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INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
 ENVIRONMENTAL HEALTH CRITERIA
 FOR
 1-PROPANOL
 Second Draft - 15 August 1987



**Programme international sur la Sécurité
des Substances Chimiques**

**Internal Technical Report
Rapport Technique Interne**



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International Labour Organization
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INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
ENVIRONMENTAL HEALTH CRITERIA

FOR

1-PROPANOL

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1. SUMMARY

1-Propanol is a colourless, highly flammable, volatile liquid at room temperature and normal atmospheric pressure. The annual world production in 1979 exceeded 130 000 tonnes. It is produced in nature by a variety of micro-organisms and plants. It occurs in fusel oils. The major use of 1-propanol is as a multi-purpose solvent in industry and in the home. Second in importance is its use as a chemical intermediate in the manufacture of a variety of chemical compounds.

The main pathway of entry of 1-propanol into the environment is through its emission into the atmosphere during production, handling, storage, transport, and use, and following waste disposal. Emissions into water and soil also occur. Because of the wide uses of the compound, it is difficult to estimate the emission into each compartment, but the total release into the environment may amount to over 75% of the production volume.

1-Propanol rapidly disappears from the atmosphere because of photochemical degradation and rain-out. It is readily biodegradable, both aerobically and anaerobically. Emission of the compound into surface water could therefore lead to oxygen depletion. Because of the rapid removal of 1-propanol from both air and water, measurable levels are not normally encountered. However, the compound has been detected in urban air, at waste-disposal sites, and also in leaching water from wells within a landfill.

Exposure of the general population may occur through accidental or intentional ingestion, through ingestion via food (containing 1-propanol as a natural or added flavour volatile or as a solvent residue) and alcoholic beverages, and through inhalation during use. Exposure of the general population via inhalation is negligible because of its rapid disappearance from ambient air. Workers are potentially exposed through inhalation during manufacture, processing, and use. However, no data on the extent of exposure of both the general population and workers were found and it is not possible to make a complete risk assessment.

1-Propanol is rapidly absorbed and distributed following ingestion. It is also rapidly eliminated. The possibility of dermal absorption cannot be neglected.

1-Propanol is partly converted to propionic acid mainly by liver alcohol dehydrogenase. Propionic acid is further oxidized through the citric acid cycle.

1-Propanol is practically non-toxic for aquatic organisms, insects, and plants. The toxic threshold for cell multiplication of one of the more sensitive phyla of aquatic species, the protozoa, was 38 - 568 mg/litre. Taking into account all the available data, it was concluded that 1-propanol does not pose a significant hazard for aquatic and terrestrial life, except in the case of accident or inappropriate disposal.

1-propanol is only slightly toxic or practically non-toxic for mammals (most oral LD₅₀ values reported for rats are above 1800 mg/kg body weight). At these lethal levels, rats showed liver and kidney injury and depression of the central nervous system. Single oral doses of 3000 or 6000 mg/kg body weight resulted in a reversible accumulation of triglycerides in the liver of rats. High vapour concentrations at approximately 30 000 mg/m³ caused sensory irritation in mice. Behavioural effects in mice and rats following a single oral dose have been observed at levels of 2000 mg/kg body weight or more. The threshold for these effects following intraperitoneal exposure was approximately 800 mg/kg body weight. The depression of the central nervous system induced by 1-propanol was shown to be related to interactions with neuronal membranes.

Human beings ingesting 1-propanol may experience symptoms at a dose of 20 ml. The major effect of acute overexposure is depression of the central nervous system. In adults, aqueous 1-propanol may be irritating to the hydrated skin. In a group of volunteers, the irritating action was totally blocked after pretreatment with an inhibitor of alcohol dehydrogenase. One report suggested local allergic reactions, but this has not been confirmed.

Data are insufficient to evaluate the possible irritating and sensitizing properties of 1-propanol, its effects on reproduction and the newborn, effects following long-term inhalation exposure, and carcinogenic effects.

An abstract of one teratogenicity study available to the Task Group was reported to show an increase in major malformations and embryoletality.

One study on small groups of Wistar rats, exposed throughout their lifetime to doses of 240 mg/kg body weight or to subcutaneous doses of 48 mg/kg body weight twice a week showed induction of a variety of tumours and of non-neoplastic liver lesions. The tumour incidences were low and were not analysed statistically. The incidences of the non-neoplastic lesions were not reported. As this study is considered inadequate and human data are not available, the carcinogenic risk of 1-propanol for man cannot be assessed. From the limited data available, there is no evidence of mutagenicity.

Data on the long-term oral exposure of human beings are not available. Two short-term drinking-water studies were reported in which groups of rats received

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WHO TASK GROUP MEETING ON ENVIRONMENTAL HEALTH CRITERIA FOR
1-PROPANOL

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Manger of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 988400 - 985850).

ENVIRONMENTAL HEALTH CRITERIA FOR 1-PROPANOL

A WHO Task Group on Environmental Health Criteria for 1-Propanol met ----- from ----- to ----- . Dr . . . ----- opened the meeting on behalf of the Director-General. The Task Group reviewed and revised the draft criteria document and made an evaluation of the health risks of exposure to 1-propanol.

The drafts of this document were prepared by DR T. VERMEIRE, NATIONAL INSTITUTE OF PUBLIC HEALTH AND ENVIRONMENTAL HYGIENE, BILTHOVEN, NETHERLANDS.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

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a daily dose of approximately 3000 mg/kg body weight for 4 months and 16 000 mg/kg body weight for up to 13 weeks, respectively. Both studies concentrated on liver pathology. At 3000 mg 1-propanol/kg body weight, no adverse effects were found. At 16 000 mg/kg body weight, the Wistar rats became weak, lost their appetites, and showed a decreased body weight and abnormal liver pathology. Taking 3000 mg/kg body weight per day as a no-observed-adverse-effect level (in spite of major defects in these studies), a tolerable dose for the long-term exposure of human beings to 1-propanol can be calculated to be 3 mg/kg body weight per day.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Chemical formula:	C ₃ H ₈ O
Chemical structure:	$\begin{array}{ccccccc} & & \text{H} & \text{H} & \text{H} & & \\ & & & & & & \\ \text{H} & - & \text{C} & - & \text{C} & - & \text{C} & - & \text{OH} \\ & & & & & & \\ & & \text{H} & \text{H} & \text{H} & & \end{array}$
Common name:	propyl alcohol
Abbreviation:	NPA
Common synonyms:	ethyl carbinol, 1-hydroxypropane, propanol, <i>n</i> -propanol (IUPAC name), propanol-1, propan-1-ol, <i>n</i> -propyl alcohol, 1-propyl alcohol, propylic alcohol
Common trade names:	Albacol, Optal, Osmosol extra, UN 1274
CAS chemical name:	1-propanol
CAS registry number:	71-23-8
RTECS registry number:	UH 8225000
Specifications:	commercial 1-propanol contains 99.0% or more of the compound and, as main impurities, water (F0.1% by weight), aldehydes (F0.2% by weight), ethanol (F10 mg/kg), and methanol (F100 mg/kg) (CEC, 1982).
Conversion factors:	1 ppm 1-propanol = 2.46 mg/m ³ air; and 1 mg 1-propanol/m ³ air = 0.41 ppm, at 25 °C and 101.3 kPa (760 mmHg).

2.2 Physical and Chemical Properties

1-Propanol is a highly flammable, volatile, colourless liquid at room temperature and normal atmospheric pressure. Its odour is described as alcohol-like, sweet, and pleasant (Hellman & Small, 1974). Continuous exposure can result in loss of sensitivity to the odour (olfactory adaptation) (Stone et al., 1972). The compound is completely miscible with water and with most organic solvents. It undergoes all chemical reactions typical of primary alcohols. 1-Propanol reacts violently with oxidizing agents.

Some physical and chemical data on 1-propanol are given in Table 1.

Table 1. Some physical and chemical properties of 1-propanol

Physical state	liquid
Colour	colourless
Relative molecular mass:	60.09
Odour perception threshold	< 0.07 - 100 mg/m ^{3a}
Odour recognition threshold	0.32 - 150 mg/m ^{3b}
Melting point (°C)	-127
Boiling point (°C)	97
Water solubility	infinite
log n-octanol/water partition coefficient	0.34 ^c
Specific density (20 °C)	0.804
Relative vapour density	2.07
Vapour pressure (20 °C)	1.9 kPa (14.5 mmHg)
Flash point (open cup)	25 °C
(closed cup)	15 °C
Flammability limits	2.1 - 13.5% by volume

^a From: May (1966); Corbit & Engen (1971); Oelert & Florian (1972); Stone et al. (1972); Dravnieks (1974); Hellman & Small (1974); Laing (1975); and Punter (1983).

^b From: May (1966) and Hellman & Small (1974).

^c Experimentally derived by Hansch & Anderson (1967).

2.3 Analytical Methods

A summary of methods for the determination of 1-propanol in air, water, and biota is presented in Table 2.

The sensitivity of the gas chromatographic determination of alcohols with electron capture or photoionization detection can be greatly improved by prior derivatization with pentafluorophenyldimethylsilyl chloride (Krull et al., 1984).

