Isopropylamine

(CAS No: 75-31-0

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of isopropylamine by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of isopropylamine has been based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG98). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in April 1999, literature was searched in the on-line databases Medline, Toxline, Chemical Abstracts, and NIOSHTIC, starting from 1966, 1965, 1967, and 1973, respectively, and using the following key words: 2-propanamine, isopropylamine, 1-methylethylamine, 2-aminopropane, 2-propylamine, monoisopropylamine, sec-propylamine, and 75-31-0.

In February 2001, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: R. Rossbacher (BASF, Ludwigshafen, FRG). These comments were taken into account in deciding on the final version of the document.

An additional search in Toxline and Medline in January 2004 did not result in information changing the committee's conclusions.

2 Identity

name	:	isopropylamine
synonyms	:	2-aminopropane; 2-propanamine; 1-methylethylamine; 2-propylamine; monoisopropylamine; *sec*-propylamine
molecular formula	:	C_3H_9N
structural formula	:	$(CH_3)_2CHNH_2$
CAS number	:	75-31-0

3 Physical and chemical properties

molecular weight	:	59.1
boiling point	:	33°C
melting point	:	-101°C
flash point	:	-37.2°C (closed cup); -26°C (open cup)
vapour pressure	:	at 20°C: 61-64 kPa
solubility in water	:	miscible
log $P_{octanol/water}$	:	0.26 (experimental); 0.27 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 ppm = 2.5 mg/m^3 1 mg/m^3 = 0.41 ppm

Data from ACG98, Lun91, NLM04, http://esc.syrres.com.

Isopropylamine is a flammable, highly volatile, colourless liquid, with an ammonia-like odour. It is a strong alkaline compound (ACG98, Lun91).

Odour thresholds of 0.5-3 mg/m^3 (0.2-1.2 ppm) have been reported (Amo83, Rut86).

4 Uses

Isopropylamine is used as a solvent, as a depilating agent, and as an intermediate in the synthesis of rubber accelerators, pharmaceuticals, dyes, insecticides, herbicides, bactericides, textile specialities, and surface-active agents (ACG98, Ben94, NLM04).

5 Biotransformation and kinetics

In mongrel dogs intravenously infused with isopropylamine (0.25 mg/kg/min, 45 min), an initial rapid and a subsequent slow decline in plasma levels with half-life times ($t_{1/2}$) of 5 and 146 min, respectively, were observed. These values indicate redistribution of isopropylamine into a tissue compartment followed by a slow release into and elimination from the blood. Examinations of tissues 2 hours post-infusion showed highest tissue/plasma ratios (ranging from approximately 5-17) for the kidneys (medulla, cortex), the spleen, the liver, the adrenal glands, and the lungs while significant amounts were found in sections of the brains (ratios of about 3-3.5) and the heart (ratios: ca. 2-3.5) (Pri82). Following a single intravenous injection of ^{14}C-isopropylamine.HCl of 0.3 mg/kg bw into male Wistar rats, radioactivity was rapidly eliminated from the body via the urine with a half-life of about 2 to 4 h. Following a single

intraperitoneal injection of a similar dose, 97% of the radioactivity was excreted in the urine, all being identified as isopropylamine, 1.2% in the faeces, and 1% in exhaled air. In *in vitro* experiments in which isopropylamine was incubated with rat liver microsomes in the presence of a NADPH-generating system, more than 94% was recovered as unchanged compound (Bak73).

The committee did not find additional data on the biotransformation and kinetics of isopropylamine.

6 Effects and mechanism of action

Human data

The committee did not find data on workers occupationally exposed to isopropylamine.

Animal data

Irritation and sensitisation

When 0.1 mL of undiluted test compound was instilled into the cupped conjunctival sac of the right eye of male and female rabbits (n=3/sex), severe redness (grade 3) and swelling (grades 2-4) of the conjunctiva and maximum corneal opacity (grade 4) were observed at all observation points (i.e., at 1 hour and 1, 2, 3, 7, and 14 days; washout after 24 hours) in all animals. By day 14, after which the study was terminated because of the severity and probable irreversibility of the effects, there were eschar tissue formation on the cornea and/or conjunctivae and corneal ulcerations in all animals, as well as scar tissue on the conjunctivae or eye lid in 2 (Wal85a). Instillation of 0.005 mL of undiluted compound resulted in severe corneal opacity while 0.5 mL of a 1% solution in water caused severe corneal opacity and iritis (no details available) (Mye96). In an older study, isopropylamine scored an injury grade of 10 (i.e., a severe burn from 0.5 mL of a 1% solution) on a scale from 1 to 10 (Smy51).

