Isocyanuric acid indicated toxic effects at 600 mg/kg in both sexes. Excretion of reddish urine was evident. In addition, depression of body weight gain was observed in males. Urinalyses of males revealed appearance of crystals, which is considered this chemical precipitated from urine, and increases of erythrocytes and leukocytes. In hematological examination of males, significant decreases in erythrocyte counts, hemoglobin concentrations and hematocrit values were observed. In blood chemical examination of males, increases in urea nitrogen and creatinine, and a decrease of sodium were revealed. In histopathological examination, dilatation of the renal tubules, necrosis or hyperplasia of the tubular epithelium, increased basophilic tubules, neutrophilic infiltration, mineralization and fibrosis in the kidney, hyperplasia of the mucosal epithelium in the urinary bladder and vacuolization of the zona fasciculata in the adrenals were observed in both sexes. In addition, the incidence of atrophic thymus also showed a tendency for increase in females. Absolute and relative kidney weights and relative adrenal weights were increased in both sexes.
	Method:	OECD Combined Repeat Dose and Reproductive/ Developmental Toxicity Screening Test
	GLP:	Yes [X] No [ ] ? [ ]
	Test substance:	purity: 99.8 %
	Reference:	MHW, Japan: 1997
(b)	Species/strain:	Rats/Rochester strain (Wistar-derived)
	Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
	Route of Administration:	Oral (in diet)
	Exposure period:	20 weeks
	Frequency of treatment:	Daily
	Post exposure observation period:	
	Dose:	0, 0.8, 8 % (calculated daily dose: 0, 56, 560 mg/kg)
	Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
	NOAEL:	0.8 % (56 mg/kg/day)
	LOAEL:	8 % (560 mg/kg/day)
	Results:	14/20 males and 4/20 females died at 8 %, but no died at 0.8 %. Considerable decrease in body weight gain was observed at 8 %. Urine samples taken prior to the start of feeding and again near termination of the study showed normal concentrations of protein and sugar. In hematological examination no change was observed. There were no changes in organ weights (thyroid, liver, brain, lungs, heart, etc.), expect for kidney weight, which increased at 8 % in females. In histologic study, dilatation of distal collecting tubules and dusts of Bellini, with focal areas of epithelial proliferation were observed at 8 % in both sexes.
	Method:	Other
	GLP:	Yes [ ] No [X] ? [ ]
	Test substance:	Sodium isocyanurate, purity: unknown
	Reference:	Hodge *et al.*: 1965

(c) Species/strain: Mice/B6C3F1
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Oral (in drinking water)
Exposure period: 90 days
Frequency of treatment: Daily
Post exposure observation period:
Dose: 896, 1,792, 5,375 ppm
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment[X];Concurrent vehicle[X];Historical[ ]
NOAEL: 5,375 ppm (male: 1,994 mg/kg/day, female: 2,200mg/kg/day)
LOAEL:
Results: Although increase in water consumption in both sexes and absolute and relative weights of ovaries in females were observed, these changes were considered due to the high sodium content. No adverse effect was observed.
Method: Other
GLP: Yes [X] No [ ] ? [ ]
Test substance: Sodium isocyanurate, purity: unknown
Remarks: Sodium hippurate was used as a second control in order to have the sodium burden as the top concentration.
Reference: Hazleton U.S.: 1982

(d) Species/strain: Dogs/Beagle
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Oral (in diet)
Exposure period: 6 months
Frequency of treatment: Daily
Post exposure observation period:
Dose: 0 (vehicle), 0.8 % (calculated daily dose: 291 mg/kg)
Control group: Yes [ ]; No [X]; No data [ ];
Concurrent no treatment[ ]; Concurrent vehicle[ ]; Historical[ ]
NOAEL: 0.8 % (291 mg/kg/day)
LOAEL:
Results: There were no changes in body weight gain, organ weight, and sugar and protein in urine. In addition, hematological and histological changes were not observed.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: Sodium isocyanurate, purity: unknown
Reference: Hodge *et al.*: 1965

(e) Species/strain: Dogs/Beagle
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Oral (in diet)
Exposure period: 2 years
Frequency of treatment: Daily
Post exposure observation period:
Dose: 8 % (calculated daily dose: 2,912 mg/kg)
Control group: Yes [ ]; No [X]; No data [ ];

		Concurrent no treatment[ ]; Concurrent vehicle[ ]; Historical[ ]
	NOAEL:	
	LOAEL:	8 % (2912 mg/kg/day)
	Results:	Two of three dogs died after 16 and 21 months on the regimen, respectively. No change or slight increase in body weights was observed. Periodic urinalyses gave normal trace values for sugar and protein. In hematologic study, only a survival dog showed changes, which are low red blood cell counts, hemoglobin values, and hematocrits. There was no change in organ weights (thyroid, liver, brain, lungs, heart, etc.), expect for decrease in kidney weight of two dogs surviving more than 20 months. In these dogs, there was gross evidence of kidney fibrosis. Sections revealed numerous linear streaks of gray fibrous tissue extending from the papillary tip to the cortical surface. Microscopically, similar changes were observed in the kidneys of all three dogs. The collecting tubules were more uniformly and severely involved, but all portions of the nephron were compressed by fibrosis. There were slight focal dilatation and epithelial proliferation in the ducts of Bellini. In survival dog, focal areas of thyroid atrophy were found with lymphocytic infiltration, but without evidence of hyperplasia.
	Method:	Other
	GLP:	Yes [ ] No [X] ? [ ]
	Test substance:	Sodium isocyanurate, purity: unknown
	Reference:	Hodge *et al.*: 1965
(f)	Species/strain:	Rabbits/Albino
	Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
	Route of Administration:	Dermal
	Exposure period:	Approx. 3 months
	Frequency of treatment:	5 days/week
	Post exposure observation period:	
	Dose:	5 ml of 0.8 % or 8 % aqueous suspension
	Control group:	Yes [ ]; No [X]; No data [ ]; Concurrent no treatment[ ]; Concurrent vehicle[ ]; Historical[ ]
	NOAEL:	0.8 %
	LOAEL:	8 %
	Results:	Urinalyses (sugar and protein) and hematological study showed no change. There were no irritation or other adverse effects on the skin. In histological findings of liver and skin from treated and untreated area, no change was observed at the termination of the study. In the kidneys of the rabbits treated with the 8 % isocyanurate suspension, slight dilatation of the ducts of Bellini and mild tubular changes were found.
	Method:	Other
	GLP:	Yes [ ] No [X] ? [ ]
	Test substance:	Sodium isocyanurate, purity: unknown
	Reference:	Hodge *et al.*: 1965
(g)	Species/strain:	Rabbits/Albino
	Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]

Route of Administration:	Eye application
Exposure period:	Approx. 3 months
Frequency of treatment:	5 days/week
Post exposure observation period:	
Dose:	0.1 ml of 0.8 % or 8 % aqueous suspension
Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment[X]; Concurrent vehicle[ ];Historical[ ]
NOAEL:	0.8 %
LOAEL:	8 %
Results:	Increase in body weight was observed during the period of the study in all treated groups. No eye injury was caused and no eye irritation was observed in rabbits treated with an 8 % aqueous suspension of the sodium salt.
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Sodium isocyanurate, purity: unknown
Reference:	Hodge *et al.*: 1965

*5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type:	Ames test
System of testing:	*Salmonella typhimurium* TA1535, TA1537, TA98, TA100
Concentration:	100 to 1000 µg/plate
Metabolic activation:	With [ ]; Without[ ]; With and Without [X]; No data [ ]
S9:	Hamster liver - Arochlor 1254
Results:	
	Cytotoxicity conc: With metabolic activation: Without metabolic activation:
	Precipitation conc:
	Genotoxic effects: + ? -
	With metabolic activation: [ ] [ ] [X]
	Without metabolic activation: [ ] [ ] [X]
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	Hayworth *et al.*: 1983

Type:	Other: Inductest Pasteur
System of testing:	Induction of bacteriophage Lambda in *Escherichia Coli* K12 en VA UVRB
Concentration:	0.2 to 2000 µg/plate
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:	
	Cytotoxicity conc: With metabolic activation: Without metabolic activation:
	Precipitation conc:
	Genotoxic effects: + ? -
	With metabolic activation: [ ] [ ] [X]

Without metabolic activation: [ ] [ ] [X]
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: NORSOLOR/APC: 1977

B. NON-BACTERIAL IN VITRO TEST

Type: Chromosomal aberration test
System of testing: Chinese hamster lung (CHL/IU) cells
Concentration: +S9 (short-term treatment): 0, 0.33, 0.65, 1.3 mg/ml
-S9 (continuous treatment): 0, 0.33, 0.65, 1.3 mg/ml
-S9 (short-term treatment): 0, 0.33, 0.65, 1.3 mg/ml
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavone
Results:

Cytotoxicity conc: Not observed
Precipitation conc:

Genotoxic effects:	clastogenicity			polyploidy		
	+	?	-	+	?	-
With metabolic activation:	[ ]	[ ]	[X]	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]	[ ]	[ ]	[X]