Ramsey & Flanagan (1982) reported a method for the detection and identification of 1-propanol and other volatile organic compounds in the headspace of blood, plasma, or serum, using gas chromatography with flame ionization and electron capture detection. The method is applicable to samples obtained from victims of poisoning, for which a high sensitivity is not desirable. After preincubation of the samples with a proteolytic enzyme, the method can be used for the analysis of tissues. Gas chromatographic methods, using flame ionization detection, are available for the determination of 1-propanol in milk and milk products (Palo & Ilkova, 1970), in alcoholic beverages (Horwitz, 1975; Goodman & Rao, 1984; Gelsomini, 1985; Preuss & Zipfel, 1985), in foodstuffs (Preuss & Zipfel, 1985), in food packaging (Eiceman & Karasek, 1981), in digestive contents, silage juices and microorganism growth cultures (Jouany, 1982), and in drug raw materials (Matsui et al., 1984). Methods for the identification of 1-propanol as flavour volatile have also been described (Table 4, section 5.2).

Table 2. Sampling, preparation, and analysis of 1-propanol

Medium	Sampling method	Analytical method	Detection limit	Sample size	Comments	Reference
air	sampling on charcoal, desorption by carbon disulfide	gas chromatography with flame ionization detection			suitable for personal and location monitoring	US NIOSH (1984)
air	sampling on charcoal, desorption by a 1:1 mixture of carbon disulfide and water	gas chromatography with flame ionization detection, packing by Oronite NIW on Carbo-pack B	0.25 mg/m ³	24 dm ³	suitable for location monitoring, applicable mixtures of both polar and non-polar solvents	Larywardt & Melcher (1979)
air	condensation, pre-concentration by microdistillation, purging by nitrogen, trapping on porous polymer, desorption by heating	gas chromatography with flame ionization detection, packing by Poropak QS and S	5×10^{-6} mg/m ³		suitable for analysis of oxygenated organic compounds in ambient air	Snider & Dawson (1985)
water	concentration by microdistillation, purging by nitrogen, trapping on porous polymer, desorption by heating	gas chromatography with flame ionization detection, packing by Poropak QS and S	0.0001 mg/litre	60 ml	suitable for analysis of oxygenated organic compounds in water	Snider & Dawson (1985)

Table 2 (contd).

water	direct injection	gas chromatography with flame ionization detection, packing by porous polymer Tenax GC	1 mg/litre	0.001 ml	suitable for analysis of a mixture of a wide variety of compounds	Kouth & Høglund (1984)
water	direct injection	gas chromatography with steam as carrier and flame ionization detection, packing by Chromosorb P AW modified with phosphoric acid	0.04 mg/litre	0.002 ml	suitable for analysis of a mixture of aliphatic compounds	Urano et al. (1981)
water	derivatization by 2-fluoro-1-methylpyridinium sulfonate in presence of tridodecyl amine	paper electrophoresis with detection by Dragendorff's reagent	40 mg/litre	0.1 ml	suitable for analysis of mixtures of primary and secondary alcohols, such as in alcoholic beverages	Bald & Mazurkiewicz (1980)
water	derivatization with 4-(6-methylbenzothiazol-2-yl)phenyl isocyanate in presence of triethylenediamine in xylene	TIC (silicagel G) or HPTLC (RP-18) or HPLC (Silicagel Si 60 or Li-Chrosorb RP-18) with fluorimetric detection	0.05 mg/litre (TLC)	0.005 ml		Wintersteiger et al. (1982)
water	direct application	spot test detection using 0.1% vanadium(V)-N-phenylbenzohydroxamate in alcohol-free chloroform	20 000 mg/litre		interference by other alcohols, phenols, cresols, dioxane, methylisobutyl ketone, acetone, reaction is immediate	Sahu & Tandon (1983)

Table 2 (contd).

Medium	Sampling method	Analytical method	Detection limit	Sample size	Comments	Reference
serum, urine	extraction by dichloromethane	gas chromatography with mass spectrometric detection, column was coated with Emulphor OM-870	0.002 mg/litre	1 ml	suitable for analysis of aliphatic alcohols	Liebich et al. (1982)
blood, urine, tissue	addition of potassium carbonate; headspace sampling	gas chromatography with flame ionization detection; split columns packed with polypropylene glycol on Chromosorb W NAW and SP1000 on Carbowpack, respectively	0.01 mg/litre	1.1 ml	whole blood is pre-treated with sodium fluoride or perchloric acid; the method is applicable to tissue after equilibration with water	Bonte et al. (1981c); Bilzer & Gruner (1983); Kuhnholz (1985)
blood	addition of sodium sulfate; headspace sampling	gas chromatography with flame ionization detection, split fused silica columns: DB 1701 and CP Sil 8 CB	< 0.01 mg/litre	0.1 ml		Wolf et al. (1985)

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural Occurrence

1-propanol occurs in fusel oils. It has been identified as a metabolic product of microorganisms and as a flavour volatile in foodstuffs (section 5) (Unruh & Spinelli, 1981). Other potential sources of atmospheric alcohols are photochemical reactions of hydrocarbons, combustion, and, perhaps, oceans (Snider & Dawson, 1985).

3.2 Man-Made Sources

3.2.1 *Production levels and processes*

The global production capacity for 1-propanol in 1979 exceeded 130 000 tonnes with most of this capacity in the USA (Unruh & Spinicelli, 1981) where it is produced by 3 companies. In 1975, the total production amounted to 57 000 tonnes, and 6600 tonnes were exported (SRI, 1984). In 1979, 85 000 tonnes were produced (Unruh & Spinicelli, 1981). The production in the countries of the European Economic Community was estimated at 5100 tonnes in 1979 and 3300 tonnes over the first 9 months of 1983. The imports from the USA rose from 4000 tonnes in 1979 to 8700 tonnes over the first 9 months of 1983 (Anon., 1984). 1-Propanol was not manufactured in eastern Europe or in the Far East in 1979, but one company in Japan was reported to produce this compound by Unruh & Spinicelli (1981).

1-Propanol is recovered commercially as a by-product of the high pressure synthesis of methanol from carbon monoxide and hydrogen (CEC, 1982). It is produced during the oxidation of propane-butane mixtures and during the reduction of propene-derived acrolein (Allinger et al., 1971; CEC, 1982). The compound can also be manufactured by the hydroformylation of ethene (reaction with carbon monoxide and hydrogen) to propionaldehyde, which is subsequently hydrogenated to 1-propanol (Unruh & Spinicelli, 1981). Earlier, 1-propanol was fractionally distilled from the fusel oils that form in the yeast fermentation process for the manufacture of ethanol (CEC, 1982).

3.2.2 *Uses*

The major use of 1-propanol is as a solvent. It is used as carrier and extraction solvent for natural products such as flavourings, vegetable oils, resins, waxes, and gums, and as a solvent for synthetic polymers, such as polyvinyl butyral, cellulose esters, lacquers, and PVC adhesives. Other solvent applications include the use of 1-propanol in the polymerization and spinning of acrylonitrile, in flexographic printing inks, and in the dyeing of wool. 1-propanol is used for both its solvent and antiseptic properties in drugs and cosmetics, such as lotions, soaps, and nail polishes. It is also used as a chemical intermediate, e.g., in the manufacture of propanal, 1-bromopropane, *O,O*-dipropyl phosphorodithioic acid, *n*-propyl amines, esters (propyl acetate, propyl carbamate), alcoholates, and xanthates.

Miscellaneous uses include the application of 1-propanol in degreasing agents, polishing compositions (window cleaners, flow polishes), brake fluid, as coupling and dispersing agent, and as ruminant feed supplement. It reportedly improves the water tolerance of motor fuels (Hawley, 1981; Unruh & Spinicelli, 1981; CEC, 1982; Verschueren, 1983).

3.2.3 *Waste disposal*

1-Propanol may enter the atmosphere, water, and/or soil following waste disposal (section 4.1). At landfill sites, 1-propanol has been identified in the air and leachates (section 5.1). Emission of 1-propanol via waste gases and waste water occurs in industry, and diffuse airborne emissions occur during the use of the compound (section 4.1).

1-Propanol can be removed from waste water by biodegradation (section 4.3.1). Activated carbon adsorption is not feasible, because the compound is poorly adsorbed (Giusti et al., 1974). Removal of the compound from waste water by reverse osmosis (hyperfiltration) may be successful, depending on the type of membrane. Cellulose acetate membranes yielded an average of 40% separation of 1-propanol (Duvel & Helfgott, 1975), while cross-linked polyethyleneimine membranes yielded 60 - 85% separation for a primary alcohol, such as ethanol (Fang & Chian, 1976). Ozonization of 1-propanol appears a too slow process to be of any significance for water treatment (Hoigne & Bader, 1983).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Transport and Distribution Between Media

In view of the physical properties and the use pattern of 1-propanol, it can be concluded that the main pathway of entry of this compound into the environment is through its emission into the atmosphere during production, handling, storage, transport, and use, and following waste disposal. Second in importance is its emission into water and soil. In the USA, industrial airborne emissions were estimated at 1.5% of the production in 1976, and 75% of the 1-propanol produced was estimated to be released into the atmosphere (Dorigan et al., 1976).

