SCOEL/REC/177
Isoamyl Alcohol

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B — Employment
Unit B.3 — Health and Safety

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RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR ISOAMYL ALCOHOL

8-hour TWA:	5 ppm (18 mg/m^3)
STEL:	10 ppm (37 mg/m^3)
BLV:	None
Additional categorisation:	None
Notation:	None

This evaluation is based on ACGIH (2001), BIBRA (1996), BG-Chemie (1997), ECB (2000) and HCN (2003), the references cited in these reviews and a PubMed search in November 2013.

The present Recommendation was adopted by SCOEL on 2016-03-07

RECOMMENDATION EXECUTIVE SUMMARY

The critical effect of inhalation exposure to isoamyl alcohol is considered to be sensory irritation.

Nelson *et al* (1943) reported slight throat irritation in some of 10 subjects exposed for 3-5 min at 100 ppm and slight eye and nose irritation in most subjects at 150 ppm, whereas 200 ppm was objectionable to all volunteers. No further details on the experiment were given.

Throat irritation was also noted by 3 subjects exposed to 25 ppm isoamyl alcohol via the mouth only (Kumagai *et al* 1999).

In a more recent study, 30 volunteers exposed for 2 hours to 0.27 ppm isoamyl alcohol reported slightly increased perceptions of eye irritation (mean value 5 mm on the 100-mm visual analogue scale) compared to clean air exposure (mean rating 3 mm), verbally corresponding to "hardly at all". No effects were found for other ratings, blinking frequency, tear film break-up time in the eyes, vital staining of the eye, nasal lavage biomarkers, lung function, and nasal swelling. In conclusion, 0.27 ppm can be regarded as a NOAEC for irritation in this study (Ernstgård *et al* 2013).

Respiratory depression (RD_{50}) in mice has been reported at 730 ppm (Muller and Greff 1984).

The limited data available on sensory irritation of aliphatic alcohols in humans suggest that the potency increases with increased carbon chain length. The same trend is seen more clearly in RD_{50} studies of respiratory depression in mice.

Studies by Frantik *et al* (1994) of electrically induced hind limb seizures indicate that 1 700 and 950 ppm isoamyl alcohol cause a 30 % depression in rats and mice, respectively.

Retarded weight gain (rats and rabbits) and eye irritation (rabbits only) were observed in dams at 2 725 ppm with a NOAEC of 681 ppm in a developmental toxicity inhalation study (Klimisch and Hellwig 1995). No exposure-related effects were seen in the offspring (NOAEC 2 725 ppm). The 90-day rat study by Schilling *et al* (1997) suggests a systemic NOAEL of 295 mg/kg bw/day. Considering that occupational exposure occurs 5 days per week and assuming that a 70-kg worker inhales 10 m^3 of air during an 8-hour work shift with a respiratory retention of 63 %, the oral NOAEL in rats corresponds to an inhalation NOAEC in humans of 1250 ppm ($295 \times 7/5 \times 70/10 / 0.63 = 4\,589$ mg/m^3).

Largely negative *in vitro* data and only marginal increases of chromosomal aberrations in one *in vivo* study suggests little potential for genotoxicity of isoamyl alcohol. The only cancer study available (Gibel *et al* 1974, 1975) is of limited quality, therefore, no conclusion on the carcinogenic potential of isoamyl alcohol can be drawn.

There were no data on fertility effects due to isoamyl alcohol exposure. There were no signs of embryotoxicity or teratogenicity after exposure of pregnant rats and rabbits up to 10 000 mg/m^3 during organogenesis.

In recommending a health-based OEL for isoamyl alcohol, the following aspects are considered:

1. Weak data suggest sensory irritation effects of isoamyl alcohol during short exposure (3–5 min) at 25 ppm (Kumagai *et al* 1999) or 100 ppm (Nelson *et al* 1943).
2. The irritation potency of aliphatic alcohols tends to increase with increased carbon chain length, this trend is supported by scattered human data and by RD_{50} studies with mice.
3. Isoamyl alcohol is thus likely to have considerably lower irritation potency than *n*-octanol and 2-ethylhexanol, for which mild sensory irritation has been demonstrated at 6.4 ppm (van Thriel *et al* 2003) and 10 ppm (Kieswetter *et al* 2005), respectively.