Method: Guidelines for Screening Mutagenicity Testing of Chemicals (Japan), and OECD TG (473).
GLP: Yes [X] No [ ] ? [ ]
Test substance: purity: 99.5 %
Remarks: Exposure period: short-term treatment: 6 hr
continuous treatment: 24, or 48 hr
Positive control: -S9: Mitomycin, +S9: Cyclophosphamide
Reference: MHW, Japan: 1997

Type: Mouse lymphoma assay
System of testing: L 5178 TK +/-
Concentration: 50 to 2000 µg/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:

Cytotoxicity conc: With metabolic activation:
Without metabolic activation:
Precipitation conc:

Genotoxic effects:	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: Other
GLP: Yes [X] No [ ] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: Industry ad hoc Committee for Isocyanurates: 1981a

Type: Sister chromatid exchange assay
System of testing: CHO cells

Concentration:	93 to 1500 µg/plate
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:	
	Cytotoxicity conc: With metabolic activation:
	Without metabolic activation:
	Precipitation conc:
	Genotoxic effects: + ? -
	With metabolic activation: [ ] [ ] [X]
	Without metabolic activation: [ ] [ ] [X]
Method:	Other
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	purity: unknown
Remarks:	
Reference:	Industry ad hoc committee for Isocyanurates: 1981b

* 5.6 GENETIC TOXICITY IN VIVO

Type:	Chromosomal aberration test
Species/strain:	Rats
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No data [X]
Route of Administration:	Oral (single gavage administration)
Exposure period:	
Doses:	Up to 5000 mg/kg
Results:	
	Effect on mitotic index or P/N ratio:
	Genotoxic effects: + ? -
	[ ] [ ] [X]
Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Sodium isocyanurate, purity: unknown
Remarks:	Rats were killed 24 and 48 hr after dosing, and bone marrow cells were collected and examined for chromosomal aberrations.
Reference:	Hammond *et al.*: 1985

5.7 CARCINOGENICITY

(a)	Species/strain:	Rats/CD
	Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
	Route of Administration:	Oral (in drinking water)
	Exposure period:	2 years
	Frequency of treatment:	Daily
	Postexposure observation period:	
	Doses:	0 (vehicle), 400, 1,200, 2,400, 5,375 ppm (Estimated daily doses were indicated only for 2,400 and 5,375 ppm (male: 154 and 371 mg/kg/day, female: 266 and 634 mg/kg/day))
	Control group:	Yes [X]; No [ ]; No data [ ]; tap water Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
	Results:	No test article related carcinogenesis.

Method:	Other
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Sodium isocyanurate, purity: unknown
Remarks:	Sodium hippurate was administered at the equivalent amount of sodium to the highest dose group as a second control. Treatment-related mortality was observed in some males of highest dose group, which died during the first 12 months of the study. This mortality was due to the development of calculi in the urinary tract. In some males that died on test and in some that were sacrificed at 12 months, there were pathologic changes, including hyperplasia, bleeding, and inflamed ureters, and renal tubular nephrosis. Although slight tubular nephrosis was also observed in a few females of highest dose group during the first 12 months, these animals did not exhibit bladder calculi. Inflammatory lesions in the heart were also apparent in some of the highest dose males that died early.
Reference:	Cascieri *et al.*: 1985

(b)

Species/strain:	Mice/B6C3F1
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration:	Oral (in drinking water)
Exposure period:	2 years
Frequency of treatment:	Daily
Postexposure observation period:	
Doses:	0 (vehicle), 100, 400, 1,200, 5,375 ppm
Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
Results:	There was no evidence of test article related carcinogenesis.
Method:	Other
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Sodium isocyanurate, purity: unknown
Remarks:	Sodium hippurate was administered at the equivalent amount of sodium to the highest dose group as a second control. Apparent swollen enlarged abdomen was observed at the highest dose groups (both isocyanurate and hippurate). There were no effects on survival, clinical pathology (except for urinary sodium), organ weight, gross and histopathology.
Reference:	Industry Ad hoc Committee for Isocyanurates, Hazleton laboratories, Report 2169-100 (1986)

(c)

Species/strain:	Rats
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No data [X]
Route of Administration:	Subcutaneous
Exposure period:	2 years
Frequency of treatment:	Once a week
Postexposure observation period:	
Doses:	Total dose: 6.06 g (approx. daily dose: 8.3 mg/day)
Control group:	Yes [ ]; No [ ]; No data [X]; Concurrent no treatment[ ]; Concurrent vehicle[ ]; Historical[ ]

Results: A lymphosarcoma in lungs has been observed in 1 of the 5 surviving rats after 28 months, and a subdermal lipoma in 1 of the other rats after 30.5 months.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: Toxikologische Bewertung.: 1993

(d) Species/strain: Mice
Sex: Female [ ]; Male [ ]; Male/Female [ ]; No data [X]
Route of Administration: Subcutaneous
Exposure period: 2 years
Frequency of treatment: Once a week
Postexposure observation period:
Doses: Total dose: 0.6 g (estimated daily dose: 0.82 mg/day)
Control group: Yes [ ]; No [ ]; No data [X];
Concurrent no treatment[ ];Concurrent vehicle[ ]; Historical [ ]
Results: No tumours were observed.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: purity: unknown
Remarks:
Reference: Toxikologische Bewertung.: 1993

*5.8 TOXICITY TO REPRODUCTION

(a) Type: Fertility [ ]; One-generation study [ ]; Two-generation study [ ]; Other [X]
Species/strain: Rats/Crj: CD (SD)
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Oral (by gavage)
Exposure period: Male: 14 days before mating
Female: 14 days before mating to day 3 of lactation
Frequency of treatment: Daily
Post exposure observation period:
Premating exposure period: 14 days
Duration of the test:
Dose: 0, 10, 40, 150, 600 mg/kg/day
Control group: Yes [X]; No [ ]; No data [ ]; Sesame oil
Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
NOEL Parental: Male: 600 mg/kg/day, Female: 600 mg/kg/day
NOEL F1 Offspring: 600 mg/kg/day
NOEL F2 Offspring:
Results:

General parental toxicity:
Isocyanuric acid indicated no alteration in reproductive parameters including the copulation index, fertility index, gestation length, numbers of corpora lutea or implantations, implantation index, gestation index, delivery index, and behavior at delivery and lactation.

Toxicity to offspring:
There were no significant differences in offspring parameters including number of offspring or live offspring, the sex ratio, live birth and viability indices, and body weight. No external or visceral abnormalities related to the test substance were detected in any of the offspring.

Method: OECD Combined Repeat Dose and Reproductive/ Developmental Toxicity Screening Test
GLP: Yes [X] No [ ] ? [ ]
Test substance: purity: 99.8 %
Remarks:
Reference: MHW, Japan: 1997

(b) Type: Fertility [ ]; One-generation study [ ]; Two-generation study [ ]; Other [X] *Three generation study
Species/strain: Rats/CD
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: Oral (in drinking water)
Exposure period: P0: A minimum of 100 days from 36 days of age to mating
F1 and F2: 120 days after weaning
F3: 4 weeks
Frequency of treatment: Daily
Post exposure observation period:
Premating exposure period: A minimum of 100 days
Duration of the test:
Dose: 0 (vehicle), 400, 1,200, 5,375 ppm
Control group: Yes [X]; No [ ]; No data [ ]; tap water
Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
NOAEL Parental: 5,375 ppm (Approx. 370 mg/kg/day for male, 634 mg/kg/day for female)
NOAEL F1 Offspring: 5,375 ppm
NOAEL F2 Offspring: 5,375 ppm
NOAEL F3 Offspring: 5,375 ppm
Results:

General parental toxicity:
No compound related changes were observed in mortality, body weight, food consumption, and gestation length. In pathological and histological findings, there were also no changes.

Toxicity to offspring:
No compound-related changes were observed in mortality, body weights, food consumption litter size, pup survival to weaning, sex ratio, and pup weight. In pathological and histological findings, epithelial hyperplasia with chronic cystitis was observed in a few of high-dose treated males in F2 offsprings, which were attributed to chronic irritation by the calculi in the urinary bladder. In other treated groups, there were no changes.

