ISOPROPANOL

Data were last reviewed in IARC (1977) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

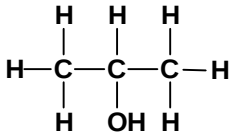
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Reg. No.: 67-63-0

Systematic name: 2-Propanol

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_3H_8O Relative molecular mass: 60.09

1.1.3 *Physical properties* (for details, see IARC, 1977)

(*a*) *Boiling-point*: 82°C

(*b*) *Melting-point*: –89.5°C

(*c*) *Conversion factor*: $mg/m^3 = 2.46 \times ppm$

1.2 Production and use

Isopropanol is manufactured in the United States by the indirect hydration of propylene in processes which may involve the use of concentrated or dilute sulfuric acid, whereas, in European countries and Japan, a direct hydration process is used in which propylene reacts with water in the presence of a catalyst. It is used mainly for the production of acetone, but also as a solvent and in the manufacture of other chemicals and in pharmaceutical and cosmetic formulations (IARC, 1977).

1.3 Occurrence

1.3.1 *Occupational exposure*

Occupational exposure to isopropanol may occur in polypropylene production plants (IARC, 1977).

1.3.2 *Environmental occurrence*

Isopropanol has been detected in trace quantities in some samples of drinking-water in the United States and as a constitutent of tar-water resulting from the distillation of shale tar. It has also been detected in the volatile fractions of grapefruit essence oil, roasted filbert nuts, lime essence, Reunion geranium oil, *Pinus densiflora* logs and milk products (IARC, 1977).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 983 mg/m^3 as the threshold limit value for occupational exposures to isopropanol in workplace air. Similar values have been used as standards or guidelines in many countries, except in Denmark (490 mg/m^3) and Sweden (350 mg/m^3) (International Labour Office, 1991).

No international guideline for isopropanol in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

An increased incidence of cancer of the paranasal sinuses was observed in workers at factories where isopropyl alcohol was manufactured by the strong-acid process (IARC, 1987). The risk for laryngeal cancer may also have been elevated in these workers. It is unclear whether the cancer risk was due to the presence of diisopropyl sulfate, which is an intermediate in the process, to isopropyl oils, which are formed as by-products, or to other factors, such as sulfuric acid.

In the Montreal case–control study carried out by Siemiatycki (1991; see the monograph on dichloromethane in this volume), the investigators estimated the associations between 293 workplace substances and several types of cancer. Isopropanol was one of the substances. About 4% of the study subjects had ever been exposed to isopropanol. Among the main occupations to which isopropanol exposure was attributed in this study were fire fighters, machinists and electricians. For most types of cancer examined (oesophagus, stomach, colon, rectum, pancreas, prostate, bladder, kidney, skin melanoma, lymphoma), there was no indication of an excess risk due to isopropanol. For lung cancer, based on 16 cases exposed at the 'substantial' level, the odds ratio was 1.4 (90% confidence interval, 0.8–2.7). [The interpretation of the null results has to take into account the small numbers and presumed low levels of exposure.]

3. Studies of Cancer in Experimental Animals

Isopropanol has been tested in mice by skin application, inhalation exposure and subcutaneous injection. These studies were inadequate for evaluation (IARC, 1977).

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 55 male and 55 female CD-1 mice, approximately seven weeks old, were exposed by inhalation to target concentrations of 0 (control), 500, 2500 and 5000 ppm [0, 1225, 6125 and 12 250 mg/m^3] isopropanol vapour (purity, 99.9%) for 6 h per day on five days per week for 78 weeks. The mean actual concentrations were 504 ± 14, 2509 ± 58 and 5037 ± 115 ppm, respectively. The highest concentration (5000 ppm) was selected as a result of the mortality observed at 10 000 ppm in a previous nine-day inhalation study and the toxic effects observed at 5000 ppm in a previous 13-week study. Animals were killed immediately after the last exposure and a complete autopsy was carried out on each animal. No adverse effect on weight gain was observed among treated and control animals. Almost all organs were examined histologically in the high-dose and control groups. Histological evaluations of the kidneys, testes and gross lesions were performed for the mid- and low-dose groups. No difference in mean survival time was noted for any of the exposure groups. [Mortality and mean survival time were indicated only in bar graphs.] No increased incidence of neoplastic lesions was noted for either sex of mice from any exposure group, but no data were presented (Burleigh-Flayer *et al*., 1997). [The Working Group noted the limited duration of the study.]