4. Isoamyl alcohol is, on the other hand, likely to have higher irritation potency than *n*-butanol with reported effect levels of 25 ppm (Nelson *et al* 1943) and 100 ppm (Sterner *et al* 1949).

In view of these aspects, irritation effects at 25 and 100 ppm after 3–5 min of exposure, mild sensory irritation of the more potent alcohols *n*-octanol and 2-ethyhexanol at 6.4 ppm and 10 ppm, respectively, and irritation effects of the less potent alcohol *n*-butanol at 25 ppm, *an 8-hour OEL of 5 ppm is recommended, with a 15-min STEL of 10 ppm.* Systemic toxicity is of no concern at these levels.

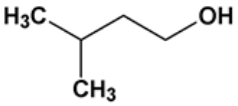
The similarity between dermal and oral LD_{50} data suggests that dermal uptake may be significant, however, as systemic effects occur only at much higher exposure levels than the recommended OEL, a skin notation is not warranted.

Measurement and measurement systems

Analytical measurement systems exist to determine the recommended levels with an appropriate level of precision and accuracy.

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	Isoamyl alcohol
Synonyms:	3-Methylbutan-1-ol; isopentyl alcohol; isopentanol
Molecular formula:	$C_5H_{12}O$
Structural formula:	
EC No.:	204-633-5
CAS No.:	123-51-3
Molecular weight:	88.148 g/mol
Conversion factors: (20 °C, 101.3kPa)	1 ppm = 3.67 mg/m^3 1 mg/m^3 = 0.273 ppm

Isoamyl alcohol is a colourless liquid with a pungent taste and a disagreeable odour. The boiling point of the substance is 130–132 °C. Reported vapour pressure values are in the range of 3.1–4.9 hPa at 20 °C, corresponding to 3 059-4 836 ppm (11 200–17 700 mg/m^3) saturation concentration. The water solubility of isoamyl alcohol is 25 g/l at 20 °C and the log P_{OW} is 1.16–1.28. The substance has a flash point of 43–45 °C (closed cup) and a density of 0.81 g/cm^3 (ACGIH 2001, HCN 2003, ECB 2000).

2. EU HARMONISED CLASSIFICATION AND LABELLING

EU harmonised classification: Not classified (ECHA, 2015)

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Isoamyl alcohol is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Isoamyl alcohol is not a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits for aniline exist in a number of countries, as shown in the table below. The values presented below represent examples and are not an exhaustive listing of all limit values within the EU and other countries.

Table 1: Existing OELs for isoamyl alcohol; adapted from the GESTIS database (GESTIS 2015)

EU-countries	TWA (8 hrs)		STEL (15 min)		
	ppm	mg/m³	ppm	mg/m³	References
Austria	100	360	200	720	GKV (2011)
Belgium	100	366	125	459	Royal Decision (2014)
Denmark	100	360	200	720	BEK (2011)
European Union	5	18	10	37	SCOEL (2014)
Finland	100	370	150	550	MoSH (2012)
France	100	360			INRS (2012)
Germany (DFG)	20	73	80	292	DFG (2015)
Hungary		360		1440	MHSFA (2000)
Ireland	100	360	125	450	HSA (2011)
Latvia		5			GESTIS (2015)
Spain	100	366	125	458	INSHT (2011)
United Kingdom	100	366	125	458	HSE (2011)
Non EU-countries	ppm	mg/m³	ppm	mg/m³	
Australia	100	361	125	452	Safe Work Australia (2011)
Canada (Ontario)	100		125		Ontario Ministry of Labour (2013)
Canada (Québec)	100	361	125	452	IRSST (2010)
Japan	100				JSOH (2015)
New Zealand	100	361	125	452	HS (2013)
Norway	50	180			NLIA (2011)
Singapore	100	361	125	452	GESTIS (2015)
South Korea	100	360	125	450	GESTIS (2015)
Switzerland	100	360	200	720	SUVA (2015)
USA (NIOSH)	100	360	125	450	NIOSH (2007)
USA (OSHA)	100	360			OSHA (2006)