Method: Other
GLP: Yes [X] No [ ] ? [ ]
Test substance: Sodium isocyanurate, purity: unknown

Remarks: Sodium hippurate was provided an equivalent amount of sodium administered to high-dose sodium isocyanurate animals as second control.
Weanlings from the F1 and F2 litters were randomly selected as parents for the next generation and continued on treatment. Related litters and F3 offsprings were sacrificed 4 weeks after weaning and organ weight measurements and microscopic examination of tissues were carried out.
Reference: Wheeler *et al.*: 1985

(c) Type: Fertility [ ]; One-generation study [ ]; Two-generation study [ ]; Other [X]
Species/strain: Mice/CD-1
Sex: Female [ ]; Male [X]; Male/Female [ ]; No data [ ]
Route of Administration: i.p.
Exposure period: 6 weeks
Frequency of treatment:
Post exposure observation period:
Premating exposure period:
Duration of the test: 6 weeks
Doses: 0 (vehicle), 125 and 250 mg/kg/day
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
NOAEL Parental: 250 mg/kg/day
NOAEL Foetal: 250 mg/kg/day
Results:
General parental toxicity:
Any treatment related effects were not observed in females, mated with sodium isocyanurate treated males.
Toxicity to fetus:
Any toxicity was not observed.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: Sodium isocyanurate, purity: unknown
Remarks: As positive control, methyl methane sulfonate was used at dose of 50 mg/kg/day.
Non-treated females are mated with the treated males every week.
As a result, early resorptions were observed in females mated with males treated with methyl methane sulfonate.
Reference: FMC Corporation: 1972

*5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Species/strain: Rabbits/Dutch belted
Sex: Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration: Oral (by gavage)
Duration of the test: 22 days
Exposure period: Days 6-18 of gestation
Frequency of treatment: Daily
Doses: 0 (vehicle), 50, 200, 500 mg/kg/day

Control group: Yes [X]; No [ ]; No data [ ]; 20 mL/kg water
Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
NOAEL Maternal Toxicity: 50 mg/kg/day
NOAEL teratogenicity: 200 mg/kg/day
Results:
Maternal general toxicity:
Although slight decrease in body weight were observed in mid- and high-dose groups during the treatment period, compensatory weight gains occurred after termination of treatment on day 18. There were no compound related mortality or other adverse reactions.
Pregnancy/litter data:
Foetal data:
The mean number of live fetus/dam and the sex ratio were essentially comparable for all groups. Body weights and crown/rump lengths were reduced slightly in high-dose groups, compared to control. There was no evidence of external or internal malformations or skeletal anomalies.
Method: Other
GLP: Yes [ ] No [X] ? [ ]
Test substance: Sodium isocyanurate, purity: unknown
Remarks:
Reference: FMC Corporation, unpublished observations

Species/strain: Rats/Sprague-Dawley
Sex: Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration: Oral (by gavage)
Duration of the test: 20 days
Exposure period: Days 6-15 of gestation
Frequency of treatment: Daily
Doses: 0 (vehicle), 200, 1,000, 5,000 mg/kg/day
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment[ ];Concurrent vehicle[X]; Historical[ ]
NOAEL Maternal Toxicity: 5,000 mg/kg/day
NOAEL teratogenicity: 5,000 mg/kg/day
Results:
Maternal general toxicity:
There were no treatment-related effects on maternal appearance, behavior and body weight gain in all groups treated with sodium isocyanurate.
Pregnancy/litter data:
Foetal data:
No teratogenic effects were observed in all groups treated with sodium isocyanurate.
Method: Other
GLP: Yes [X] No [ ] ? [ ]
Test substance: Sodium isocyanurate, purity: unknown
Remarks: Sodium control groups received sodium hippurate at doses of 1,118 and 5,590 mg/kg/day.

In sodium control group, decrease in body weight and crown/rum length, and increase in post-implantation loss and incidence of incomplete ossification were observed.

Reference: Industry ad hoc Committee for Isocyanurates: 1982

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

There is no available data.

B. Toxicodynamics, toxicokinetics

Type: Toxicokinetics

Results: Toxicokinetics study of sodium isocyanurate was performed in rats, using [^{14}C] sodium isocyanurate. The elimination half-life was 30 to 60 min after oral or intravenous administration at 5 mg/kg and 2.5 hr after oral administration at 500 mg/kg. At 5 mg/kg, this chemical was completely absorbed and largely eliminated in urine, while at 500 mg/kg, this chemical was incompletely absorbed and largely eliminated in feces. The remainder of radioactivity in most tissues was below the level of detection (0.1-1.0 μg/g) 7 days after treatment. In second study, rats were administered unlabeled sodium isocyanurate orally at 5 mg/kg/day for 14 days followed by the single exposure on day 15. As results of second study, no bioaccumulation and no significant changes in disposition or metabolism were observed, compared to the single exposure. In excreta, only unchanged isocyanurate was found.

Remarks:

References: Barbee *et al.*: 1983

Type: Toxicokinetics

Results: Toxicokinetics study of sodium isocyanurate was conducted in dogs, using [^{14}C] sodium isocyanurate. Administration was performed at 5 mg/kg by oral or intravenous route and at 500 mg/kg by oral route. At 5 mg/kg, this chemical was completely absorbed and largely eliminated in urine, while at 500 mg/kg, this chemical was only partially absorbed and largely eliminated in feces. Sodium isocyanurate distributed into an apparent volume of distribution of 0.7 L/kg, which is somewhat greater than total body water volume. The elimination half-life was from 1.5 to 2 hr after administration. Dogs were also administered unlabeled sodium isocyanurate orally at 5 mg/kg/day followed by the single exposure of 5 mg/kg radiolabeled sodium isocyanurate on day 15. The remainder of radioactivity in most tissues was below the level of detection (0.1-3.3 μg/g) for all sampling times for both single and repeated dose administration. In excreta, only unchanged isocyanurate was found.

Remarks:

References: Barbee *et al.*: 1984

Type: Toxicokinetics
Results: Toxicokinetics study by dermal route was performed, in which species was not indicated. After dermal application, the ^{14}C-labelled substance is not detectable in the blood and < 0.01% of the administered dose is found in the urine.
Remarks:
References: Toxikologische Bewertung: 1993

* 5.11 EXPERIENCE WITH HUMAN EXPOSURE

Results: Toxicokinetics of isocyanuric acid was investigated in 5 volunteers, who soaked in a swimming pool for 120 minutes. As a result, the cumulative excretion of isocyanuric acid was 0.03-2.8 mg, equivalent to 3.0-3.6 ml of pool water and the elimination half-life is caluculated as 3 hr. On the other hand, recovery of ingested isocyanuric acid is 98 % in urine. No correlation observed between toxicokinetics and gamma glutamyl transpeptidase activity.
Distribution 1 compartment open model.
Remarks:
Reference: Allen *et al.*: 1982

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Appendix 1

scenario 1

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	1,000	9.5.E-08	9.5.E+02	0.1	2.4E+00	9.5.E+00
water	0	4.2.E-02	8.4.E+05	46.5	6.8E+01	8.4.E+02
soil	0	6.0.E-01	9.7.E+05	53.3	7.7E+01	
sediment		3.3.E-02	3.3.E+03	0.2	2.7E-01	6.7.E-02
		total amount	1.8.E+06			

scenario 2

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	4.3.E-12	4.3.E+02	0.0	1.1.E-04	4.3.E-04
water	1000	4.6.E-02	9.3.E+05	99.6	7.4.E+01	9.3.E+02
soil	0	2.7.E-05	4.3.E+01	0.0	3.5.E-03	
sediment		3.7.E-02	3.7.E+03	0.4	2.9.E-01	7.3.E-02
		total amount	9.3.E+05			

scenario 3

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	0	7.9.E-10	7.9.E+00	0.0	2.0.E-02	7.9.E-02
water	0	4.2.E-02	8.3.E+05	40.5	6.7.E+01	8.3.E+02
soil	1000	7.6.E-01	1.2.E+06	59.3	9.8.E+01	
sediment		3.3.E-02	3.3.E+03	0.2	2.6.E-01	6.6.E-02
		total amount	2.1.E+06			

scenario 4

	emission rate	conc.	amount	percent	transformation rate [kg/h]	
	[kg/h]	[g/m^3]	[kg]	[%]	reaction	advection
air	600	5.7.E-08	5.7.E+02	0.0	1.5.E+00	5.7.E+00
water	300	4.3.E-02	8.7.E+05	55.1	7.0.E+01	8.7.E+02
soil	100	4.4.E-01	7.0.E+05	44.6	5.6.E+01	
sediment		3.4.E-02	3.4.E+03	0.2	2.7.E-01	6.9.E-02
		total amount	1.6.E+06			

Physico-chemical parameter

molecular weight		129.08	Measured
melting point		330	Measured
vapor pressure [Pa]		5.00E-03	Measured
water solubility [g/m^3]		2700	Measured
log Kow		0.3	Measured
half life [h]	in air	272	Estimated
	in water	8640	Estimated
	in soil	8640	Estimated
	in sediment	8640	Estimated

Temp. []	25

Environmental parameter

		volume	depth	area	organic	lipid content	density	residence
		[m^3]	[m]	[m^2]	carbon []	[]	[kg/m^3]	time [h]
bulk air	air	1.0E+13					1.2	100
	particles	2.0E+03						
	total	1.0E+13	1000	1E+10				
bulk water	water	2.0E+10					1000	1000
	particles	1.0E+06			0.04		1500	
	fish	2.0E+05				0.05	1000	
	total	2.0E+10	10	2E+09				
bulk soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8.0E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
bulk sediment	water	8.0E+07					1000	
	solid	2.0E+07			0.06		2400	50000
	total	1.0E+08	0.05	2E+09				

Intermedia Transport Parameters m/h

air side air-water MTC	5	soil air boundary layer MTC	5
water side air water MTC	0.05	sediment-water MTC	1E-04
rain rate	1E-04	sediment deposition	5E-07
aerosol deposition	6E-10	sediment resuspension	2E-07
soil air phase diffusion MTC	0.02	soil water runoff	5E-05
soil water phase diffusion MTC	1E-05	soil solid runoff	1E-08