Inter-compartmental transfer of 1-propanol can occur between water, soil or waste, and air, and between soil or waste and water. Volatilization of the compound will be significant in view of its rather high vapour pressure. Transport of 1-propanol from the atmosphere to soil or water will occur via rain-out, as it is highly soluble in water. Data on the behaviour of 1-propanol in soil are scarce. With respect to adsorption, there is one study showing that the compound is poorly adsorbed on activated carbon (Giusti et al., 1974). Since 1-propanol is completely miscible with water, it can be expected to be very mobile in the soil. In studies using constant flow permeameters, the hydraulic conductivity of alcohols (methanol, ethanol, 2-propanol) in a completely dry natural clay was between 10^{-6} and 10^{-5} cm/second compared with 10^{-8} cm/second for that of the reference solution (0.01 N CaSO_4) at a void ratio of unity. The soil system became flocculated as the thickness of the double layer decreased. Permeation of water-saturated, compacted clay with water-soluble alcohols resulted in extensive removal of the pore water and an increase of up to 10-fold in hydraulic conductivity as a result of this flocculation. When subsequently the clay was permeated with simple water-insoluble aromatic compounds, the hydraulic conductivity increased 1000-fold above the alcohol values and 10 000-fold above the water values. Permeation of water-saturated, compacted clay by these aromatic compounds alone did not affect the hydraulic conductivity (Fernandez & Quigley, 1985).

4.2 Abiotic Degradation

Once in the atmosphere, 1-propanol is mainly degraded by hydroxyl radicals. It is not expected to react at significant rates with other reactive species

such as ozone, and hydroperoxy-, alkyl-, and alkoxy-radicals. Since the compound does not absorb ultraviolet radiation within the solar spectrum, photodegradation will not occur (Carter et al., 1979). Experimentally determined rate constants for the reaction between 1-propanol and hydroxyl radicals are 0.43×10^{-11} cm³/molecule per second at 19 °C (Campbell et al., 1976), and 0.54×10^{-11} cm³/molecule per second at 23 °C (Overend & Paraskevopoulos, 1978). Atmospheric residence times of 2.7 and 2.2 days, respectively, can be calculated on the basis of these rate constants (Cupitt, 1980). These short lifetimes will prevent migration of the chemical to the stratosphere.

The initial reaction products are α -hydroxyradicals. By analogy to the irradiation of ethanol in an NO_x-air atmosphere, these radicals are expected to react almost exclusively with oxygen, with hydrogen abstraction from the hydroxyl group to produce propionaldehyde (Carter et al., 1979).

Hydrolysis or light-induced degradation of 1-propanol in water cannot be expected. No data are available on abiotic degradation in soil.

4.3 Biotransformation

4.3.1 Biodegradation

The results of the determination of the biological oxygen demand (BOD) at 20 °C, of 1-propanol in various sources using dilution methods, are summarized in Table 3. Unless otherwise stated, they are expressed as percentage of the theoretical oxygen demand (ThOD), which is 2.40 g oxygen/g 1-propanol. The chemical oxygen demand (COD) was reported to be 91% of the ThOD (Price et al., 1974).

Gerhold & Malaney (1966) added 1-propanol to undiluted activated sludge and found an oxygen uptake of 37% of the ThOD in 24 h.

There are 2 reports on anaerobic biodegradation. Typical 1-propanol removal efficiencies for an anaerobic lagoon treatment facility with a retention time of 15 days were 77% and 81% after loading with concentrated wastes (Hovious et al., 1973). In closed bottle studies, 1-propanol was completely degraded anaerobically by an acetate enriched culture, derived from a seed of domestic sludge. The culture started to utilize cross-fed 1-propanol after 4 days at a rate of 110 mg/litre per day. In a mixed reactor with a 20-day retention time, seeded by the same culture, 41% removal was achieved after 70 - 90 days of acclimation to a final 1-propanol concentration of 10 000 mg/litre (Chou et al., 1978).

Table 3. BOD of 1-propanol

Dilution water	Source or seed	Adapta- tion (+/-)	BOD _x ^a	Value (%)	Reference
Fresh	domestic waste water	-	BOD	64	Price et al. (1974)
		-	BOD	75	
	domestic waste water	-	BOD	93	Wagner (1976)
	synthetic waste water	-	BOD	97	Wagner (1976)
	activated sludge	+	BOD	99 & COD ^b	Pitter (1976)
Salt	domestic waste water	-	BOD	43	Price et al. (1974)
		-	BOD	91	

^a BOD - biological oxygen demand after x days of incubation.

^b Expressed as percentage of the COD; the rate of biodegradation was 71 mg COD/g of dry inoculum/h.

4.3.2 Bioaccumulation

1-Propanol is completely miscible with water. Its log *n*-octanol/water partition coefficient is 0.34 (Hansch & Leo, 1967). A bioconcentration factor of 0.7 can be calculated using the formula of Veith & Kosian (1983). In addition, the compound is biodegradable. In view of these data, no bioaccumulation is expected.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental Levels

There are very few data indicating that 1-propanol is present in the ambient air or in water. This is probably a reflection of its rapid chemical and physical removal from these compartments (section 4.2). No data are available on the occurrence of the compound in soil.

In 11 samples of air from a city in the USA in 1982, the average concentration of 1-propanol was 0.00005 mg/m³, while the compound was not detected in 18 rural samples (Snider & Dawson, 1985). In Denmark, 0.15 mg 1-propanol/m³ air was measured in the headspace over building materials (Beall & Ulsamer, 1981).

1-Propanol at a concentration of 73 mg/m³ was detected in the air beneath the surface of 1 out of 6 land-fill sites sampled in the United Kingdom. The site was used for the disposal of domestic waste. In general, alcohols were the most abundant groups of compounds present in the air (Young & Parker, 1983). 1-Propanol was also detected in the leachate from 2 sanitary land-fill sites in the USA. This would, at least partly, have originated from the anaerobic degradation of organic compounds by microorganisms (Burrows & Rowe, 1975; Khare & Dondero, 1977). 1-Propanol was identified as a metabolic product of rotten blue-green algae (Yasuhara & Fuwa, 1982), fish spoilage bacteria (Ahamed & Matches, 1983), and *Kluyveromyces lactis* yeast (Hanssen et al., 1984). The compound was measured in fresh swine manure (Yasuhara et al., 1984).

5.2 General Population Exposure

1-Propanol was detected in drinking-water samples in the USA at a concentration of 0.001 mg/litre (Scheiman et al., 1974).

When 1-propanol is used as an extraction or carrier solvent for food constituents, the compound may be found in the final product. However, no data are available to support this statement.

Alcoholic beverages nearly always contain 1-propanol as a product of fermentation. Beer contains up to 195 mg/litre (Bonte, 1978), wine up to 116 mg/litre (Bonte, 1979), and various types of spirit, up to 3520 mg/litre (Murphree et al., 1967), and pure ethanol, up to 2910 mg/litre (Beaud & Ramuz, 1978; Bonte et al., 1978; Postel & Adam, 1978; Otsuka et al., 1979; Tandoi et al., 1984; Preuss & Zipfel, 1985).

Analytical data summarized in Table 4 show the presence of low levels of 1-propanol as a flavour volatile in a variety of foodstuffs and non-alcoholic drinks. In all the reports, the volatiles were identified by gas chromatography with flame ionization and/or flame photometric and/or mass spectrometric detection. According to Stoffberg & Grundschober (1984), most of the 1-propanol that they found in the foodstuffs and drinks (Table 4) was of natural origin, i.e., not added. In the USA, the total annual amounts of 1-propanol consumed as a flavour volatile in tomatoes, white bread, Cheddar and Swiss cheese combined, apple juice, apples, and butter were estimated to be 12.7, 9.7, 7.1, 5.7, 4.8, and 0.014 tonnes, respectively.

Table 4. 1-Propanol as a flavour volatile in foodstuffs and non-alcoholic drinks

Foodstuff/drink		Reference
Common name	Scientific name	
Kefir culture		Palo & Ilkova (1970)
Cream culture		Palo & Ilkova (1970)
Filberts (roasted)	<i>Corylus avellana</i>	Kinlin et al. (1972)
Raw milk		Jaddou et al. (1978)
Heat-treated milk		Jaddou et al. (1978)
Kumazasa	<i>Sasa albo-marginata</i>	Nguyen & Kato (1982)
Deep-fat-fried triolein		May et al. (1983)
Boiled buckwheat flour	<i>Fagopyrum esculentum</i> Moench	Yajima et al. (1983)
Ripe tomato, tomato juice, puree, and paste	<i>Lycopersicon esculentum</i>	Chung et al. (1983)
Kogyoku apple		Yajima et al. (1984)
Apple and apple juice		Stoffberg & Grundschober (1984)
Tomato	<i>Lycopersicon esculentum</i>	Stoffberg & Grundschober (1984)
White bread		Stoffberg & Grundschober (1984)
Butter		Stoffberg & Grundschober (1984)
Cheddar/Swiss cheese		Stoffberg & Grundschober (1984)
Swiss Gruyere cheese		Bosset & Liardon (1984)
Soy sauce (Shoyu)		Nunomura et al. (1984)
Fish sauce (Patis)		Sanceda et al. (1984)
Pigweed	<i>Amaranthus retroflexus</i>	Flath et al. (1984)
Winged bean (raw/roasted)	<i>Psophocarpus tetragonalobus</i>	Del Rosario et al. (1984)
Soybean (raw, roasted)	<i>Glycine max</i>	Del Rosario et al. (1984)
Potato tuber	<i>Solanum tuberosum</i>	Waterer & Pritchard (1985a,b)
Roasted watermelon seeds	<i>Citrullus colocynthis</i>	Soliman et al. (1985)
Babaco fruit	<i>Carica pentagona</i> Heilborn	Shaw et al. (1985)
Tilsit cheese		Ney (1985)
Endive	<i>Cichorium endivia</i>	Gotz-Schmidt & Schreier (1986)

5.3 Occupational Exposure

Workers are potentially exposed to 1-propanol during the production of the compound itself or its derivatives, or during its use in solvent-type applications. No data are available on levels of exposure.