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence and use

Isoamyl alcohol has been reported to occur in nature;

- with the highest quantities observed in the brassica species of mustard (VCF 2009);
- as an ester among the constituents of Roman camomile oil, and in the oils of French peppermint, Java citronella, Reunion geranium, tea, Teucrium chamaedrys, Eucalyptus amigdalina, Achitlea ugeratum, Aitemisia camphorara and others: it is also present in the aromas of strawberry and raspberry and has been identified in rum (Fenarali's Handbook of Flavor Ingredients 1975).

It also occurs;

- as the primary constituent of fusel oil (by-product of alcoholic carbohydrate fermentation) (ACGIH 2001, BG-Chemie 1997, HCN 2003).
- as one among the most commonly reported volatile organic compounds of microbial origin (MVOC) in buildings with moisture and microbial damage and in occupational settings related to agriculture and composting.

Isoamyl alcohol is a biodegradable solvent from a renewable source obtained from sugarcane. It is a narcotic and is about four times as toxic as ethanol. It has the highest narcotic effect among all the amyl alcohols (SEVAS 2015).

Isoamyl alcohol is a main ingredient in the production of banana oil. It's also the main ingredient of Kovac's reagent. It is also used as an antifoaming agent in chloroform. Isoamyl alcohol is used in a phenol–chloroform extraction mixed with chloroform to further inhibit RNase activity and prevent solubility of RNAs with long tracts of poly-adenine. It is one of the components of the aroma of black truffle. It has been identified as a chemical in the pheromone used by hornets to attract other members of the hive to attack (Wikipedia 2015).

5.2. Production and use information

Isoamyl alcohol was first derived by purifying fusel oil (Opdyke 1978), a byproduct during the production of ethyl alcohol by fermentation of molasses. It has also been derived from the chlorination of pentanes followed by hydrolysis. More recently, it has been manufactured by the Oxo Process in the frame of the production of C4 and higher alcohols (SEVAS 2015).

Isoamyl alcohol is mainly used in the manufacture of photographic chemicals and pharmaceutical products. It also serves as a solvent for oils, fats, resins and waxes, as a component of paint strippers and is used in the plastics industry (spinning of polyacrylonitrile).

In addition, according to ACGIH (2001); BG-Chemie (1997); HCN (2003); Mc Ginty *et al* (2010); Belsito *et al* (2010) the isoamyl alcohol is used

- in various cosmetics household products as a fragrance ingredient, as the disagreeable alcohol odour becomes a pleasant fruity-winey odour at high dilutions;
- as an intermediate for the production of fragrances used in decorative cosmetics;
- in fine fragrances, shampoos, toilet soaps, and other toiletries;
- in non-cosmetic products such as household cleaners and detergents. and herbicides.

It is in public use since the 1930's (Opdyke 1978). Its use in fragrance compounds (mixtures) in all finished consumer product categories worldwide is in the region 0.1–1.0 metric tons/annum (IFRA 2004).

5.3. Occupational exposure

Isoamyl alcohol is among the most commonly reported volatile organic compounds of microbial origin (MVOC) in buildings with moisture and microbial damage and in occupational settings related to agriculture and composting. The air levels are typically in the lower µg/m^3 range (Pasanen *et al* 2006).

5.4. Routes of exposure and uptake

The substance can enter into the body by inhalation and ingestion (NIOSH 2015).

6. MONITORING EXPOSURE

Isoamyl alcohol can be monitored in the air of the workplace by applying the following methods (NIOSH 2011):

- NIOSH method 1402
- NIOSH method 1405

In both methods isoamyl alcohol is sampled from the air in the workplace by adsorption onto a coconut shell charcoal solid sorbent, followed by extraction of isoamyl alcohol with isopropanol /carbon disulphide (5:95). The isoamyl alcohol-containing extract can then be analysed by gas chromatography (GC), using flame ionisation detection (FID) as shown in Table 2.