EXTRACT FROM IRPTC LEGAL FILES

File: 17.01 LEGAL rn : 303375

systematic name:1,3,5-Triazine-2,4,6(1H,3H,5H)-trione
common name :cyanuric acid
reported name :ISOCYANURIC ACID
cas no :108-80-5
area : CAN type : REG

subject	specification	descriptor
USE	OCC	RQR
STORE		
LABEL		

INGREDIENT DISCLOSURE LIST CONCENTRATION 1% WEIGHT/WEIGHT. THE WORKPLACE HAZARDOUS MATERIALS INFORMATION SYSTEM (WHMIS) IS A NATIONAL SYSTEM TO PROVIDE INFORMATION ON HAZARDOUS MATERIALS USED IN THE WORKPLACE. WHMIS IS IMPLEMENTED BY THE HAZARDOUS PRODUCTS ACT AND THE CONTROLLED PRODUCTS REGULATIONS (ADMINISTERED BY THE DEPARTMENT OF CONSUMER AND CORPORATE AFFAIRS). THE REGULATIONS IMPOSE STANDARDS ON EMPLOYERS FORTHE USE, STORAGE AND HANDLING OF CONTROLLED PRODUCTS AND ADDRESS LABELLING AND IDENTIFICATION, EMPLOYEE INSTRUCTION AND TRAINING, AS WELL AS THE UPKEEP OF A MATERIALS SAFETY DATA SHEET (MSDS). THE PRESENCE IN A CONTROLLED PRODUCT OF AN INGREDIENT IN A CONCENTRATION EQUAL TO OR GREATER THAN SPECIFIED IN THE INGREDIENT DISCLOSURE LIST MUST BE DISCLOSED IN THE SAFETY DATA SHEET.
entry date: APR 1991 effective date: 31DEC1987

amendment: CAGAAK, Canada Gazette Part II, 122 , 2 , 551 ,

****

File: 17.01 LEGAL rn : 1122611

systematic name:1,3,5-Triazine-2,4,6(1H,3H,5H)-trione
common name :cyanuric acid
reported name :cyanuric acid
cas no :108-80-5
area : RUS type : REG

subject	specification	descriptor
AIR	OCC	MAC CLASS

CLV : 0.5 MG/M3 (AEROSOL) HAZARD CLASS: II
entry date: MAY 1990 effective date: 01JAN1989

amendment: GOSTS*, GOSUDARSTVENNYI STANDART SSSR(STATE STANDARD OF USSR), 12.1.005 , , , 1988

****

File: 17.01 LEGAL rn : 1123035

systematic name:1,3,5-Triazine-2,4,6(1H,3H,5H)-trione
common name :cyanuric acid
reported name :cyanuric acid
cas no :108-80-5
area : RUS type : REG

subject	specification	descriptor
AQ	SURF	MAC CLASS

6.0 MG/L HAZARD CLASS: III
entry date: JUL 1990 effective date: 1JAN1989

amendment: SPNPV*, SANITARNYE PRAVILA I NORMY OKHRANY POVERKHNOSTNYKH VOD OT ZAGRIAZNENIA (HEALTH REGULATION AND STANDARDS OF SURFACE WATER PROTECTION FROM CONTAMINATION), 4630-88 , , , 1988

****

File: 17.01 LEGAL rn : 1320069
systematic name:1,3,5-Triazine-2,4,6(1H,3H,5H)-trione
common name :cyanuric acid
reported name :cyanuric acid
cas no :108-80-5
area : USA type : REG

subject	specification	descriptor
CLASS		RQR
MANUF		PRMT

REGISTRATION STANDARD, CHLORINATED ISOCYANURATES, 1987.; Summary - THIS SUBSTANCE IS INCLUDED ON A LIST OF ACTIVE INGREDIENTS FOR WHICH REGISTRATION STANDARDS HAVE BEEN ISSUED AS OF DECEMBER 24, 1988. A REGISTRATION STANDARD IS A DOCUMENT DESCRIBING THE AGENCY'S SCIENTIFIC CONCLUSIONS AND REGULATORY FINDINGS ABOUT CHEMI CALS THAT ARE INGREDIENTS IN PESTICIDE PRODUCTS. REGISTRANTS OF THESE PESTICIDES MUST SUBMIT DATA ON THOSE SUBSTANCES FOR WHICH THEY ARE RESPONSIBLE. INFORMATION WILL BE INCLUDED INTO A DATABASE WHICH WILL ALLOW EPA TO EVALUATE HEALTH AND ENVIRONMENTAL E FFECTS AND DETERMINE APPROPRIATE REREGISTRATION STANDARDS. THIS LIST STATES THE REGISTRATION STANDARD TITLE AND THE YEAR OF THE ISSUANCE OF THE REGISTRATION STANDARD.
entry date: JAN 1992 effective date: 1988

title: FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT: PESTICIDES FOR WHICH REGISTRATION STANDARDS HAVE BEEN ISSUED. LIST A.
original : FEREAC, Federal Register, 54 , 34 , 7740 , 1989
amendment: FEREAC, Federal Register, 54 , 34 , 7740 , 1989

ANNEXES

I U C L I D

D a t a S e t

Existing Chemical	Substance ID: 629-11-8
CAS No.	629-11-8
EINECS Name	hexane-1,6-diol
EINECS No.	211-074-0
Molecular Formula	C6H14O2
Producer Related Part	
Company:	BASF AG
Creation date:	17-FEB-97
Substance Related Part	
Company:	BASF AG
Creation date:	17-FEB-97
Memo:	OECD 1997
Printing date:	12-JAN-00
Revision date:	17-FEB-97
Date of last Update:	**17-FEB-97**
Number of Pages:	**42**
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC

1.0.1 OECD and Company Information

-

1.0.2 Location of Production Site

-

1.0.3 Identity of Recipients

-

1.1 General Substance Information

-

1.1.1 Spectra

-

1.2 Synonyms

.alpha.,.omega.-Hexanediol

.omega.-Hexanediol

1,6-Dihydroxyhexane

1,6-Hexanediol (8CI, 9CI)

1.6-Hexandiol

Hexamethylene glycol

Hexamethylenediol

Hexan-1,6-diol

1.3 Impurities

-

1.4 Additives

-

1.5 Quantity

-

1.6.1 Labelling

Labelling: no labelling required (no dangerous properties)

(1)

1.6.2 Classification

Classification: no classification required (no dangerous properties)
Class of danger:
R-Phrases:

(1)

1.7 Use Pattern

-

1.7.1 Technology Production/Use

-

1.8 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value:
Remark: No MAK-value available

(2)

1.9 Source of Exposure

-

1.10.1 Recommendations/Precautionary Measures

-

1.10.2 Emergency Measures

-

1.11 Packaging

-

1.12 Possib. of Rendering Subst. Harmless

-

1.13 Statements Concerning Waste

-

1.14.1 Water Pollution

Classified by: KBwS (DE)
Labelled by:
Class of danger: 0 (generally not water polluting)

1.14.2 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: no

(1) (3)

1.14.3 Air Pollution

-

1.15 Additional Remarks

1.15 Last Literature Search

-

1.16 Reviews

-

1.17 Listings e.g. Chemical Inventories

-

2.1 Melting Point

Value: 39 - 42 degree C (4)

Value: = 40 - 42 degree C (1) (5)

Value: = 40.7 degree C
Method: other: measured
Year: 1968
GLP: no (6)

Value: ca. 41 degree C (7)

Value: = 41.5 degree C
GLP: no (8)

Value: = 42 degree C (9)

2.2 Boiling Point

Value: = 243 degree C at 1013 hPa
GLP: no (8)

Value: ca. 245 degree C (7)

Value: = 250 degree C
GLP: no (9)

Value: = 253 - 260 degree C (1)

Value: = 253 - 260.5 degree C
GLP: no (4)

2.3 Density

Type: density
Value: = .967 g/cm3 at 0 degree C (9)

Type: density
Value: = .99 g/cm3 at 20 degree C
GLP: no
Remark: For the undercooled liquid below the normal freezing point.
(8)

Type: density
Value: = 1.12 g/cm3 at 20 degree C
(5)

Type: density
Value: = .96 g/cm3 at 50 degree C
(1)

Type: density
Value: = .965 g/cm3 at 50 degree C
GLP: no
(9)

Type: relative density
Value: = .967
(4)

Type: relative density
Value: = 4.08
Remark: Air = 1
(9)

Type: bulk density
Value: = 530 kg/m3
(1)

2.3.1 Granulometry

-

2.4 Vapour Pressure

Value: < .01 hPa at 20 degree C
(1) (5)

Value: = 4.07 hPa at 20 degree C
(4)

Value: = 1 hPa at 100.9 degree C
Method: other (measured): Dynamic measurement (under Argon)
(10)

Value: ca. 6.5 hPa at 126 degree C
(7)

Value: = 12 hPa at 132 degree C

(9)

2.5 Partition Coefficient

log Pow: = -.92
Method: other (calculated): Leo and Hansch
Year:
Remark: Organic phase: Diethyl ether.