The potential skin-irritating properties were tested by applying 0.5 mL of undiluted material to 2 intact clipped sites per male and female rabbit (n=3/sex) under semi-occluded and occluded conditions for 4 and 24 hours, respectively. At all observation points (i.e., 30 minutes, 24, 48, and 72 hours, and 7 days after removal of the patches), maximum (Draize) scores for erythema and oedema and dark discolouration of the entire test site at all sites were observed in all animals. For all animals, there was eschar formation at the observation time of

24 and 48 hours at the occluded and semi-occluded sites, respectively. This persisted throughout the study, which was terminated after post-treatment day 7 because of the maximum irritation observed and the probable irreversibility of the damage (Wal85b). Applying 0.01 mL of undiluted material to the uncovered, clipped, ventral skin of rabbits for 30 minutes (or less depending on absorption or evaporation) induced necrosis while moderate capillary injection was found in 1/5 animals following similar treatment with a 10% solution (in water) (no more details available) (Mye96). In an older study, isopropylamine scored an injury grade of 6 (i.e., necrosis) on a scale from 1 to 10 (Smy51).

The committee did not find data on the possible sensitising effects of isopropylamine

The upper respiratory tract irritation was evaluated in mice (male Swiss OF_1) during a 15-minute oronasal exposure to increasing concentrations of isopropylamine. The airborne concentration resulting in a 50% decrease in the respiratory rate (RD_{50}) was 393 mg/m^3 (157 ppm). Isopropylamine was also tested for pulmonary toxicity in mice and for the effects of a 120-minute exposure on the respiratory rates of non-anaesthetised, tracheally cannulated mice ($RD_{50}TC$). The $RD_{50}TC$ value for isopropylamine was found to be 1223 mg/m^3 (489 ppm). From these results, it was concluded that isopropylamine is essentially an upper respiratory tract-irritating compound (Gag89).

Acute toxicity

A 4-hour exposure to 10,000 mg/m^3 (4000 ppm) was not lethal to 6 out of 6 rats while all 6 rats died due to exposure to 20,000 mg/m^3 (8000 ppm). Exposure to a saturated vapour caused the death of all rats within 2 minutes (Smy51). When rats (n=6/sex/group) were exposed to 5000 or 5100 mg/m^3 (2050 and 2100 ppm), only one male animal exposed to 5100 mg/m^3 died (on day 2). During exposure, laboured breathing, discharges around nose and mouth, lachrymation, and hypoactivity were noted. Post-exposure observations included laboured breathing, encrustation of the nose and eyes, opacity of eyes, urine-stained fur. Opacity of the eyes persisted throughout the 14-day observation period, as did one observation of laboured respiration and encrustation of the nose. At day 2, there was a decrease in mean body weight. Although animals gained weight until sacrifice, only female animals had body weights comparable to control animals. At necropsy, only focal corneal opacity was found (Bec85). A 4-hour LC_{50} of 22,900 mg/m^3 (9160 ppm; 95% confidence limits: 20,250-26,000 mg/m^3 or 8100-10,400 ppm) was established in rats; times to death were 2 to 14 days (Mye96). Without presenting details or reference, a 4-hour LC_{50} (rat) of 9800

mg/m^3 (4018 ppm) was listed (Gre98). In an English abstract of a Russian paper, 2-hour LC_{50}s of 1738 and 2500 mg/m^3 (710, 1025 ppm) were reported for rats and mice, respectively. Exposure caused irritation of the eyes and the respiratory tract, CNS effects (excitation followed by depression), and, upon post-mortem microscopic examination, circulatory disorders, oedema, haemorrhage, cell degeneration, and necrosis (Gus69).