Table 2: Overview of sampling and analytical methods for monitoring isoamyl alcohol in the workplace

Method	Sorbent	Desorption solution	Analysis	Recovery (%)	LOQ	Concentration range	Refs
NIOSH method 1402	Coconut shell charcoal	isopropanol /carbon disulphide (5:95)	GC-FID	107.6	10 µg /sample	195-680 mg/m^3	NIOSH (1994)
NIOSH method 1405	Coconut shell charcoal	isopropanol /carbon disulphide (5:95)	GC-FID	107.6	1 µg /sample	195-680 mg/m^3	NIOSH (2003)

n.d not determined

NIOSH method 1402 is a partially evaluated method. High humidity reduces sampling capacity. The method was validated using a 3 m x 3-mm stainless steel column packed with 10% FFAP on Chromosorb W-AW; other columns with equal or better resolution (e.g., capillary) may also be used.

NIOSH method 1405 is a partially evaluated method. This method combines and updates methods 1401 and 1402. Estimated LOD for each substance is approximately ten times lower than that of the old methods. Also with this method high humidity reduces sampling capacity.

7. HEALTH EFFECTS

7.1. Toxicokinetics and absporption, distribution, metabolism, excretion (ADME)

7.1.1. Human data

Isoamyl alcohol is well absorbed by inhalation. In a human experimental study, 3 healthy volunteers were exposed at rest through a mouthpiece to 25 ppm (92 mg/m^3) isoamyl alcohol for 10 min. The mean respiratory absorption during the last 5 min of exposure was 63 %. The amount of solvent in exhaled air reached a steady-state level within a few minutes (Kumagai *et al* 1999).

No quantitative data for the uptake rate by the oral or dermal route were available.

3-Methylbutanal and 3-methylbutanoic acid were identified as metabolites in the blood of humans (BG-Chemie 1997).

Some individuals (orientals) show a deficiency of a specific aldehyde dehydrogenase isoenzyme and may therefore have elevated 3-methylbutanal blood levels after exposure to isoamyl alcohol (HCN 2003).

7.1.2. Animal data

The nasal uptake of isoamyl alcohol in rats was estimated to be 80 % (by using a physiologically-based pharmacokinetic model) (HCN 2003).

No quantitative data for the uptake rate by the oral or dermal route were available.

After oral or intraperitoneal exposure of rats to high doses (1–2 g/kg bw), only low amounts of the parent compound were found in blood. Small amounts of isoamyl alcohol were detected in urine and exhaled air. A rapid oxidation in the liver is assumed. The main metabolites in blood were 3-methylbutanal and 3-methylbutanoic acid. In rabbits given isoamyl alcohol via the oral route, 9 % of a single dose (733 mg/kg bw) was excreted in urine as glucuronide of triacetyl-ß-isoamylmethylester within 24 hours (BG-Chemie 1997; HCN 2003; McGinty *et al* 2010).

Co-administration of isoamyl alcohol and ethanol led to a slowing down of the metabolism of isoamyl alcohol in rats (BG-Chemie 1997, HCN 2003).

7.1.3. In vitro data

7.1.4. Biological monitoring

No adequate data for establishing a qualified strategy for biological monitoring were available, although 3-methylbutanoic acid in urine would potentially be a useful biological exposure marker.

7.2. Acute toxicity

7.2.1. Human data

Acute respiratory effects of airborne exposure are described in Section 7.4. Acute central nervous depression is associated with exposure to isoamyl alcohol for all exposure pathways. However, no quantitative data are provided for inhalation exposure. Humans who had ingested 50–100 ml isoamyl alcohol experienced central nervous system

depression, weakness, pain, nausea, headache, sleep within 10–15 min, terminal coma and death within 1 hour to 6 days (Avdeev 1966).