(11)

log Pow: = -.11
Method: other (calculated)
Year:

(5)

log Pow: = 0 at 25 degree C
Method: OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year: 1981
GLP: no

(12)

log Pow: = 0
Method:
Year:

(1)

log Pow: = .198
Method: other (calculated): Method with increments of Rekker with computerprogram of CompuDrug Ltd.
Year:

(13)

2.6.1 Water Solubility

Value: at 20 degree C
Qualitative: miscible
pH: = 7.6 at 500 g/l and 20 degree C

(1)

Qualitative: miscible

(4)

2.6.2 Surface Tension

-

2.7 Flash Point

Value: = 101 degree C
Type:
Method:
Year:
(4) (9)

Value: ca. 140 degree C
Type:
Method: other: DIN 51 758
Year:
(7)

Value: = 147 degree C
Type: closed cup
Method: other: DIN 51 758
Year:
(1)

Value: ca. 150 degree C
Type: closed cup
Method: other: DIN 51758
Year:
(5)

2.8 Auto Flammability

Value: = 320 degree C
Method: other: DIN 51 794
(1)

Value: ca. 320 degree C
Method: other: DIN 51794
(5)

Value: ca. 335 degree C
Method: other: DIN 51 794
Remark: ignition temperature
(7)

2.9 Flammability

Result:

2.10 Explosive Properties

Result: other: explosive limits: 1.6 - 8.4 by vol.
(7)

Result: other: explosive limits: 6.6 - 16 % by vol.

(1) (5)

2.11 Oxidizing Properties

-

2.12 Additional Remarks

Remark: Viscosity: ca. 59.3 mPa s at 40 degree C.

(7)

3.1.1 Photodegradation

Type: air
DIRECT PHOTOLYSIS
Halflife t1/2: = 1.2 day
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm3
Rate constant: = .000000000013 cm3/(molecule * sec)
Degradation: = 50 % after 1.2 day
Method:
Year: **GLP:**
Test substance:

(14)

Type: water
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: molecule/cm3
Method:
Year: **GLP:**
Test substance:
Remark: secondary quotation
The rate constant for the reaction between photochemically produced hydroxyl radicals in water and 1,6-hexandiol is 4.7*10+9 L/mole-sec;assuming that concentration of hydroxyl radicals in brightly sunlit natural water is 1*10-17 M, the half-life would be about 171 days of continous (24 h/day) sunlight.

(15) (16)

3.1.2 Stability in Water

Type:
Method: other
Year: **GLP:**
Test substance:
Remark: Glycols are generally resistant to aqueous environmental hydrolysis; therefore, 1,6-Hexandiol is not expected to chemically hydrolyze in environmental waters.

(17)

3.1.3 Stability in Soil

Type: other **Radiolabel:**
Concentration:
Cation exch. capac.
Microbial biomass:
Method:
Year: **GLP:**
Test substance:
Remark: Based upon an estimated log Koc of -0.106, the Koc for 1,6-hexanediol can be estimated to be 21 from a recommended regression-derived equation. This estimated Koc suggests that 1,6-hexanediol is very highly mobile in soil.
(18) (19) (20)

3.2 Monitoring Data (Environment)

Type of measurement: other
Medium:
Remark: no data are available

3.3.1 Transport between Environmental Compartments

Type: other
Media:
Method:
Year:
Remark: According to vapor pressure Ps less than 0.01 hPa (20 deg C) and water solubility of 5000 g/l (20 deg C)a henry constant of equal/less than 2.36*10E-5 Pa*m3/mol can be calculated. According to Thomas and in correspondance with henry constant 1,6-hexandiol is known as hardly volatile from aquatic milieu.
(21)

3.3.2 Distribution

Media: other
Method:
Year:
Remark: According to Mackay level I water is the aiming compartment for 1,6-hexanediol (99%).
(22)

3.4 Mode of Degradation in Actual Use

Remark: Inhibition of degradation activity in activated sludge is not to be anticipated during correct introduction of low concentrations.

(1)

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: > 90 % after 7 day
Result: readily biodegradable
Method: OECD Guide-line 301 A (new version) "Ready Biodegradability: DOC Die Away Test"
Year: **GLP:**
Test substance:

(23)

Type: aerobic
Inoculum: activated sludge
Degradation: ca. 75 % after 28 day
Result: readily biodegradable
Method: OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year: **GLP:**
Test substance:
Remark: DOC reduction measured with CO2 production

(24)

Type: aerobic
Inoculum: other: fresh sludge taken from sewage treatment plant which received predominantly domestic sewage (Reinach, Switzerland)
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 98 % after 28 day
Result: readily biodegradable
Method: OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year: **GLP:**
Test substance:
Remark: DOC removal
ThCO2(%)=91

(25)

Type: aerobic
Inoculum: other: preconditioned sludge
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 98 % after 28 day
Result: readily biodegradable
Method: OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year: **GLP:**
Test substance:
Remark: ThCO2(%)=98; DOC removal(%)=98

(25)

Type: aerobic
Inoculum: other: municipal activated sludge without preconditioning
Concentration: 100 mg/l related to Test substance
Degradation: = 95 % after 28 day
Result: readily biodegradable
Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year: 1988 **GLP:** no
Test substance:
Remark: BOD of THOD
DOC-removal after 28 days: 98%

(26)

Type: aerobic
Inoculum: other: municipal activated sludge, preconditioned for 1 week without any carbon-source
Concentration: 100 mg/l related to Test substance
Degradation: = 87 % after 28 day
Result: readily biodegradable
Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year: 1988 **GLP:** no
Test substance:
Remark: BOD of THOD
DOC-removal after 28 days: 98%

(26)

Type: aerobic
Inoculum: other: fresh sludge from a sewage treatment plant which received predominantly domestic sewage (Reinach, Switzerland)
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 94 % after 28 day
Result: readily biodegradable
Method: OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year: **GLP:**
Test substance:
Remark: DOC removal

(25)

Type: aerobic
Inoculum: other: preconditioned sludge
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 96 % after 28 day
Result: readily biodegradable
Method: OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year: **GLP:**
Test substance:
Remark: DOC removal

(25)

Type: aerobic
Inoculum: other: municipal activated sludge
Degradation: = 69 - 100 % after 28 day
Method: other: According to Directive 84/449/EEC, C.5 (Modified Sturm-Test)
Year: 1988 **GLP:** no
Test substance:
Remark: CO2-evolution
Concentration: 20-50 mg/l related to test substance
Degradation by fresh inoculum: 75-123% (range of 6 results from 6 different laboratories); degradation by preconditioned inoculum (aerated for 1 week): 69-99% (range of 8 results from 8 laboratories).

(26)

Type: aerobic
Inoculum: other: predominantly municipal activated sludge
Degradation: = 23 - 100 % after 28 day
Method: other: BOD-Test
Year: 1988 **GLP:** no
Test substance:
Remark: BOD of THOD
Concentration: 20-50 mg/l related to test substance
Degradation by fresh inoculum: 23-96% (range of 7 results from different laboratories); degradation by preconditioned inoculum (aerated for 1 week): 55-100% (range of 16 results from different laboratories).

(26)

Type: aerobic
Inoculum: other: predominantly municipal activated sludge
Degradation: = 43 - 92 % after 28 day
Method: other: Closed-Bottle-Test according to J.Blok
Year: 1988 **GLP:** no
Test substance:
Remark: BOD of THOD
Concentration: 20-50 mg/l related to test substance
Degradation by fresh inoculum: 43-89% (range of 4 results from different laboratories); degradation by preconditioned inoculum (aerated for 1 week): 52-92% (range of 4 results from different laboratories).

(26)

Type: aerobic
Inoculum: other: municipal activated sludge
Degradation: = 91 - 100 % after 28 day
Result: readily biodegradable
Method: other: Modified DOC Die Away Test
Year: 1988 **GLP:** no
Test substance:
Remark: Concentration: 20-50 mg/l related to test substance
Degradation by fresh inoculum: 97-100% (range of 13 results from different laboratories); degradation by preconditioned inoculum (aerated for 1 week): 91-112% (range of 19 results from different laboratories).
DOC

(26)

Type: aerobic
Inoculum: other: particulate fraction of G. oxydans (suboxydans) Strain SU
Method: other: Respirometric test (Warburg)
Year: **GLP:**
Test substance:
Remark: Oxygen uptake after 200 min.: 1.98 mole O2 uptake/mole substrate; presumed end product: adipic acid
Test condition: 30 deg C

(27)

Type: aerobic
Inoculum: other: secondary effluent from an activated sludge plant treating domestic sewage
Degradation: = 85 % after 22 day
Result: readily biodegradable
Method: other: Sealed Vessel Test
Year: **GLP:**
Test substance:
Remark: 2 to 10 mg/l of test substance as organic carbon
DOC reduction measured with CO2 production

(24)

Type: aerobic
Inoculum: activated sludge, non-adapted
Concentration: 400 mg/l
Degradation: > 90 % after 10 day
Result: readily biodegradable
Kinetic:
3 hour(s) = 6 - 9 %
1 day = 23 - 33 %
5 day = 94 - 98 %
7 day = 91 - 92 %
9 day = 97 %
Method: other: Zahn-Wellens test
Year: 1977 **GLP:** no
Test substance:
Remark: Concentration related to theoretical TOC.