Dermal LD_{50}s of 550 and 688 mg/kg bw were reported in rabbits (Mye96, Smy51). In the latter case, time to death was 1 to 3 days (Mye96). These data are conflicting with the results of a study in which 2000 and 5000 mg of undiluted compound/kg bw was applied to the intact clipped skin of rabbits (n=5/sex/group) for approximately 24 hours. One female animal in the high-dose group died (on day 2). During the 14-day observation period, no remarkable signs of toxicity or effects on body weight were observed. At necropsy, there were local effects (dark discolouration, hardened and thickened skin) in all animals, but, apart from petechial haemorrhage in the stomach glandular mucosa of one high-dose animal, no visible internal abnormalities were observed (Wal85c)

In rats, an oral LD_{50} of 122 mg/kg bw for combined male and female animals was estimated from dosing undiluted material at levels of 70, 118, 200, and 338 mg/kg bw. Toxic signs most frequently observed were decreased activity and staining around nose and mouth at all dose levels and laboured breathing at 118 and 338 mg/kg bw. There were no effects on body weight. At necropsy of the treatment-related deaths, mild to severe congestion of the stomach non-glandular and/or glandular mucosa was seen in most animals, while there were no remarkable findings in the animals sacrificed at the end of the 14-day observation period (Wal85d). In a separate experiment, the LD_{50}s for undiluted material and a 10% solution were <172 and 736 mg/kg bw, respectively; animals died 7 minutes to 4 days and 4 hours to 14 days following administration of the undiluted and diluted test substance, respectively (Mye96). Other LD_{50}s reported in rats were 820 (Smy51) and 550 mg/kg bw (listed without reference) (Gre98).

In dogs, a single intravenous injection of 1 or 30 mg/kg bw caused a dose-dependent increase in arterial pressure, heart rate, and contractile force (Ish74). In a follow-up experiment, a 45-minute intravenous infusion of approximately 110 mg/kg bw (rate: 0.25, 2.5 mg/kg/min) caused an initial increase in arterial pressure and heart rate followed by a prolonged hypotension and bradycardia. A lower dose of ca. 10 mg/kg bw (similar infusion rate and time) produced only hypertension. There was a significant positive correlation between plasma isopropylamine levels and the decrease in mean arterial pressure; levels of 2 µg/mL and higher were associated with decreases in mean arterial pressure (Pri82).

Repeated-dose toxicity

In an unpublished study, reported in an abstract, rats (Sprague-Dawley; n=15/sex/group) were exposed to 0, 100, 500, and 1350 mg/m^3 (41, 205, 555 ppm), 6 hours/day, 5 days/week, for 4 weeks. In the animals of the high-concentration group, there were body weight depressions throughout the exposure interval and effects on eyes and nose (irritation: ocular opacity, sneezing, nasal encrustation; microscopic lesions indicative of inflammatory and degenerative changes), changes in serum chemistry, as well as a decrease in the number of lymphocytes in the male animals. For the animals of the mid-concentration group, microscopic eye and nose lesions indicative of inflammatory and degenerative changes were reported. The no-observed-adverse-effect level (NOAEL) in this study was placed at 100 mg/m^3 (41 ppm) (Dud91).

In an English abstract of a Russian study, it was reported that chronic exposure (time and exposure levels not indicated) induced reduced weight gain, slowed respiration, and decreases in haemoglobin and erythrocyte levels and in arterial pressures. A level of 10 mg/m^3 (4 ppm) also should have caused increases in central nervous system stimuli thresholds (Gus69).

Mutagenicity and genotoxicity

Isopropylamine was negative when tested in *S. typhimurium* strains TA98 and TA100 both with and without a metabolic activating system (derived from induced hamster livers) at concentrations up to 8.3 mg/plate (i.e., toxic doses) (Spe82). Isopropylamine was stated to be negative in Ames tests (no details or reference presented) (Gre98).

Isopropylamine did not induce unscheduled DNA synthesis in cultured rat hepatocytes treated with 100-3000 mM test substance for 4 hours (Haa91).