7.2.2. Animal data

No lethal concentration after inhalation exposure is reported. Exposure of rats to "saturated vapour" (at room temperature, concentration not given) for 8 hours (Smyth *et al* 1969) or to "enriched atmosphere" (concentration not given) for 7 hours (BASF 1979) caused no mortality. In the latter study, the animals showed panting and a loss of pain reflex.

The range of reported oral LD_{50} values in rats is 1.3–7.1 g/kg. The oral and dermal LD_{50} values in rabbits are 3.4 and 3.2– > 5.0 g/kg, respectively. Toxic symptoms after oral or parenteral application are dyspnoea, apathy, staggering, atony, pareses of the hind limbs, poor general condition and apnoea (ACGIH 2001, BG-Chemie 1997, HCN 2003, McGinty 2010). The similar oral and dermal LD_{50} values suggest efficient dermal absorption.

Male Wistar rats and female H-strain mice were used to study the neurotoxicity of isoamyl alcohol. Whole body exposures were carried out in 80-l flow-through glass chambers with one rat or two mice per experiment. In total 16 rats (4 per group) and likewise 32 (8 per group) mice were exposed at four levels including clean air. Most animals went through three or four exposures at different solvent concentrations in addition to two sham exposures. The exposures were carried out in different order with at least 3 weeks intervals. The duration and latency of seizures (tonic extensions) in the hind limbs following electric stimulation of the ears were reported, as these endpoints were considered the most sensitive and reproducible. The concentration of isoamyl alcohol (interpolated from the three exposure levels) that evoked a 30 % depression (shortened duration and increased latency of seizures) in recorded activity was determined to be 1 700 ppm in rats and 950 ppm in mice (Frantik *et al* 1994).

7.2.3. In vitro data

In vitro data were not available.

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

Human data on effects of repeated exposure were not available.

7.3.2. Animal data

Inhalation

In a report in which developmental effects in rats and rabbits after inhalation exposure were examined, pregnant rats and rabbits were exposed (whole body) to nominal concentrations of 500, 2 500 and 10 000 mg/m^3 isoamyl alcohol (136, 681 and 2 725 ppm, the highest level being close to the saturation concentration), 6 hours/day, on gestational days 6–15 and 7–19, respectively. In the high concentration groups of both species, maternal toxicity was seen (reduced body weight gain in both species, eye irritation in rabbits). Respiratory irritation was not examined. The no observed adverse effect concentration (NOAEC) in rats and rabbits (maternal effects) was 2 500 mg/m^3 (681 ppm) (Klimisch and Hellwig 1995). For developmental effects, see Section 7.8.2.

Oral exposure

In a 90-day rat (Wistar) study by Schilling *et al* (1997) performed according to OECD guideline, 10 animals per sex and group were exposed to 0, 1 000, 4 000 and 16 000 mg/l via the drinking water (corresponding to 0, 73, 295 and 1 068 mg/kg bw/day for males and 0, 91, 385 and 1 657 mg/kg bw/day for females, according to the authors). Up to the highest dose, there were no effects except slight but significant haematological alterations. Males of the mid- and high-dose groups showed significantly increased red blood cell counts (control: $7.76 \pm 0.2 \times 10^{12}$ cells/l; low dose: $8.10 \pm 0.37 \times 10^{12}$ cells/l; mid dose: $8.18 \pm 0.34 \times 10^{12}$ cells/l; high dose $8.41 \pm 0.38 \times 10^{12}$ cells/l). For males at the highest dose, a significantly decreased mean corpuscular volume ($46.55 \pm 1.60 \times 10^{-15}$ l vs. $48.63 \pm 1.81 \times 10^{-15}$ l in controls) as well as a significantly reduced mean corpuscular haemoglobin content ($1.16 \pm 0.03 \times 10^{-15}$ mol vs. $1.23 \pm 0.04 \times 10^{-15}$ mol in controls) were reported. As the effect on erythrocyte counts in the 4 000-mg/l group was within the range of biological variation and since there were no other treatment-related findings, 295 mg/kg bw/day is considered a no observed adverse effect level (NOAEL).