(28)

Type:
Inoculum: other bacteria: effluent from municipal wastewater treatment plant
Degradation: = 25 - 100 % after 28 day
Method: other: Closed-Bottle-Test according to J.Blok
Year: **GLP:**
Test substance:
Remark: BOD of THOD
Concentration: 2-5 mg/l related to test substance
Degradation by fresh inoculum: 25-83% (range of 9 results from different laboratories); degradation by preconditioned inoculum (aerated for 1 week): 43-106% (range of 16 results from different laboratories).

(26)

3.6 BOD5, COD or BOD5/COD Ratio

Method: other: DEV (DIN), Weinheim 1982, Determination of BOD (H5)
Year: 1985 **GLP:** no

C O D

Method: other: DEV (DIN 38409/43), Weinheim 1982, Determination of COD
Year: 1985 **GLP:** no
COD: = 2180 mg/g substance

R A T I O B O D 5 / C O D

BOD5/COD: = .6

Remark: BOD5 =1312 mg/g

(29)

3.7 Bioaccumulation

Species: other
Exposure period:
Concentration:
BCF:
Elimination:
Method:
Year: **GLP:**
Test substance:
Remark: Based upon an estimated log Kow of -0.106, the BCF for 1,6-hexanediol can be estimated to be 0.5 from a recommended regression-derived equation. This estimated BCF indicates that bioconcentration in aquatic organisms is not important environmentally.

(18) (20)

Species:
Exposure period:
Concentration:
BCF:
Elimination:
Method: other: OECD Guideline 107 (log Pow)
Year: **GLP:**
Test substance:
Remark: Due to the water solubility and the measured log Pow of the compound (calculate log Pow = -0,92 to 0,198), the potential for bioaccumulation is low.

(21)

3.8 Additional Remarks

-

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC50: > 1000
Method: other: DIN 38412 part 15
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4

(30)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: 460
LC50: 460 - 1000
Method: other: closely following guideline of DIN 38412; Testverfahren mit Wasserorganismen Gruppe L, Teil 15
Year: 1982 **GLP:** no
Test substance: other TS
Test substance: hexane-1,6-diol, crude 65%, water content about 5%

(31)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: 2200
LC50: 4600 - 10000
Method: other: closely following guideline of DIN 38412; Testverfahren mit Wasserorganismen Gruppe L, Teil 15
Year: 1982 **GLP:** no
Test substance: no data
Test substance: hexane-1,6-diol flakes, no data on purity of the compound

(32)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: other aquatic arthropod: Daphnia magna Straus
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC0: = 500
EC50: > 500
EC100: > 500
Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year: 1988 **GLP:** no
Test substance:
Remark: Same results when exposure period = 24 h.

(33)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC10: = 810
EC50: = 2200
EC90 : = 5500
Method: other: Scenedesmus-growth inhibition test, DIN 38412/9
Year: 1989 **GLP:** no
Test substance:

(34)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC10: = 8400
EC50: > 10000
EC90 : > 10000
Method: other: According to "Pseudomonas-cell multiplication inhibition test, DIN 38412/8 (draft)"
Year: 1988 **GLP:** no
Test substance:

(35)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 18 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: = 5200
Method: other: Bringmann-Kuehn-Test (vgl. Z.Wasser Abwasser Forschung 10, 87-98, 1977)
Year: 1977 **GLP:** no
Test substance:
Remark: secondary quotation

(36)

Type: aquatic
Species: other bacteria: activated sludge, industrial
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 1000
EC10: > 1000
Method: ISO 8192 "Test for inhibition of oxygen consumption by activated sludge"
Year: 1985 **GLP:** no
Test substance:
Remark: 20% stimulation of respiration at 1000 mg/l.

(37)

Type:
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 205
Method: other: Microtox-Test
Year: **GLP:** no
Test substance:
Remark: unit: mg/l analogous to ppm

(38)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

-

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: other
Endpoint:
Exposure period:
Unit: Analytical monitoring:
Method:
Year: GLP:
Test substance:
Remark: no data are available

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

Type: other
Species:
Endpoint:
Exposure period:
Unit:
Method:
Year: GLP:
Test substance:
Remark: no data are available

4.6.2 Toxicity to Terrestrial Plants

Species:
Endpoint:
Expos. period:
Unit:
Method: other
Year: GLP:
Test substance:
Remark: no data are available

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

Species:
Endpoint:
Expos. period:
Unit:
Method: other
Year: **GLP:**
Test substance:
Remark: Testing of toxicity to terrestrial organisms is not indicated because entry of 1.6-Hexanediol into soil is not expected.

4.7 Biological Effects Monitoring

Remark: no data are available

4.8 Biotransformation and Kinetics

Type: other
Remark: no data are available

4.9 Additional Remarks

-

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: ca. 3000 mg/kg bw
Method: other: BASF-test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: approximate lethal dose (ALD50); 7-days observation period
(39)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 3730 mg/kg bw
Method: other: Smyth-Carpenter
Year: 1962 **GLP:** no
Test substance: no data
Test substance: hexane-1,6-diol, no data on purity of the compound
(40) (41)

Type: other
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value:
Method: other: BASF-test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Result: Three rabbits were given a single oral dose of 2000 mg/kg ofthe test substance. None of the rabbits died during the study (duration of test unspecified). Clinical signs of toxicity (disequilibrium, atonia and anorexia) were observedat the day of treatment and at the first day of the postexposure observation. Urinalysis on day 4 after treatment revealed pathologically altered urinary parameters(erythrocytes in the sediment) in 2 out of 3 rabbits.
(42)

Type: other
Species: cat
Sex:
Number of Animals:
Vehicle:
Value:
Method: other: BASF-test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Result: Two cats were given a single oral dose of 300 mg/kg and another 4 cats were given 1000 mg/kg of the test substance. Mortality was 0/2 and 2/4, respectively, in the 300 and 1000mg/kg dose groups. Clinical signs of toxicity (asynchronism,atonia, anorexia, salivation and emesis) were observed at the day of treatment and at the first days of the postexposure observation. Changes of blood and urinary parameters were observed.

(42)

5.1.2 Acute Inhalation Toxicity

Type: other: IRT
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 8 hour(s)
Value:
Method: other: BASF-test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: No mortality was observed when 6 rats were exposed for 8 hours to an atmosphere that had been saturated at 100 degrees centigrade with the volatile part of the compound.

(39)

Type: other: IRT
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 8 hour(s)
Value:
Method: other: Smyth-Carpenter
Year: 1962 **GLP:** no
Test substance: no data
Remark: No mortality was observed when rats were exposed for 8 hoursto an atmosphere that had been saturated at room temperaturewith the volatile part of the compound.
Test substance: hexane-1,6-diol, no data on purity of the compound

(40)

5.1.3 Acute Dermal Toxicity

Type:	LD50
Species:	rabbit
Sex:	
Number of Animals:	
Vehicle:	
Value:	> 2500 mg/kg bw
Method:	other: BASF-test
Year:	**GLP:** no
Test substance:	as prescribed by 1.1 - 1.4
Remark:	Five male and 5 female rabbits were applied a 50% aqueous preparation of the test substance under occlusive conditionsfor 24 h. The rabbits were observed for 8 days. No mortalityoccured at a dose of 2500 mg/kg (only one dose tested). Slight, reversible skin irritation was observed in one male and one female rabbit.

(43)

Type:	LD50
Species:	rabbit
Sex:	
Number of Animals:	
Vehicle:	
Value:	> 10000 mg/kg bw
Method:	other: Smyth-Carpenter
Year:	1962 **GLP:** no
Test substance:	no data
Test substance:	hexane-1,6-diol, no data on purity of the compound

(40) (41)

5.1.4 Acute Toxicity, other Routes

Type:	LD50
Species:	mouse
Sex:	
Number of Animals:	
Vehicle:	
Route of admin.:	i.p.
Value:	ca. 2300 mg/kg bw
Method:	other: BASF-test
Year:	**GLP:** no
Test substance:	as prescribed by 1.1 - 1.4
Remark:	approximate lethal dose (ALD50); 7-days observation period

(39)

Type:	LD50
Species:	mouse
Sex:	
Number of Animals:	
Vehicle:	
Route of admin.:	i.p.
Value:	= 1738 mg/kg bw
Method:	other: no data
Year:	**GLP:** no data
Test substance:	no data
Remark:	6-days observation period
Test substance:	hexane-1,6-diol, no data on purity of the compound

(44) (45)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species:	rabbit
Concentration:	
Exposure:	
Exposure Time:	
Number of Animals:	
PDII:	
Result:	not irritating
EC classificat.:	
Method:	other: BASF-test
Year:	**GLP:** no
Test substance:	as prescribed by 1.1 - 1.4
Result:	No irritation was observed after 1, 5, 15 min and after 20 h exposure of the rabbit skin with a 80% aqueous preparation of the test substance (occlusive, intact skin). Scoring was carried out 24 h and 8 d following treatment.