6. KINETICS AND METABOLISM

6.1 Absorption

6.1.1 *Animals*

Data on absorption following inhalation or dermal exposure are not available.

Oral exposure of Wistar rats to one dose of 3004 mg 1-propanol/kg body weight in water resulted in a maximum blood concentration of 1860 mg 1-propanol/litre, 1.5 h after exposure (Beaugé et al., 1979).

In rabbits receiving single intraperitoneal doses of 800, 1200, or 1600 mg 1-propanol/kg body weight in saline, maximum blood concentrations, attained within 0.5 h, were proportional to the exposure levels (Oerskov, 1950).

In one study on anaesthetized mongrel dogs, it was shown that 1-propanol, as well as other primary alcohols, could increase the permeability of the blood-brain barrier. The dogs received a sodium fluorescein solution and 0.578 mg 1-propanol in saline, intravenously. The concentration of sodium fluorescein in the cerebrospinal fluid rose to a maximum within 10 min and returned to control levels, 3 h after exposure (Gulati et al., 1985).

6.1.2 *Human beings*

Ten human volunteers drank 1-propanol in ethanolic orange juice at doses of 3.75 mg 1-propanol and 1200 mg ethanol/kg body weight over a period of 2 h. At the end of this period, the average peak blood concentration of 1-propanol was 0.85 mg/litre. When the blood was analysed after incubation with aryl sulfatase (EC 3.1.6.1), an average peak concentration of 0.92 mg/litre was measured, just after exposure (Bonte et al., 1981a).

6.1.3 *Kinetics*

6.1.3.1 *Animals*

Available *in vivo* data, reviewed by Rietbrock & Abshagen (1971), showed that the elimination of 1-propanol appeared independent of the dose above a single oral dose of 1000 mg/kg body weight in rats and above a single

intraperitoneal dose of 1200 mg/kg body weight in rabbits (Oerskov, 1950; Abshagen & Rietbrock, 1970; Beaugé et al., 1979). The rate of the zero-order elimination of the compound from the blood of rats administered one dose of 3000 mg/kg body weight, was found to be 510 mg/kg body weight per h (Beaugé et al., 1979). At lower doses, the elimination curve was exponential. When rats were given a single dose of 1000 mg/kg body weight, the half-life of 1-propanol was 45 min (Abshagen & Rietbrock, 1970). In mice, a half-life of 57 min was estimated for the exponential elimination phase (Maickel & Nash, 1985).

In vitro, the elimination of 1-propanol from the perfusate of rat liver was also shown to be saturable, a zero-order phase being succeeded below a concentration of 78 mg/litre by an exponential phase with a half-life of 14 min (Auty & Branch, 1976).

6.1.3.2 *Human beings*

In groups of 14 and 18 human volunteers, ingesting doses of 2.53 and 0.5 mg 1-propanol/kg body weight, respectively, in ethanolic drinks (section 6.2.2), the elimination of 1-propanol was apparently linear with rates of 0.45 and 0.1 mg/kg body weight per h, respectively. However, it was noted that the elimination curve was very slightly bent (Bilzer & Penners, 1985; Bilzer et al., 1985).

6.2 Distribution

6.2.1 *Animals*

As expected for a compound with high water solubility, 1-propanol is rapidly distributed throughout the body. Abshagen & Rietbrock (1970) administered one oral dose of 1000 mg/kg body weight to Wistar rats and calculated an apparent distribution volume of 98%. In their review of earlier data, they reported apparent distribution volumes of 78% for dogs and 74 and 95% for rabbits (Rietbrock & Abshagen, 1971).

6.2.2 *Human beings*

In one group of 18 volunteers, drinking whisky containing alcohols at doses of 0.5 mg 1-propanol, 1000 mg ethanol, and 1.1 mg isobutanol/kg body weight for 1 h, the average apparent distribution volume of 1-propanol was calculated

to be 62% (Bilzer & Penners, 1985). In another group of 14 volunteers, drinking rum-cola containing alcohols at doses of 2.53 mg 1-propanol, 650 mg ethanol, and 0.29 mg isobutanol/kg body weight for 15 min, the average apparent distribution volume was calculated to be 113% (Bilzer et al., 1985).

1-Propanol was shown *in vitro* to bind to human α -foetoprotein with a higher affinity than methanol or ethanol, which is in accordance with its higher hydrophobicity (Hirano et al., 1985).

6.3 Metabolic Transformation

6.3.1 *Animals*

When rabbits received 1-propanol in saline intraperitoneally at single doses of 800 - 1600 mg/kg body weight, peak concentrations of toluene-extractable acids or ether-soluble acids (which were only partly toluene-extractable) were found in serum at 1 h after exposure. The toluene-extractable acids appeared to be propionic acid. The ether-extractable acids that were not toluene extractable were presumed to be lactic acid (Oerskov, 1950). Apparently, 1-propanol is oxidized via propionaldehyde to propionic acid. Propionic acid can be converted into succinyl-CoA via subsequently activation by Coenzyme A, carboxylation to methylmalonyl-CoA, and transcarboxylation. Succinyl-CoA is oxidized through the citric acid cycle (Rietbrock & Abshagen, 1971).

The extent of the metabolic pathway described above has not been established. Evidence for a minor metabolic pathway was found in rabbits. Of the total dose of 1-propanol (800 mg/kg body weight), 0.9% was found in the urine as β -propyl-glucuronide (Kamil et al., 1953).

Sufficient evidence is available that 1-propanol is oxidized to propionic acid, mainly by the non-specific cytosolic enzyme alcohol dehydrogenase (ADH) (EC 1.1.1.1). 1-Propanol inhibited the elimination of 2-propanol and ethanol, compounds that are also oxidized mainly through ADH. 1-Propanol seems to be a better substrate for ADH than ethanol and 2-propanol. This is confirmed by the enzyme kinetics data: the value of the Michaelis-Menten constant K_m of ADH, purified from rat or dog liver *in situ* or from horse or human liver, with 1-propanol as substrate, is lower than that with ethanol or 2-propanol as substrate (Dalziel & Dickinson, 1966; Auty & Branch, 1976; Goresky et al. 1983). For example: the K_m of purified horse liver ADH at pH 7 and a temperature of 23.5 °C was 0.061 mmol, using 1-propanol as substrate, 0.18 mmol, using ethanol as substrate, and 12.6 mmol, using 2-propanol as a substrate (Dalziel & Dickinson, 1966).

It has been shown *in vitro* that rat and rabbit liver microsomal oxidases (EC 1.14.14.1) are also capable of oxidizing 1-propanol to propionaldehyde. The compound did not prove to be an effective substrate for the peroxidative activity of catalase (EC 1.11.1.6) (Teschke et al., 1975; Morgan et al., 1982).

6.3.2 *Human beings*

When 10 volunteers drank 1-propanol in ethanolic orange juice at doses of 3.75 mg 1-propanol and 1200 mg ethanol/kg body weight for 2 h, the compound was detected in the blood, partly as sulfate (section 6.1.2), and in the urine, partly as glucuronide. The total urinary excretion of 1-propanol was 2.1% of the dose. The urinary levels of 1-propanol were lower when the amount of simultaneously ingested ethanol was less, showing competition for ADH between 1-propanol and the ethanol overdose (Bonte et al., 1981a,b).

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

7.1 Aquatic Organisms

A summary of acute aquatic toxicity data is presented in Table 5. In none of these studies was the concentration of 1-propanol reported to be measured. In view of the volatility of the compound, it can be expected that the toxic effects observed in the open-system studies occurred at lower concentrations than the nominal ones.

Several short-term studies have also been conducted. Seiler et al. (1984) determined the breakpoint of bioinhibition for a total of 20 strains of several bacterial groups prevalent in a waste-water treatment plant in the chemical industry, i.e., *Zoogloea*, *Alcaligenes*, and *Pseudomonas*. After one week of static exposure to 1-propanol in an open system at 30 °C, 100% growth inhibition occurred at concentrations of 10 000 - 30 000 mg/litre of medium. No analysis for the compound was reported.