In another subchronic study, isoamyl alcohol at doses of 150, 500 and 1 000 mg/kg bw per day was given to rats (15 per sex and group, Ash/CSE strain) by gavage on 7 days/week for 17 weeks. The only compound-related effect seen in this study was a slight reduction in body weight gain in high-dose males. This effect was attributed to a 5–10 % decrease in food intake during the first 6 weeks and may have been caused by local irritation due to the high feed concentrations administered. Reductions in some organ weights were regarded as a reflection of the lower body weights. Haematological alterations were not observed in this study (Carpanini *et al* 1973).

Dermal exposure

Data on effects of repeated dermal exposure of animals were not available.

7.3.3. In vitro data

7.4. Irritancy and corrosivity

7.4.1. Human data

Isoamyl alcohol

The odour of isoamyl alcohol was detected at levels of 0.022–0.028 ppm and recognised at levels of 0.044–0.072 ppm (AIHA 1997).

Thirty healthy volunteers (16 men and 14 women) were exposed in random order to 1 mg/m^3 (0.27 ppm) isoamyl alcohol or clean air for 2 hours at controlled conditions. Ratings with visual analogue scales revealed slightly increased perceptions of eye irritation and smell compared with control exposure. The median rating of eye irritation during exposure to isoamyl alcohol reached 5 mm at 1 hour of exposure, versus 3 mm for clean air. Zero - 0 - mm on the visual analogue scale corresponds to "Not at all" and 6 mm to "Hardly at all". The other ratings were not significantly affected (irritation in nose and throat, dyspnoea, headache, fatigue, dizziness, nausea, and intoxication). No effects were found for blinking frequency, tear film break-up time in the eyes, vital staining of the eye, nasal lavage biomarkers, lung function and nasal swelling (Ernstgård *et al* 2013). The SCOEL considers that 1 mg/m^3 (0.27 ppm) can be regarded as the NOAEC for eye irritation in this study as the effect was minimal (below "hardly at all").

In a study by Nelson *et al* (1943), 10 male and female volunteers were exposed in an inhalation chamber to air concentrations of isoamyl alcohol of 100, 150 and 200 ppm (367, 551 and 734 mg/m^3) for 3–5 min. Chamber air concentrations of the substance were not disclosed to the exposed persons. Each individual classified the effects on the eyes, nose and throat (no effect, slightly irritating, very irritating). According to the investigators, 100 ppm caused slight throat irritation in some subjects, whereas a majority estimated that this level would not be acceptable for an 8-hour exposure period.

Exposure to 150 ppm evoked irritation of eyes and nose in the majority of subjects and 200 ppm was objectionable to all (Nelson *et al* 1943). A drawback of the study is that the concentrations were not confirmed by measurements but only calculated from dilution of vapour-saturated air which was added to the air flow. A second drawback is that the exposure duration was very short (HCN 2003).

In a study aimed at elucidating the respiratory uptake of polar organic solvents, 4 volunteers inhaled ten different solvent vapours via a mouth piece for 3–5 minutes. Three subjects inhaling 25 ppm (92 mg/m^3) isoamyl alcohol complained about throat irritation, therefore the fourth volunteer was never exposed. Isoamyl alcohol was considered to be the causative agent, as no irritation was reported during exposure to nine other polar solvent vapours using the same protocol (50 ppm methyl isobutyl ketone, up to 100 ppm ethylene glycol monobutyl ether, methyl acetate, methanol, methyl propyl ketone and propylene glycol monomethyl ether, and up to 200 ppm acetone, ethyl acetate and isopropanol) The respiratory measurements revealed increased breathing frequency during the isoamyl alcohol exposure, interpreted by the authors as being a result of irritation. No further details were given (Kumagai *et al* (1999).

Dermal application of 25 µl 75 % aqueous isoamyl alcohol for 5 min provoked erythema on the forearms of 12 test persons within 60 min after exposure. No irritation was observed in a 48-hour closed patch test on volunteers with an 8 % formulation of isoamyl alcohol in petrolatum (BG-Chemie 1997, HCN 2003).