3.1.2 *Rat*

Groups of 65 male and 65 female Fischer 344 rats, approximately seven weeks old, were exposed by inhalation to target concentrations of 0 (control), 500, 2500 and 5000 ppm [0, 1225, 6125 and 12 250 mg/m^3] isopropanol vapour (purity, 99.9%) for 6 h per day on five days per week for 104 weeks. The mean actual concentrations were 504 ± 14, 2509 ± 58 and 5037 ± 115 ppm, respectively. The highest concentration (5000 ppm) was selected as a result of the mortality observed at 10 000 ppm in a previous nine-day inhalation study and the toxic effects observed at 5000 ppm in a previous 13-week study. Animals were killed immediately after the last exposure and a complete autopsy was carried out on each animal. Almost all organs were examined histologically in the high-dose and control groups. Histological evaluations of the kidneys, testes and gross lesions were performed for the mid- and low-dose groups. Survival was poor in male rats but was adequate in females. Increased mortality (100% versus 82% for controls) and decreased mean survival time (577 versus 631 days for controls; $p < 0.01$ by life-table analysis) were noted for high-dose male rats. No difference in mean survival time was noted for female rats. [The mortality and mean survival time in other groups were indicated only in bar graphs.] Chronic renal disease was attributed as the main cause of death for male and female rats in the high-dose groups and was also considered to account for much of the mortality observed in mid-dose males. Extensive data were presented on clinical and microscopic renal pathology, but no tumour data were presented. The main cause of death for male controls was mononuclear-cell leukaemia. Concentration-related increases in interstitial-cell adenoma of the testes were observed in male rats found dead or moribund during the study (57.5% of control, 72.2% of low-dose, 84.7% of mid-dose and 93.8% of

high-dose animals) as well as for all animals in the study (64.9% of control, 77.3% of low-dose, 86.7% of mid-dose and 94.7% of high-dose animals) [effective number of animals and statistical significance not indicated]. No increased incidence of neoplastic lesions was observed for female rats from any exposure group but no data were presented (Burleigh-Flayer *et al*., 1997). [The Working Group noted the poor survival in male rats, most marked in the high-dose groups.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

The metabolism and pharmacokinetics of isopropanol have been reviewed (Dhillon & Von Burg, 1995).

4.1.1 *Humans*

Although there are a number of publications on the pharmacokinetics and disposition of isopropanol in humans, most of these are case reports of accidental or deliberate self-administration rather than systematic studies. However, a range of important features of the behaviour of isopropanol have been defined.

Isopropanol is rapidly absorbed from the gastrointestinal tract, with more than 80% absorbed within 30 min and 100% within 3 h. In contrast, absorption through the skin is low (Martinez *et al*., 1986; McGrath & Einterz, 1989) but may be sufficient to be involved in isopropanol toxicity. The volume of distribution of isopropanol is 0.6–0.7 L/kg, similar to total body water.

The metabolism of isopropanol is via oxidation by aldehyde dehydrogenase (ADH) to acetone. In common with other α-substituted (secondary) alcohols, isopropanol is a relatively poor substrate for ADH (WHO, 1990; Light *et al*., 1992). The primary metabolite, acetone, is eliminated in the expired air and in the urine and also undergoes further oxidation to acetate, formate and, ultimately, CO_2.

Isopropanol is excreted unchanged in the urine and the expired air, these routes together accounting for approximately 50% of the dose. In adults, the elimination half-life ranges from 2.9 to 16.2 h and this is shorter in alcoholics. Values observed in children poisoned with isopropanol fall within this range. The elimination of acetone formed from isopropanol is slower (Daniel *et al*., 1981), with levels remaining elevated up to 38 h after ingestion: it was not possible to calculate a half-life as the levels were essentially constant during the study period.

Acetonaemia is a clinical feature seen in diabetes and starvation and is thus not diagnostic of isopropanol exposure. However, Kawai *et al*. (1990) have suggested that urinary acetone levels provide a valuable index of workplace exposure to isopropanol. They found a good correlation (r = 0.84) between isopropanol exposure assessed by

diffusive samplers worn by workers during an 8-h shift and the acetone concentration in spot urine samples collected 6 h into the shift.

4.1.2 *Experimental systems*

Martinez *et al*. (1986) compared the absorption and metabolism of isopropanol in rabbits after oral, dermal and inhalation exposure. The highest blood levels were seen after oral dosing, lower after inhalation and lowest after dermal application. Blood levels after doses of 4 mL/kg were approximately twice those seen after 2 mL/kg, but concentrations of acetone were the same after both doses, regardless of the route of administration.

Jerrard *et al*. (1992) gave anaesthetized dogs 60 mL of 70% aqueous isopropanol (approximately 2 mL/kg) and determined blood levels of isopropanol and acetone for up to 6 h. The peak isopropanol level occurred at 3 h, while acetone concentrations increased throughout the 6-h experiment.

4.2 Toxic effects

4.2.1 *Humans*

Isopropanol has sensitizing properties but is not a dermal irritant. Volunteers inhaling this compound for several minutes developed irritation to the eyes and rhinopharynx. Oral intake of low doses (2.6–6.4 mg/kg bw) had no effect on blood cells, serum or urine and produced no symptoms (IARC, 1977).