(39)

Species:	rabbit
Concentration:	
Exposure:	
Exposure Time:	
Number of Animals:	
PDII:	
Result:	not irritating
EC classificat.:	
Method:	other: Smyth-Carpenter
Year:	**GLP:** no
Test substance:	no data
Remark:	grade 2 on a 10-point-scale
Test substance:	hexane-1,6-diol, no data on purity of the compound

(40)

5.2.2 Eye Irritation

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: other: BASF-test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Result: Instillation of the undiluted test substance (50 mg) into the eye resulted in slight chemosis and slight corneal opacity after 1 h. Slight corneal opacity was still present after 24 h; no findings were recorded after 8 d.

(39)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: irritating
EC classificat.:
Method: other: Smyth-Carpenter
Year: **GLP:** no
Test substance: no data
Remark: grade 3 on a 10-point-scale
Test substance: hexane-1,6-diol, no data on purity of the compound

(40)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification: not sensitizing
Method: Directive 84/449/EEC, B.6 "Acute toxicity (skin sensitization)"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: In a preliminary test after two 24-h percutaneous occlusive applications within 96 hours the minimum irritant concentration was found to be a 50% test substance preparation in water and the maximum non-irritant concentration a 25% test substance preparation in water.

In the main study, 5 animals were used per control group andl0 animals were used in the treatment group. Intradermal induction was carried out with a 5% test substance solution;percutaneous induction was carried out one week after intradermal induction with a 50% test substance solution in water. Challenge treatment was done with a 25% solution (24 h) 21 days after intradermal induction and readings were performed 24 and 48 h after challenge-patch removal.

(46)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** no data
Strain: Sprague-Dawley
Route of admin.: drinking water
Exposure period: 12 weeks
Frequency of treatment: continuously in the drinking water
Post. obs. period: none
Doses: ca. 500 mg/kg/d (0.5% in drinking water)
Control Group: yes, concurrent no treatment
Method: other: no data
Year: **GLP:** no data
Test substance: no data
Result: The study was carried out to determine the molecular configuration of aliphatic hydrocarbons for the production of nervous system disease of a type characterized by giant axonal degeneration in the distal regions of long and large,central and peripheral nerve fibers (central-peripheral distal axonopathy). Tissues removed from the nervous system of six animals treated with 1,6-hexanediol were indistinguishable from those obtained

from control rats. 1,6-Hexanediol produced no signs of neurotoxicity.
By comparison, 2,5-hexanedione and 2,5-hexanediol caused weekness of hindlimbs and several degenerative changes of the distal part of large, long axons.

Test substance: hexane-1,6-diol, no data on purity of the compound

(47) (48)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: gavage
Exposure period: 28 days
Frequency of treatment: daily
Post. obs. period: none
Doses: 100, 400 or 1000 mg/kg/d
Control Group: yes, concurrent vehicle
NOAEL: = 1000 mg/kg bw
LOAEL: > 1000 mg/kg bw
Method: OECD Guide-line 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
Year: 1981 **GLP:** yes
Test substance: other TS
Remark: Five male and five female rats were used per group. Food consumption and body weight were determined weekly. The state of health was checked each day. During the weekly weighing the animals were subjected to an additional comprehensive clinical examination. Clinicochemical and hematological examinations and urinalyses were carried out toward the end of the treatment period. All rats were assessed by gross pathology, followed by histopathological examinations.
Result: There were no substantial substance-related effects concerning food consumption, body weight, body weight change, clinical, clinicochemical, gross pathological and histopathological observations.
The observed statistical significances for the values of body weight (-13% at 400 mg/kg/d) and body weight gain (-31 and -25%, respectively, at the 400 and 1000 mg/kg/d dose level) toward the end of the study in female rats are regarded as incidental, because of missing dose-response relationship. In parallel, the values for food consumption were also reduced, but without showing statistical significance. Furthermore, all these changes were within ranges of historical controls.

Thus, under the study conditions, the test substance at doses of 100, 400 or 1000 mg/kg/d caused no substance-related effects in rats.

Test substance: hexane-1,6-diol, purity 97%

(49)

Species:	rat **Sex:** male
Strain:	Sprague-Dawley
Route of admin.:	i.p.
Exposure period:	7, 15 or 24 days
Frequency of treatment:	daily
Post. obs. period:	none
Doses:	414 mg/kg/d
Control Group:	yes
Method:	other: no data
Year:	**GLP:** no data
Test substance:	no data
Result:	The study served to demonstrate neurotoxic effects of 2,5-hexanedione. 1,6-Hexanediol was maintained in parallel as non-neurotoxic substance for reasons of comparison. In comparison to the saline solution control group there was a slight drop in body weight, but no muscular weekness or changes of the protein phosphorylation in the nervous tissue as observed with 2,5-hexanedione was found.
Test substance:	hexane-1,6-diol, no data on purity of the compound

(50)

Species:	rat **Sex:** male
Strain:	Sprague-Dawley
Route of admin.:	i.p.
Exposure period:	24 days
Frequency of treatment:	daily
Post. obs. period:	none
Doses:	414 mg/kg/d
Control Group:	yes
Method:	other: no data
Year:	**GLP:** no data
Test substance:	no data
Result:	The effects of acrylamide, 2,5-hexanedione, 1,6-hexanediol and N,N'-methylene-bis-acrylamide on brain mitochondrial respiration were studied in vitro and in vivo. Rats treated with 1,6-hexanediol did not develop hindlimb weakness (as observed in rats treated with either acrylamide or 2,5-hexanedione) and gained weight comparable to the saline-treated control rats. Mitochondrial respiration parameters were neither affected by chronic daily administration (in vivo) nor by incubation with the test substance (in vitro).
Test substance:	hexane-1,6-diol, no data on purity of the compound

(51)

Species:	rat **Sex:** female
Strain:	Wistar
Route of admin.:	s.c.
Exposure period:	40 days
Frequency of treatment:	daily
Post. obs. period:	none
Doses:	207 mg/kg/d
Control Group:	yes
Method:	other: no data
Year:	**GLP:** no data
Test substance:	no data
Result:	The study was carried out to compare the effects of chronic treatment with 2,5-hexanedione and 1,6-hexanediol on activities of some brain and liver enzymes involved in glucose metabolism. Administration of 1,6-hexanediol did notaffect body weights, liver and brain weights. Food intake and liver glycogen content both were increased in rats treated with the test substance compared to the saline-control rats. The specific activities of brain and liver lactic dehydrogenase (LDH) and enolase, as well as of the mitochondrial enzyme malate dehydrogenase (MDH) were notaffected by either 2,5-hexanedione or 1,6-hexanediol treatment. In contrast, 2,5-hexanedione administration significantly reduced body weight and brain weight, whilst liver weights were unchanged; water intake was significantlyincreased.
Test substance:	hexane-1,6-diol, no data on purity of the compound

(52)

Species:	rabbit **Sex:** male/female
Strain:	no data
Route of admin.:	gavage
Exposure period:	up to 5 weeks (3-25 applications)
Frequency of treatment:	5 applications/week
Post. obs. period:	several weeks (no further data)
Doses:	50, 100, 500, 1000 or 2000 mg/kg
Control Group:	no data specified
Method:	other: BASF-test
Year:	**GLP:** no
Test substance:	as prescribed by 1.1 - 1.4
Result:	Three rabbits were used per dose group; some rabbits were survivors of a previous acute toxicity study. The animals were observed for clinical signs of toxicity, changes in body weight, urinary and blood parameters, liver and kidney function. The heart, lung, liver, kidney, adrenal, pancreas and spleen was evaluated histopathologically. Mortality was 1, 2 (after 3 and 5 applications), 2 (after 3 and 11 applications), 3 (after 5, 8 and 10 applications) and 2 (after 5 applications) out of 3 rabbits each in the 50, 100,500, 1000 and 2000 mg/kg dose group, respectively; the

lethality in the 50 mg/kg group was due to difficulties during gavage. Clinical signs of toxicity were atonia, apathy, disequilibrium, reduced reflexes, altered breathing and anorexia, primarily in the two highest dose groups; no clinical signs of toxicity were observed in the low-dose group. Granulocytosis and increased blood nitrogen was observed in some rabbits. Erythrocytes, leukocytes and epithelia were observed in the urine of rabbits at the 500, 1000 and 2000 mg/kg dose level. Urinary glucose was increased in 2/3 rabbits at the highest dose level. Liver damage (miliar necroses and necrobioses, karyopyknosis, and homogenization of cellular plasma) was observed in all animals that died during the study. This was explained by the authors with thromboses of small hepatic vessels, which were found in the histopathological examination. The capacity of the blood to clot is increased by one third, which is assumed as being responsible for this finding. Slight morpholcgical alterations (karyopyknosis, loss of plasma and glomerular nuclear proliferation) were observed in the kidneys.