The cell multiplication of blue algae (*Microcystis aeruginosa*) and green algae (*Scenedesmus quadricauda*) was just inhibited after 8 days of static exposure in a closed system at 27 °C and a pH of 7 to 255 and 3100 mg/litre water, respectively, (Bringmann, 1975; Bringmann & Kuhn, 1977).

7.2 Terrestrial Organisms

7.2.1 *Insects*

The toxicity of 1-propanol for insect larvae is summarized in Table 5. In static tests, the 48-h LC₅₀ values for adults of the fruit fly strains *Drosophila melanogaster* and *Drosophila simulans* were between 18 490 and 24 120 mg/litre of medium and 11 260 and 12 860 mg/litre of medium, respectively (David & Bocquet, 1976).

7.2.2 *Plants*

The effects of 1-propanol on the rate of seed germination have been investigated on several occasions. Total inhibition of the germination of barley grains was reached after incubation for 4 days at 18 °C on filter papers soaked in a solution containing 8050 mg 1-propanol/litre water (Chvapil et al., 1962). The germination of white amaranth (*Amaranthus albus*) seeds was

Table 5. Acute aquatic toxicity of 1-propanol

Organism	Temperature (°C)	pH	Dissolved Oxygen (mg/litre)	Hardness (mg CaCO ₃ /litre)	Stat./Exposure flow; sure open/period closed ^b	Parameter	Concentration (mg/litre)	Reference
Freshwater								
<u>Bacteria</u> <u>Pseudomonas putida</u>	25	7			stat. 16 h closed	TP ^b	2700	Bringmann & Kühn (1977)
<u>Microorganisms</u> Activated sludge	21	7.4-8			stat. 3 h closed	50% inhibition of respiration	> 1000	Klecka & Landi (1985)
Acclimated mixed waste-water culture	30	6.8			stat. 1.2 h closed	50% inhibition of respiration	19 085	Vaishnav & Iopas (1985)
<u>Protozoa</u> <u>Entosiphon sulcatum</u>	25	6.9			stat. 72 h closed	TP ^b	38	Bringmann (1978)
<u>Chilomonas paramecium</u>	20	6.9			stat. 48 h closed	TP ^b	175	Bringmann et al. (1980)
<u>Uronema parduizi</u>	25	6.9			stat. 20 h closed	TP ^b	568	Bringmann & Kühn (1980)
<u>Algae</u> <u>Selenastrum capricornutum</u>	25-26				stat. 96 h closed	NOAEC	2000	Slooff et al. (1983)
<u>Scenedesmus pannonicus</u>	25-26				stat. 48 h closed	NOAEC	2900	Slooff et al. (1983)
<u>Chlorella pyrenoidosa</u>	25-26				stat. 48 h closed	NOAEC	1150	Slooff et al. (1983)

Table 5 (contd).

<u>Coelenterate</u>									
<u>Hydra oligactis</u>	17	8.2-8.4	≥ 5	stat. closed	48 h	LC50	6800	Slooff (1983)	
<u>Worms</u>									
<u>Flatworm (Dugesia)</u>	20	8.2-8.4	≥ 5	stat. closed	48 h	LC50	4700	Slooff (1983)	
<u>Tubificid worm (Tubificidae)</u>	20	8.2-8.4	≥ 5	stat. closed	48 h	LC50	9200	Slooff (1983)	
<u>Molluscs</u>									
<u>Giant pond snail (Lymnaea stagnalis)</u>	20	8.2-8.4	≥ 5	stat. closed	48 h	LC50	6500	Slooff (1983)	
<u>Crustacea</u>									
<u>Water flea (Daphnia magna)</u>	20	8	≥ 2	stat. open	24 h	EC50 ^d EC0 EC100 LC50	4415 3336 5909 7080	Bringmann & Kühn (1977) Canton & Adema (1978) ^e Canton & Adema (1978) ^e Canton & Adema (1978) ^e	
<u>Water flea (Daphnia cucullata)</u>	19			stat. open	48 h	LC50	5820	Slooff (1983)	
<u>Isopod (Asellus aquaticus)</u>	20	8.2-8.4	≥ 5	stat. closed	48 h	LC50	2500	Slooff (1983)	
<u>Scud (Gammarus pulex)</u>	20	8.2-8.4	≥ 5	stat. closed	48 h	LC50	1000	Slooff (1983)	
<u>Insects</u>									
<u>Mosquito larvae (Aedes aegypti)</u>	22-24			stat. open	4 h	LC50	10 450	Kramer et al. (1983)	
<u>Mosquito larvae (Aedes aegypti, Culex pipiens)</u>	26	8.2-8.4	≥ 5	stat. open	48 h	LC50 LC0	4400, 4800 3200, 3600	Slooff et al. (1983)	
<u>Nidge larvae (Chironomus gr. thummi)</u>	20	8.2-8.4	≥ 5	stat. closed	48 h	LC50	2350	Slooff (1983)	
<u>Leech larvae (Erodella octoculata)</u>	20	8.2-8.4	≥ 5	stat. closed	48 h	LC50	1400	Slooff (1983)	

Table 5 (contd).

Organism	Temperature (°C)	pH	Dissolved oxygen (mg/litre)	Hardness (mg CaCO ₃ /litre)	Stat./flow; open/closed ^a	Exposure period	Parameter	Concentration (mg/litre)	Reference
Dragon fly larvae (<i>Ischnura elegans</i>)	20	8.2-8.4	≥ 5	209	stat. closed	48 h	LC ₅₀	4200	Slooff (1983)
Stonefly larvae (<i>Nemoura cinerea</i>)	20	8.2-8.4	≥ 5	209	stat. closed	48 h	LC ₅₀	1520	Slooff (1983)
Mayfly larvae (<i>Cloeon dipterum</i>)	20	8.2-8.4	≥ 5	209	stat. closed	48 h	LC ₅₀	3110	Slooff (1983)
<i>Corixa punctata</i> (larvae)	20	8.2-8.4	≥ 5	209	stat. closed	48 h	LC ₅₀	2000	Slooff (1983)
Fish									
Creek chub (<i>Semotilus atromaculatus</i>)	15-21	8.3		98	stat. open	24 h	LC ₀	200	Gillette et al. (1952)
Golden orfe (<i>Leuciscus idus melanotus</i>)	20	7-8	≥ 5	200-300	stat.	48 h	LC ₅₀ LC ₀	4320, 4560 3600, 4000	Juhnke & Lüdemann (1978)
Fathead minnow (<i>Pimephales promelas</i>)	20	8.2-8.4	≥ 5	209	stat. open	48 h	LC ₅₀ LC ₀	5000 2600	Slooff et al. (1983)
Rainbow trout (<i>Salmo gairdneri</i>)	15	7-8	≥ 5	98	stat. open	48 h	LC ₅₀ LC ₀	3200 2000	Slooff et al. (1983)
Packy fish (<i>Oryzias latipes</i>)	24	8.2-8.4	≥ 5	209	stat. open	48 h	LC ₅₀ LC ₀	5900 4400	Slooff et al. (1983)
Amphibia									
South African clawed toad (<i>Xenopus laevis</i>)	20	8.2-8.4	≥ 5	209	stat. open	48 h	LC ₅₀	4000	Slooff & Baerselman (1980)
Mexican axolotl (<i>Ambystoma mexicanum</i>)	20	8.2-8.4	≥ 5	209	stat. open	48 h	LC ₅₀	4000	Slooff & Baerselman (1980)

Table 5 (contd).

Sea water						
<u>Bacteria</u>						
Photobacterium	15		stat. 15 min	50% light reduction	8686	Hermens et al. (1985)
phosphoreum	15		closed			
			stat. 5 min	50% light reduction	17 700	De Zwart & Slooff (1983)
			closed		18 400	
<u>Crustacea</u>						
Brine shrimp	24		stat. 24 h	LC50	4200	Price et al. (1974) ^f
(Artemia salina)			open			
Harpacticoid copepod	21	7.9	stat. 96 h	LC50	2300	Bengtsson et al. (1984) ^g
(Nitocra spinipes)		≥ 5				
<u>Fish</u>						
Bleak (Alburnus alburnus)	10	7.9	stat. 96 h	LC50	3800	Bengtsson et al. (1984) ^g
		≥ 5	open			

a Static or flow-through test, open or closed system.

b TT = toxic threshold for inhibition of cell multiplication.

c NOAEC = no-observed-adverse-effect-level; effect is growth inhibition.

d Effect is complete immobilization.

e Age of Daphnia was ≤ 24 h for Daphnia magna and Daphnia pulex, and 1 ± days or Daphnia cucullata.

f Salinity was 2.8‰.

g Salinity was 0.7‰.

stimulated in a dose-related manner after 5 h of incubation at 25 °C on filter papers, soaked in a solution containing 3600 - 36 050 mg 1-propanol/litre water (Chadoeuf-Hannel & Taylorson, 1985). Reynolds (1977) measured 50% inhibition of germination of lettuce (*Lactuca sativa*) seeds after incubation for 3 days at 30 °C, on agar containing 3065 mg 1-propanol/litre. The percentage germination and the axis length of soya bean (*Glycine max*) seeds, with the testa removed, were not reduced after exposure to pure 1-propanol for 2 h. After treatment with a 50% (v/v) 1-propanol/water mixture for 2 min, germination was completely inhibited and axis lengths were reduced by 75% (Priestley & Leopold, 1980).