Acute inhalation exposure to isopropanol can produce central nervous system depression that may be prolonged by acetone, a metabolite of isopropanol; lethalities have occurred in very young and newborn children (Mydler *et al.*, 1993; Vicas & Beck, 1993). Ingestion of isopropanol has been implicated in the deaths of a number of adults, particularly among alcoholics. Pulmonary congestion was the most frequent post-mortem finding and is typical, although not diagnostic or specific, of deaths involving drug-induced central nervous system depression (Alexander *et al.*, 1982).

4.2.2 *Experimental systems*

Oral administration of isopropanol increased the hepatotoxicity of chlorinated hydrocarbons in mice and led to accumulation of liver triglycerides in rats (IARC, 1977).

Rats continuously inhaling 8 ppm [20 mg/m^3] isopropanol for 86 days showed increased bromosulfophthalein retention, liver parenchymal dystrophy, enlarged spleen and degenerative changes in the brain (IARC, 1977). Groups of rats inhaling isopropanol at a concentration of 8000 ppm [20 000 mg/m^3] for 20 weeks showed no change in erythrocyte numbers. There was an increase in serum cholesterol levels throughout the dosing period, which returned to normal values within four weeks in a 12-week recovery period. Serum alanine aminotransferase and aspartate aminotransferase activities were significantly increased during the first 12 weeks of the dosing period, but had returned to normal values by the end of the dosing period. No effect on these parameters was observed at 4000 ppm [10 000 mg/m^3] (Nakaseko *et al.*, 1991).

Inhalation of 400 ppm [1000 mg/m^3] isopropanol by guinea-pigs for 24 h reduced the ciliary activity in the nasal mucosa, but recovery was complete within two weeks. Higher concentrations produced damage that required longer to repair (Ohashi *et al.*, 1987, 1988).

4.3 Reproductive and developmental effects

Isopropanol administered daily in the drinking-water of rats to achieve doses of 1500, 1400 and 1300 mg/kg bw in the parents and two successive generations, respectively, had no effect upon growth, reproductive function, intrauterine or postnatal development (IARC, 1977).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

In a single in-vivo study, isopropanol did not induce micronuclei in bone marrow of mice. In single studies conducted in mammalian cells *in vitro*, it did not induce sister chromatid exchanges or gene mutations.

Isopropanol did not induce aneuploidy in *Neurospora crassa* in a single study. It was not mutagenic to bacteria.

5. Summary of Data Reported and Evaluation[1]

5.1 Exposure data

Exposure to isopropanol may occur in its production, in the production of acetone and during its use as a solvent.

5.2 Human carcinogenicity data

An increased incidence of cancer of the paranasal sinuses and laryngeal cancer was observed in workers at factories where isopropanol was manufactured by the strong-acid process. One case–control study investigated the risk associated with occupational exposure to isopropanol, but for none of the investigated cancer sites was a significant increase in risk observed.

5.3 Animal carcinogenicity data

Isopropanol was tested for carcinogenicity in mice and rats by inhalation exposure. Although no increase in tumours was observed in mice, the study had some limitations in design and adequacy. A slight increase in interstitial cell adenomas of the testis was observed in male rats.

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[1] Summary (but not the evaluation) prepared by the Secretariat after the meeting.

Table 1. Genetic and related effects of isopropanol

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	Shimizu *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Zeiger *et al.* (1992)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500	Shimizu *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Zeiger *et al.* (1992)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500	Shimizu *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Zeiger *et al.* (1992)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500	Shimizu *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	Shimizu *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Zeiger *et al.* (1992)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	5000	Zeiger *et al.* (1992)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	–	2500	Shimizu *et al.* (1985)
NCN, *Neurospora crassa*, meiotic non-disjunction, aneuploidy	–	–	NG	Brockman *et al.* (1984)
GCO, Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	–	–	5000	Kapp *et al.* (1993)
SIC, Sister chromatid exchange, Chinese hamster V79 cells *in vitro*	–	–	6000	von der Hude *et al.* (1987)
MVM, Micronucleus test, ICR mice bone-marrow cells *in vivo*	–		2500 ip × 1	Kapp *et al.* (1993)

[a] –, negative

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; ip, intraperitoneal

5.4 Other relevant data

Isopropanol is rapidly absorbed from the human gastrointestinal tract, whereas absorption through the skin is slow. It is metabolized by aldehyde dehydrogenase to acetone, but following human exposure, a large proportion is excreted unchanged in expired air and urine. It is a human sensitizer and is irritant to the eyes and rhinopharynx. Isopropanol is a central nervous system depressant and prolonged inhalation exposure of rats can produce degenerative changes in the brain. There is no evidence for genetic toxicity.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of isopropanol in humans.

There is *inadequate evidence* for the carcinogenicity of isopropanol in experimental animals.

Overall evaluation

Isopropanol is *not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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