(42)

Species: cat **Sex:** female
Strain: no data
Route of admin.: gavage
Exposure period: 5 weeks (25-26 applications)
Frequency of treatment: 5 applications/week
Post. obs. period: no data
Doses: 300 mg/kg
Control Group: no data specified
Method: other: BASF-test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Result: A total of 3 cats (survivors of a previous acute toxicity study) were used in the study. The cats were observed for clinical signs of toxicity, changes in body weights, urinaryand blood parameters, liver and kidney function. The heart, lung, liver, kidney, adrenal, pancreas and spleen were evaluated histopathologically. Two animals died after the study as a result of pneumonia. The thromboplastin time was reduced in another two cats treated 3-times with 500 mg/kg and one time with 300 mg/kg. Slight changes of urinary parameters (protein, leukocytes, epithelia) were observed. All other parameters were found within normal ranges.

(42)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration: 20, 100, 500, 2500, 5000 ug/plate
Metabolic activation: with and without
Result: negative
Method: OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year: 1983 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Standard plate test and preincubation test both with and without metabolic activation (Aroclor-induced rat liver S-9). No bacteriotoxicity was observed.
Test substance: hexane-1,6-diol, purity approximately 99%

(53)

Type: Cytogenetic assay
System of testing: Chinese hamster V79 cells
Concentration: 300, 600, 1200 ug/ml
Metabolic activation: with and without
Result: negative
Method: OECD Guide-line 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"
Year: 1983 **GLP:** yes
Test substance: other TS
Remark: Chromosomal aberration assay with and without metabolic activation (Aroclor-induced rat liver S-9). Chromosomes wereprepared 18 h (300, 600 ug/ml) or 28 h (1200 ug/ml) after test substance treatment, which lasted for about 4 hours. The tests were carried out in duplicate; 100 metaphases of each culture were analyzed for chromosome aberrations. The test substance did not cause any increase in the number of structural aberrant metaphases; an increase in the frequencyof cells containing numerical aberrations was not demonstrated. Therefore, the test substance was neither clastogenic (chromosome-damaging) nor aneugenic under the conditions of the study.
Test substance: hexane-1,6-diol flakes, purity 96.4%

(54)

Type:	HGPRT assay
System of testing:	Chinese hamster V79 cells
Concentration:	500, 1000, 2500 or 5000 ug/ml
Metabolic activation:	with and without
Result:	negative
Method:	OECD Guide-line 476 "Genetic Toxicology: In vitro Mammalian Cell Gene Mutation Tests"
Year:	1984 **GLP:** yes
Test substance:	other TS
Remark:	The study was performed in two independent experiments, using identical procedures (except treatment time), both with and without metabolic activation (Aroclor-induced rat liver S-9). In the first experiment (4-h treatment time), notoxicity was found, therefore the treatment time without metabolic activation in the second experiment was extended to 24 h.
Test substance:	hexane-1,6-diol flakes, purity 96.4%

(55)

5.6 Genetic Toxicity 'in Vivo'

-

5.7 Carcinogenicity

-

5.8 Toxicity to Reproduction

Type:	One generation study
Species:	rat **Sex:** male/female
Strain:	Wistar
Route of admin.:	gavage
Exposure Period:	throughout the whole study period (males: about 4 weeks; females: about 6 weeks)
Frequency of treatment:	daily
Premating Exposure Period	
male:	at least 14 days
female:	at least 14 days
Duration of test:	until day 4 post partum of F1 generation
Doses:	100, 400 or 1000 mg/kg/d
Control Group:	yes, concurrent vehicle
NOAEL Parental:	= 400 mg/kg bw
NOAEL F1 Offspr.:	= 1000 mg/kg bw
Method:	other: OECD guideline for testing of chemicals; method no. 421 (SIDS): reproduction/developmental toxicity screening test, revised draft document
Year:	1994 **GLP:** yes
Test substance:	other TS
Remark:	Ten male and ten female rats were used per group; the rats

were about 84 days old at the beginning of treatment. The test substance was administered to F0 rats by gavage once a day until the day before sacrifice. At least 14 days after the beginning of treatment, males and females from the same dose groups were mated at a ratio of 1:1; after the mating period, the male animals were sacrificed. The females were allowed to litter and rear their pups until day 4 post partum (p.p.). Thereafter, the pups (F1-generation) and the F0-females were sacrificed.
Parental animals were observed for food consumption, body weights, clinical signs of toxicity, male and female mating and fertility indices, gestation index, postimplantation loss and mortality; all F0 parentals were assessed by gross pathology. Histopathological studies were performed on all control and high dose F0 rats and on individual F0 rats at the mid and low dose level with special attention to reproductive organs. Offspring's number and status, viability/mortality, sex ratio, body weights, clinical observations were recorded. All pups were examined macroscopically at necropsy for external and visceral findings; skeletal examinations were carried out in low dosepups.

Result: The food consumption of F0 males at the 1000 mg/kg/d dose level was statistically significantly reduced during study weeks 0-1 and 3-4. The mean body weights of those F0 males were statistically significantly reduced at the end of the study (study week 4). The body weight gains of the high doseF0 males were statistically significantly lower compared to the control F0 males between test weeks 2-3 and over the total study period (test weeks 0-4). No substance-related effects on organ weights and no gross- and histopathologicalfindings were observed in F0 males and females; no substance- related effects were recorded in F0 male and female rats at the 400 and 100 mg/kg/d dose level and no substance-related adverse effects were observed in any of the F1 offspring.

Under the conditions of the study, the test substance produced marginal signs of parental toxicity in males at 1000 mg/kg/d; however, no signs for general toxicity were present in males at 400 and 100 mg/kg/d and in females at 1000, 400 and 100 mg/kg/d.
There were no signs for impairment of reproductive function of F0 rats and no signs of developmental toxicity in their offspring.
Therefore, the NOAEL for parental toxicity is 400 mg/kg/d for F0 males and 1000 mg/kg/d for F0 females; the NOAEL's for reproductive function and for developmental toxicity are1000 mg/kg/d.

Test substance: hexane-1,6-diol, purity 97%

(56)

5.9 Developmental Toxicity/Teratogenicity

-

5.10 Other Relevant Information

Type: Behaviour
Remark: The intoxication potency of several chemicals was determinedin male Sprague-Dawley rats by intraperitoneal injection of different doses of the compounds. The intoxication states were graded on a 7-point-scale. The dose necessary to produce a score of 3 (ED3) was 11.4 mmol/kg for hexane-1,6-diol. In this study, the score of 3 was defined as the presence of pronounced impairment of gait and motor incoordination but with the abdomen and pelvis still elevated.
Test substance: hexane-1,6-diol

(57) (58)

Type: Biochemical or cellular interactions
Remark: 1,6-Hexanediol did not inhibit the glyceroaldehyde-3-phosphate dehydrogenase activity of the nervous system in vitro as did, for example, the neurotoxic hexacarbon compound 2,5-hexanedione.
Test substance: hexane-1,6-diol

(59)

Type: Biochemical or cellular interactions
Remark: A series of homologous n-alkanols and n-alkanediols was tested for inhibition of K+ ion flux through a Ca2+ - activated K+ channel in rat glioma C6 cells. The introduction of an additional OH-group in n-hexanol, giving hexane-1,6-diol, reduced the membraneous IC50 (50% inhibitory concentration of ion flux) about 3.5-times which means that hexane-1,6-diol is 3.5-times more potent than n-hexanol. According to the authors, it seemed likely, that direct effects on protein are involved in the inhibitory action, rather than only lipid solubility criteria.
Test substance: hexane-1,6-diol

(60)

Type: Cytotoxicity
Remark: 1,6-Hexanediol in a concentration of 16 mM over 14 days or 4 or 8 mM over 60 days did not lead to cytotoxicity or aggregation of intermediary filaments in a human skin fibroblast culture.
Test substance: hexane-1,6-diol

(61)

Type: Metabolism
Result: Following oral administration to rabbits, 4 - 9% of the administered dose of 1,6-hexanediol was excreted as a glucuronide in the urine. Another urinary metabolite of the test substance was adipic acid, the product resulting from oxidation of both hydroxyl groups.
Test substance: hexane-1,6-diol

(62)

Type: Neurotoxicity
Remark: After local application to the nervous tissue 1,6-hexanediol causes no and 2,5-hexanedione causes changes of the neurofilaments and swelling of Schwann's cells. This correlates with the systemic neurotoxic effect of both substances.
Test substance: hexane-1,6-diol

(63)

Type: other
Remark: Sheeps and guinea pigs were used to measure the placental transfer index (PTI) after injection of various substances into the uterine artery. Water served as standard (PTI = 1). 1,6-Hexanediol was taken up to a low degree (PTI = 0.67 and 0.53, respectively, in guinea pigs and sheep); methanol and ethanol, however, were taken up to a higher degree (PTI > 1) into the fetal circulation system.
Test substance: (1,6-14C)1,6-hexanediol

(64)

Type: other: QSAR
Remark: title:
"Utility of the QSAR modelling system for predicting the toxicity of substances on the European inventory of existingcommercial chemicals"
Test substance: hexane-1,6-diol

(65)

Type: other: review

(66) (67) (68) (41) (69) (70)

5.11 Experience with Human Exposure

Remark: 1,6-hexandiol had no primary effect on intermediate filament distribution in human fibroblast cell cultures.

(71)

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7.1 Risk Assessment

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