1-Propanol was marginally effective in breaking the dormancy of seeds of genetically pure dormant lines of wild oat (*Avena fatua*) after 5 days of exposure to solutions containing up to 1202 mg/litre. Seed viability was affected at higher concentrations (Adkins et al., 1984).

In excised seedling roots of maize (*Zea mays*), treated by vacuum infiltration in a 5% solution of 1-propanol in water 3 times for 60 seconds and then incubated anaerobically at 28 °C, 1-propanol increased nitrite accumulation by 10 times or more, increased the utilization of nitrate, and inhibited the utilization of exogenous nitrite. These effects were enhanced under aerobic conditions, (Gray & Cresswell, 1983). Dry et al. (1981) observed that stimulation of nitrite accumulation in pea and wheat roots under aerobic conditions was accompanied by a decline in the cellular levels of glucose-6-phosphate. Gray & Cresswell (1983) suggested that an increase in membrane permeability influenced nitrite utilization and led to increased access of nitrate to the site of an unaffected nitrate reduction.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single Exposures

8.1.1 *Acute exposures*

The available acute mortality data is summarized in Table 6. Except where otherwise indicated, 1-propanol was administered undiluted.

When rats were exposed to 1-propanol vapour for 4 h at a concentration of approximately 9840 mg/m³, 2 out of 6 rats died within 14 days (Smyth et al., 1954).

8.1.2 *Systemic effects*

Osborne-Mendel or Sherman rats of both sexes receiving a lethal oral dose of undiluted 1-propanol became comatose within a few minutes and showed decreased body weights after death (Taylor et al., 1964). Rats of unspecified strain and of both sexes, killed by a single dose between 150 and 3000 mg undiluted 1-propanol/kg body weight, showed hyperaemia, vacuolation and dilated sinusoids in the liver, and hyperaemia, tubular cloudy swelling, and tubular necrosis in the kidneys. At the higher doses, the rats died within 24 h, showing hyperaemia in all organs (Purchase, 1969).

The potency of 1-propanol as a sensory irritant was investigated using a 50% reflex decrease in the respiratory rate of mice (RD₅₀) as an index. Only the heads of the mice were exposed. An exposure-related effect was found with a RD₅₀ value of 31 252 mg/m³ for Swiss Webster mice. 1-Propanol was more potent as a sensory irritant than the lower alcohols and 2-propanol (Kane et al., 1980).

1-Propanol can enter the trachea and deeper lung structures by aspiration from the oral and nasal cavities. Anaesthetized Sprague Dawley rats were made to aspire 160 mg of the undiluted compound. Survivors were sacrificed 24 h later for lung examinations. All 9 exposed rats died within 165 min, 6 of them dying immediately from respiratory arrest. All controls survived. It was not described whether the latter were sham-exposed or not. The average absolute lung weight of the exposed rats was increased by 92%. The lungs showed small areas of focal haemorrhage and oedema (Gerarde et al., 1966).

Table 6. Acute effects of 1-propanol

Species	Sex	Route of exposure	Observation period	ID ₅₀ (mg/kg body weight)	Comments	Reference
Wistar rat	male	intravenous	5 days	590	vehicle: water	Tichy et al. (1985)
H mouse	male	intravenous	5 days	697	vehicle: water	Tichy et al. (1985)
Chinchilla rabbit	female	intravenous	not reported	1090	vehicle: water	Chvapil et al. (1962)
	male, female	intravenous	5 days	483	vehicle: water	Tichy et al. (1985)
Wistar rat	male	intrapertitoneal	5 days	2247	vehicle: water	Tichy et al. (1985)
H mouse	male	intrapertitoneal	5 days	3695	vehicle: water	Tichy et al. (1985)
Syrian hamster	male	intrapertitoneal	5 days	2337	vehicle: water	Tichy et al. (1985)
Gulnea-pig		intrapertitoneal	5 days	1208	vehicle: water	Tichy et al. (1985)
Wistar rat (non-fasted)	male	oral	14 days	1870	vehicle: water	Smyth et al. (1954)
CD mouse	not reported	oral	3 days	6800		Savini (1968)
Rabbit	male, female	oral	1 day	2820		Munch (1972)
Osborne-Mendel or Sherman rat	male, female	oral	until recovery	6500		Taylor et al. (1964)
Rat		oral	10 days	560 ~ 660		Purchase (1968)
New Zealand rabbit	male	dermal	14 days	4050	1/10 of body surface exposed under cover for 24 h	Smyth et al. (1954)

8.1.3 *Skin and eye irritation; sensitization*

No data are available concerning irritation of the skin or eyes.

One skin sensitization test has been reported. It concerns an ear-swelling test on CF1 mice. Following induction by an intradermal injection of Freund's Complete Adjuvant on day 0, and topical applications of 0.1 ml undiluted 1-propanol on days 0, 1, 2, and 3 on the abdominal skin, challenge took place on day 10 by a topical application of 0.02 cm³ 1-propanol on both ears. No sensitization was observed (Gad et al., 1986).

8.2 Short-Term Exposures

Only a few data are available concerning the oral exposure of rats.

When 3 male and 3 female rats of unspecified strain were exposed to 4 daily oral doses of 2160 mg undiluted 1-propanol, no deaths occurred. Although a control group was not used, it was reported that gross liver pathology did not reveal any adverse effects (Taylor et al., 1964).

In a group of 6 male rats of unspecified strain, receiving drinking-water containing 1-propanol at a concentration of 60 090 mg/litre for 4 months, food consumption, body weight gain, and liver histopathology were comparable to those of the control group. Note: The authors reported a dose rate of 3 mg/kg body weight per day, while a dose rate of approximately 3000 µg/kg body weight per day seems more appropriate, assuming a water consumption of 20 ml/day and a body weight of 400 g (Hillbom et al., 1974).

Groups of 10 Wistar rats were exposed to 1-propanol in the drinking-water at a concentration of 320 000 mg/litre (calculated by the Task group to be equivalent to approximately 16 000 mg/kg body weight per day, on the basis of the assumptions made above) for 5, 9, or 13 weeks. Control groups comprised 10 rats each. The exposed rats gradually became weak, losing their appetites and showing a decreased body weight gain. Electron microscopy of the liver showed irregularly shaped megamitochondria with few cristae and normally sized, but irregularly shaped, mitochondria with a decreased number of cristae. Biochemical changes included a decreased state 3 respiration using glutamate as a substrate and decreased specific activities of cytochrome-c oxidase (EC 1.9.3.1) and monoamine oxidase (EC 1.4.3.4) (Wakabayashi et al., 1984).

8.3 Biochemical Effects

8.3.1 *Effects on lipids in the liver and blood*

Oral administration of single doses of 3000 or 6000 mg 1-propanol/kg body weight to Wistar rats caused a small and temporary increase in hepatic triglycerides, which was related to the duration of an elevated blood-1-propanol concentration (Beaugé et al., 1974, 1979). Gaillard & Derache (1966) did not observe an increase in hepatic triglycerides in Wistar rats 17 h after a single dose of 6000 mg 1-propanol/kg body weight.

Factors possibly responsible for hepatic triglyceride accumulation include: an increase in hepatic uptake of labelled palmitate (Beaugé et al., 1979), an increased esterification of palmitate to form liver triglycerides (Beaugé et al., 1974, 1979), and decreased palmitate oxidation (Beaugé et al., 1979). The decrease in palmitate oxidation was related to an increase in the hepatic α -hydroxybutyrate/acetoacetate ratio, implying a decrease in the intramitochondrial NAD^+/NADH ratio (Beaugé et al., 1979). An increase in extramitochondrial reducing equivalents, indicated by an increased lactate/pyruvate-ratio, was observed *in vitro* by Forsander (1967), but not *in vivo* by Beaugé et al. (1979).

The incorporation of palmitate into serum triglycerides and serum and liver phospholipids, 4.5 h after a single dose of 6000 mg 1-propanol/kg body weight to rats, was found to be inhibited, while an increase in hepatic triglyceride accumulation was only observed 8 h after dosing (Beaugé et al., 1974). Three hours after a dose of 3000 mg/kg body weight, the incorporation of palmitate in blood triglycerides was increased concomitantly with an increase in hepatic triglycerides while levels of phospholipids in the liver and blood were unaffected (Beaugé et al., 1979).

8.3.2 *Effects on microsomal enzymes*

The effects of 1-propanol on microsomal enzymes (EC 1.14.14.1) *in vivo* was only investigated by Powis (1975), who administered one oral dose of 960 mg/kg body weight to Wistar rats. Twenty four hours after exposure, no effects were observed on the activity of aniline hydroxylase and aminopyrine demethylase in liver microsomes.