Reproduction toxicity

In a range-finding study, maternal (amongst others, rales, laboured breathing, piloerection, body weight effects) and fetal (reduced mean fetal weights) toxicity were observed in rats (Sprague-Dawley; n=6/group) exposed to 919 and 1349 mg/m^3 (377, 553 ppm), 6 hours/day, on gestational days 6-15. No effects were seen at the 2 other exposure levels of 100 and 500 mg/m^3 (41, 205 ppm) (Mue87). In the subsequent teratology study, mated female rats (n=25/group) were exposed to 0, 50, 499, and 1000 mg/m^3 (0, 21, 205, 410 ppm), 6 hours/day,

on gestational days 6-15. Exposure did not induce mortality in any of the groups. In the high-exposure group, maternal toxicity was observed including significantly decreased body weights and body weight loss or decreased body weight gain for the periods of gestational days 6-10, 10-13, 13-16, and 6-20. Furthermore, rales, laboured breathing, nasal discharge, sneezing, and fur staining/encrustation were seen. In the mid-exposure group, there was a reduced weight gain for gestational days 6-10 and 6-20, but absolute maternal body weights did not differ from those from controls. Furthermore, there were low incidences of nasal discharges and sneezing. At necropsy, the only treatment-related findings were reduced abdominal fat in 9 and 2 animals of the high- and mid-exposure group, respectively. No effects were found in the dams exposed to 50 mg/m^3 (21 ppm). No statistically significant (with Bonferroni inequality applied) differences between any exposure group and controls were seen with respect to numbers of live fetuses, early and late resorptions, total implants, corpora lutea, pre- and post-implantation loss, mean fetal body weights, fetal sex distribution, and the incidences of malformations and variations (Kie88).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for isopropylamine in the Netherlands is 12 mg/m^3 (5 ppm), 8-hour TWA.

Existing occupational exposure limits in some European countries and the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find human data on the effects of (occupational) exposure to isopropylamine.

Following intravenous administration to dogs and male rats, isopropylamine was rapidly excreted from the body with half-lives of 2.4 and 2-4 h, respectively. Following intraperitoneal injection into male rats, 97% of the dose was excreted unchanged in the urine and minor amounts of about 1% each in faeces and exhaled breath.

In experimental animals, isopropylamine was corrosive to the eyes and skin. It is irritating to the respiratory tract. The committee did not find data on potential sensitising properties.

Based on acute lethality data, isopropylamine is of low toxicity following exposure by inhalation (4-hour LC_{50} rat above approximately 10,000 mg/m^3), and was toxic if swallowed (oral LD_{50} rat: 122 mg/kg bw). Data on lethality

following dermal application are conflicting (dermal LD_{50} rabbit: 550-688 and >5000 mg/kg bw).

Data on repeated exposure were limited to an abstract of a 28-day inhalation study and to a teratology study, both in rats. In the 28-day study, the critical effects were irritation of the eyes and nose. The NOAEL in this unpublished study was placed at 100 mg/m^3 (41 ppm). It was not reported whether isopropylamine had caused other effects on the respiratory tract. When administered during gestational days 6-15, isopropylamine did not induce embryotoxic, fetotoxic, or teratogenic effects at levels that did not cause maternal toxicity. From this study, the committee concludes that the NOAELs for maternal and reproduction toxicity are 50 mg/m^3 (21 ppm) and $\geq$1000 mg/m^3 (410 ppm), respectively.

In vitro, isopropylamine did not induce mutations in bacteria or DNA damage in rat hepatocytes. The committee did not find data from other *in vitro* or *in vivo* assays.

The committee considers the toxicological database on isopropylamine too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

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Annex

Occupational exposure limits for isopropylamine in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	5	12	8 h	administrative		SZW04
Germany						
- AGS	5	12	8 h			TRG03
	20	60	15 min			
- DFG MAK-Kommission	5	12	8 h		[d]	DFG03
	10	24	15 min[c]			
Great-Britain						
- HSE	-	-				HSE02
Sweden	5	12	8 h			Swe00
	10	25	15 min			
Denmark	5	12	8 h	OEL		Arb02
USA						
- ACGIH	5	-	8 h	TLV		ACG04
	10	-	15 min	STEL		
- OSHA	5	12	8 h	PEL		ACG03
- NIOSH	-	-				ACG03
European Union						
- SCOEL	-	-				EC04

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Maximum number per shift: 4, with a minimum interval between peaks of 1 hour. A momentary value of 10 ppm (25 mg/m^3) should not be exceeded.

[d] Listed among compounds with MAK values but no pregnancy risk group classification.