In vitro, 1-propanol inhibited aldrin epoxidase and *p*-aniline hydroxylase in isolated rat liver microsomes via an interaction with cytochrome P-450, which causes a reverse Type I spectral change (Cohen & Mannering, 1973; Wolff, 1978;

Testa, 1981; Sabljic & Protic-Sablic, 1983). The compound did not affect the levels of hepatic microsomal cytochrome P-450, haem, cytochrome b₅, and NADPH-cytochrome c reductase (EC 1.6.2.4) in phenobarbital-induced rats (Ivanetich et al., 1978). 1-Propanol increased the levels of cytochrome P-450 in chick embryo hepatocytes. The activities of benzphetamine demethylase and UDP-glucuronosyl transferase (EC 2.4.1.17) were also increased (Sinclair et al., 1982).

8.3.3 Other effects

The glutathione level in the liver of Wistar rats administered a single dose of 1660 mg 1-propanol/kg body weight, orally, had decreased by 20%, 6 h after exposure. Lipid peroxidation, as indicated by diene conjugates formation, was increased (Videla et al., 1982).

The activities of liver ornithine decarboxylase (EC 4.1.1.17) and liver tyrosine aminotransferase (EC 2.6.1.5) increased in partially hepatectomized rats after one oral dose of 2300 mg 1-propanol/kg body weight. No effects were observed on levels of alanine aminotransferase (EC 2.6.1.2) in the liver and kidneys, and on levels of ornithine decarboxylase in the kidneys and brain (Poso & Poso, 1980).

The effects of 1-propanol on neuronal membrane-bound adenylate cyclase (EC 4.6.1.1) and guanylate cyclase (EC 4.6.1.2) *in vitro* are discussed in section 8.4. 1-Propanol also stimulated adenylate cyclase bound to isolated rat adipocyte plasma membranes (Stock & Schmidt, 1978), pancreatic acinar cell membranes of the guinea-pig (Uhlemann et al., 1979), and bovine luteal membranes (Huang et al., 1982), especially in presence of a guanine nucleotide.

When Sprague Dawley rats inhaled 1-propanol for 6 h at a concentration of 490 mg/m³, the serum level of testosterone was decreased by 42% immediately after exposure, but not 18 h after exposure. When this exposure regimen was repeated daily over one week, no effects on serum-testosterone levels were observed. Serum levels of luteinizing hormone and corticosterone were unchanged at all times (Cameron et al., 1985)

8.4 Neurotoxic and Behavioural Effects

A few neurotoxic and behavioural effects have already been described in sections 8.1.2 and 8.2. In addition, several special studies have been performed.

The oral ED₅₀ for narcosis in rabbits exposed to 1-propanol (1440 mg/kg body weight) was 4 times lower than that for ethanol (Munch, 1972). Positional nystagmus with an inhibited rotatory response was observed in rabbits intravenously infused with 1-propanol at a rate of 9 - 30 mg/min per kg body

weight, at and above a blood concentration of 900 mg/litre (Odkvist et al., 1979).

The intraperitoneal ED₅₀ for loss of righting reflex in Swiss Webster mice (1478 mg/kg body weight) was 2.8 times lower than that for ethanol (Lyon et al., 1981). When C57BL/6J or DBA/2J mice were administered a single dose of 1-propranol intraperitoneally both strains showed decreased activity in the open field test at 392 mg/kg body weight but the decrease was not significant. All mice died at 785 and at 1570 mg/kg body weight, (Strange et al., 1976). The rotarod performance of Swiss-Cox mice decreased in a dose-related manner after single oral doses of 1-propranol of 2000 and 4000 mg/kg body weight. A dose of 1000 mg/kg body weight did not cause behavioural impairment and, when the study was repeated on days 4, 6, 7, and 8 after the first trial, tolerance did not develop (Maickel & Nash, 1985).

The threshold for the induction of ataxia in Sprague Dawley rats following intraperitoneal exposure was 799 mg/kg body weight (McCreery & Hunt, 1978). In a tilted plane test, the performance of rats decreased by an average of 71% after oral exposure to 2000 mg/kg body weight. On a molar basis, 1-propranol was 2.5 times as intoxicating as ethanol (Wallgren, 1960).

Depression of the central nervous system by 1-propranol was related by several investigators to interactions with neuronal membranes *in vitro*. Lyon et al. (1981) observed a high correlation between the narcotic potency of the chemical in mice and its potency in disordering the brain synaptosomal plasma membrane *in vitro*, as measured by electron paramagnetic resonance, which was in its turn related to membrane solubility. A change in membrane fluidity was shown to occur in isolated synaptosomal plasma membranes of rat cortex *in vitro* by a decrease in 1,6-diphenyl-1,3,5-hexatriene fluorescence polarization (Harris, 1983).

Functional loss due to disruption of membrane integrity by 1-propranol was observed *in vitro*. The action potentials of the sciatic nerves of the toad (*Bufo marinus*) (Requena et al., 1985) and of giant axons of the squid (*Loligo forbesi*) (Paternostre et al., 1983) were decreased by 1-propranol. In isolated rat phrenic nerve-diaphragm, 1-propranol increased the amplitudes of end-plate and miniature end-plate potentials and the number of quanta of acetylcholine of end-plate potentials (Gage, 1965). The compound also affected the rate of decay of postsynaptic currents in the neuromuscular junction of the crayfish (*Cherax destructor*) (Wachtel, 1984), and in the phrenic nerve-diaphragm of the rat (Gage, 1965).

Effects on the ionic currents underlying the changes in excitability described above were also investigated *in vitro*. 1-Propanol inhibited both the K^+ -stimulated and the Na^+ -dependent influx of Ca^{2+} ions into isolated rat brain synaptosomes (Stokes & Harris, 1982; Harris, 1983; Michaelis & Michaelis, 1983), and the influx of Na^+ ions into rat brain synaptosomes (Mullin & Hunt, 1985). It decreased the Na^+ and K^+ currents in the giant axons of the squid (*Loligo forbesi*) (Paternostre et al., 1983), and in sciatic nerve fibres of the clawed toad (*Xenopus laevis*) (Arhem & Van Helden, 1983). The interference of 1-propanol with the transport of Ca^{2+} ions across biological membranes was also shown *in vitro* by the inhibition of Ca^{2+} ion-induced contractions of guinea-pig ileum (Yashuda et al., 1976), and *in vivo*, in rats, by a decrease in regional brain Ca^{2+} ion levels, 30 min after one intraperitoneal dose of 2000 mg/kg body weight (Ross, 1976).

The disruption of neuronal membranes by 1-propanol was also thought to explain its inhibitory action on dihydromorphine binding to isolated mouse brain caudate membranes (Tabakoff & Hoffman, 1983) and on membrane-bound guanylate cyclase (EC 4.6.1.2) in intact murine neuroblastoma N1E-115 cells (Stenstrom et al., 1986). The activation by 1-propanol of membrane-bound adenylate cyclase (EC 4.6.1.1) from isolated mouse striatal membranes, in the presence of guanine nucleotides, was also suggested to be the result of membrane perturbation (Luthin & Tabakoff, 1984).

8.5 Reproduction, Embryotoxicity, and Teratogenicity

One abstract of a teratogenicity study was available to the Task Group. 1-Propanol was administered by gavage to Long-Evans rats on days 6 - 15 of gestation. The treatment was reported to cause a dose-dependent increase in fetal malformations and embryoletality. The EC_{50} for "embryopathic potential" was 1500 mg/kg body weight (Mankes et al., 1985). These limited data are inadequate for the evaluation of the reproductive effects of 1-propanol.

8.6 Mutagenicity

8.6.1 *Bacteria*

1-Propanol did not induce reverse mutations in *Salmonella typhimurium* TA 100 with and without metabolic activation by S9 rat liver (Stolzenberg & Hine, 1979). In an abstract concerning an unpublished study, it was reported that 1-

propanol did not induce reverse mutations in *Salmonella typhimurium* TA 1535, TA 1537, TA 1538, and TA 98 (WHO, 1980; Unruh & Spinicelli, 1981).

In a reverse mutation assay with *Escherichia coli* CA 274, 1-propanol increased the reversion rate 5-fold (Hilscher et al., 1969).

8.6.2 *Mammalian cells in vitro*

In an abstract of an unpublished study, it was reported that 1-propanol did not induce forward mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells, with or without metabolic activation (WHO, 1980; Unruh & Spinicelli, 1981). The compound did not increase the number of sister chromatid exchanges in Chinese hamster ovary cells (Obe & Ristow, 1977), and did not increase the number of micronuclei in V79 Chinese hamster lung fibroblasts (Lasne et al., 1984).

A dose-related increase in the inhibition of metabolic cooperation between V79 wild type Chinese hamster lung fibroblasts was observed by Chen et al. (1984).

8.7 Carcinogenicity

A group of 18 Wistar rats of both sexes received doses of 240 mg 1-propanol/kg body weight, by gavage, twice a week, for their lifetime. Another group of 31 Wistar rats of both sexes received subcutaneous injections of 48 mg compound/kg body weight, twice a week, for their lifetime. Control groups comprising 25 rats for each route received saline. It was not reported whether the analytical grade, double distilled test compound was analysed for the presence of impurities. The average survival time was 570 days for the orally exposed rats, 666 days for the subcutaneously exposed rats, and 643 days for both control groups. The tumour incidences found are summarized in Table 7. The data were not statistically analysed. It was reported that "nearly all rats" showed liver damage including congestion, steatosis, necrosis, fibrosis and metaplasia, and hyperplasia of the haematopoietic bone marrow parenchyma. However, the incidences of these lesions were not reported (Gibel et al., 1975).

In view of the major shortcomings, this study is considered inadequate for further evaluation.

Table 7. Tumour incidence in Wistar rats exposed orally or subcutaneously to 1-propanol for lifetime^a

Organ/ tissue affected	Tumour type	Incidence			
		Oral exposure		sc exposure	
		Exposed	Controls	Exposed	Controls
Blood	myeloid leukemia	2/18	0/25	4/31	0/25
Liver	carcinoma	1/18	0/25	0/31	0/25
Liver	sarcoma	2/18	0/25	5/31	0/25
Other	carcinoma	0/18	0/25	3/31 ^b	0/25
	sarcoma	0/18	0/25	2/31 ^c	0/25
	benign tumours ^d	10/18	3/25	7/31	2/25

^a From: Gibel et al. (1975).

^b One carcinoma each in kidney, bladder, and uterus.

^c One sarcoma each in spleen and at injection site.

^d Mostly papillomas and mammary fibroadenomas.

8.8 Interacting Agents

The metabolism of *N*-nitrosodimethylamine was inhibited by the presence of 1-propanol in isolated perfused rat livers. This effect appeared to be independent of the metabolism of 1-propanol itself (Tomera et al., 1984).

The metabolism of chloral hydrate by rat liver slices was stimulated in the presence of 2-propanol (Ho et al., 1970).

When a crude homogenate of dispersed acinar cells, prepared from guinea-pig pancreas, was incubated with 1-propanol and secretin, the secretin-stimulated activity of adenylate cyclase (EC 4.6.1.1) and cellular cyclic adenosine 3',5'-monophosphate was reversibly potentiated at low concentrations of 1-propanol and irreversibly inhibited at higher concentrations (Uhlemann et al., 1979).

9. EFFECTS ON MAN

9.1 General Population Exposure

9.1.1 *Poisoning incidents*

One case of poisoning by 1-propanol has been reported. It concerned a 46-year-old woman who was estimated to have consumed approximately half a litre of the compound as a solvent in a cosmetic preparation, probably a hair lotion. It was pointed out that the woman could have ingested this preparation more than once in the past. The woman died 4 - 5 h after ingestion. She was found unconscious. Autopsy revealed a swollen brain and lung oedema. The authors noted that studies on human volunteers had shown that an oral dose of 20 ml 1-propanol, diluted with water, caused a sensation of warmth and a slight decrease in blood pressure (Durwald & Degen, 1956).

9.1.2 *Skin and eye irritation; sensitization*

Filter papers with 0.025 ml of a 75% solution of 1-propanol in water were placed on the forearms of a group of 12 volunteers of oriental ancestry following immersion of the forearms in water at 23 °C for 10 min. The patches were covered for 5 min and then gently blotted. Nine of the 12 persons showed erythema for at least 60 min following exposure. The cutaneous reaction was totally blocked in 4 out of 4 persons after pretreatment with 40% 4-methylpyrazole in hydrophilic ointment 1 h before the challenge, showing, according to the authors, that 1-propanol must be metabolized to propanal before vasoactivity occurs (Wilkin & Fortner, 1985).

Allergic reactions developed in a laboratory worker, in a company manufacturing hair cosmetics, in patch tests with chemically pure 1-propanol solutions in water (10 - 99.5% by volume). This person also reacted to 2-propanol, 1-butanol, 2-butanol, and methanal, but not to ethanol and methanol. Controls were not tested (Ludwig & Hausen, 1977).

9.2 Occupational Exposure

Reports on adverse effects through the industrial use of 1-propanol were not available.

9.3 Interacting Agents

1-Propanol and ethanol both depress the central nervous system, and an additive effect can be expected (section 8.4).

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of Human Health Risks

1-Propanol is rapidly absorbed and distributed throughout the body following ingestion (section 6). Dermal absorption cannot be neglected in view of the acute mortality data on rabbits (dermal LD₅₀/oral LD₅₀ ≈ 1.4) (section 8.1.1), but accurate data on this subject are not available. Data on the absorption rate following inhalation are lacking, but, in view of the physical properties of the compound, it is expected to be rapid. 1-Propanol is rapidly eliminated from the body (section 6).

Exposure of the general public to potentially lethal levels may occur through accidental or intentional ingestion. Only one case of poisoning by 1-propanol has been reported.

The acute mortality data on experimental animals indicate that 1-propanol is slightly toxic following oral or inhalation exposure and practically non-toxic following dermal exposure, based on the scale of Hodge & Sterner (1943) (section 8.1.1). Exposure-effect data on human beings are not available, with the exception of a statement that symptoms may appear after ingestion of 20 ml 1-propanol diluted with water. The principle adverse effect of this compound following a single exposure is depression of the central nervous system (section 8.4 and 9.1.1). In adults, aqueous 1-propanol may be irritating to the hydrated skin (section 9.1.2). Data are not available to evaluate fully the irritating properties of this compound for the skin and eyes.

Repeated exposure of human beings to 1-propanol may occur through inhalation during manufacture, processing, and both occupational and household use, or through ingestion via food containing the compound as natural or added flavour volatile or as solvent residue, or via alcoholic beverages, which nearly always contain 1-propanol as a product of fermentation. Exposure of the general population to 1-propanol via inhalation of ambient air is probably insignificant because of its rapid disappearance from the atmosphere (sections 4 and 10.2).

Because of the absence of data on the extent of exposure of the general population and workers, a complete risk assessment is not possible. Moreover, data are insufficient to evaluate the sensitizing properties and the possible adverse effects on reproduction and on newborn offspring.

1-Propanol was not mutagenic in 2 out of 3 bacterial assays and in 3 assays with mammalian cells *in vitro*. On the basis of these limited data, some of which have been published in abstract only, it can be concluded that there is no evidence for mutagenicity. Data are inadequate to evaluate the carcinogenicity

of 1-propanol in experimental animals. There are no data on the long-term exposure of human populations to 1-propanol. Therefore, the carcinogenic risk of 1-propanol for man cannot be assessed.

No data are available to establish a tolerable exposure level for inhalation for either the general population or workers. The occupational threshold limit value of 500 mg/m³ in the USA is derived from the threshold limit values established for butanols and 2-propanol.

Data on the long-term oral exposure of human beings are not available. Limited animal data on this subject suggest that long-term exposure to 1-propanol will lead to irreversible liver injury (sections 8.2 and 8.7). In one drinking-water study on Wistar rats, liver damage was observed at a dose level of 16 000 mg/kg body weight per day, administered over 5 - 13 weeks. No liver damage was observed in another drinking-water study in which 1-propanol was administered at approximately 3000 mg/kg body weight per day for 4 months. Both studies show major defects, such as testing at one dose level only, the use of small groups, uncertainties concerning the exact daily dose, and a limited clinical and pathological examination. Taking 3000 mg/kg body weight per day as a no-observed-adverse-effect level, in spite of these defects, and applying a safety factor of 1000 (a factor 10 for inter-species variation, a factor 10 for intra-species variation, and a factor 10 for extrapolation from short-term to long-term exposure), the tolerable dose for long-term oral exposure of human beings to 1-propanol can be calculated to be 3 mg/kg body weight per day. Note: The safety factor of 10 for extrapolation from short-term to long-term exposure is subject to discussion. In addition, an extra safety factor could be considered in view of the major defects in the tests.

10.2 Evaluation of Effects on the Environment

1-Propanol can be released into the environment during production, handling, storage, transport, and use, and via waste disposal (section 3). 1-Propanol can be transferred from water, soil, and waste-disposal sites to the atmosphere by volatilization, from the atmosphere to water and soil by rain-out, and from soil and waste disposal sites to groundwater by leaching. Because of the disperse use of the compound, it is difficult to estimate its emission into each compartment, but the total emission into the environment may amount to over 75% of the production volume (section 4.1).

Through photochemical degradation and rainout 1-propanol disappears rapidly from the atmosphere, with an atmospheric residence time of less than 3 days (sections 4.1 and 4.2). Thus, measurable levels of 1-propanol are not normally encountered.

Hydrolysis and photodegradation are not expected in water and soil (section 4.2). Adsorption on soil particles is unlikely (section 4.1). The mobility of 1-propanol in soil is probably high. The compound appears to be readily biodegradable aerobically as well as anaerobically (section 4.3.1). The emission of 1-propanol into surface water could lead to oxygen depletion. Because of the rapid removal of 1-propanol from water, measurable levels are not normally encountered.

1-Propanol is practically non-toxic for mammals (sections 8.1.1 and 10.1), aquatic organisms, insects, and plants (section 7). In view of the physical properties of 1-propanol, bioaccumulation is highly unlikely (section 4.3.2).

On the basis of the above data, it can be concluded that, except in case of accidents and inappropriate disposal, 1-propanol does not pose a significant hazard for aquatic and terrestrial life.

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