Other aliphatic alcohols

As there are limited human data on irritation effects of isoamyl alcohol, it is of interest to look also at other aliphatic alcohols. Thus, the "concentrations of vapour which irritated the majority of subjects" were 800 ppm for isopropanol, 25 ppm for *n*-butanol and 100 ppm for cyclohexanol (Nelson *et al* 1943).

Regarding methanol, people using spirit duplicating machines have reported eye irritation after 25 min exposure to 1 245–1 441 mg/m^3 (950–1 100 ppm) methanol (Apol 1981).

Inhalation studies with healthy subjects indicate that 30 min exposure to ethanol (administered as an aerosol of 25 % ethanol in water) in a concentration of 1 800-2 000 ppm initially causes coughing, dry throat and temporary bronchial constriction (Zuskin *et al* 1981).

According to NIOSH, irritation of eyes, nose and throat are the usual symptoms of exposure to isopropanol in concentrations exceeding about 1 000 mg/m^3 (about 400 ppm) (NIOSH 1976).

Van Thriel *et al* (2003) exposed 24 male volunteers to isopropanol (35 and 190 ppm) and *n*-octanol (0.1 and 6.4 ppm) for 4 hours at different occasions. The high exposure (6.4 ppm) to *n*-octanol caused increased ratings of sensory irritation and annoyance, whereas up to 190 ppm isopropanol gave no such effects. The same group found increased blink frequency in young men exposed to 10 ppm or 20 ppm 2-ethylhexanol, using 1.5 ppm as control condition (Kieswetter *et al* 2005).

Sterner *et al* (1949) collected work histories and records of physical examination of men engaged in coating of photographic paper using *n*-butanol as solvent for 10 years. At 200 ppm (breathing zone), a variety of signs of severe eye irritation (blurred vision, lacrimation, photophobia, burning, moderate corneal oedema, oedematous conjunctiva) were common. When the exposure levels were reduced to an average of 100 ppm or less, very few complaints of eye irritation were reported, and these complaints "were associated with short runs where the concentration frequently exceeded 100 ppm" (Sterner *et al* 1949).

Read-across

The effect levels reported above are plotted in Figure 1. Although the findings for the different alcohols are not directly comparable, there is a clear trend of decreasing effect levels with increasing carbon chain length.

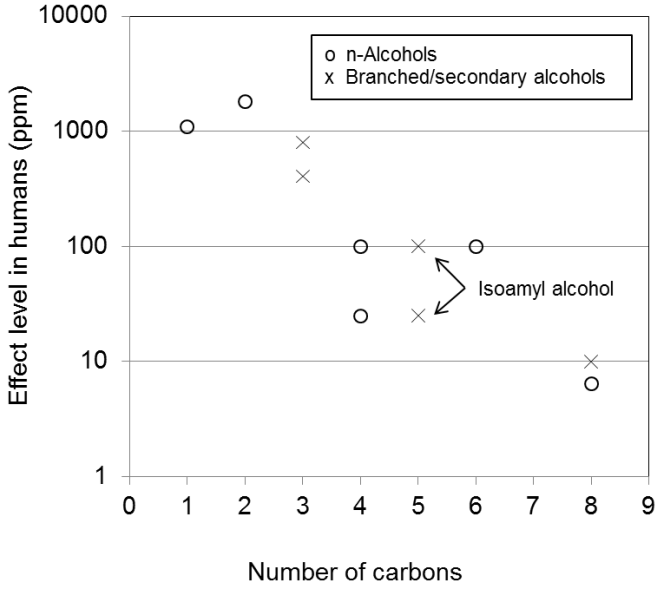


Figure 1. Reported effect levels for irritation of aliphatic alcohols in humans versus number of carbon atoms. The circles (o) represent unbranched primary alcohols and the crosses (x) branched or secondary alcohols (see text for description of the studies)

7.4.2. Animal data

Skin

Dermal application of undiluted isoamyl alcohol for 24 hours to the intact, abraded or scarified skin of rabbits caused slight (semi-occlusive exposure) or moderate irritation (occlusive exposure) (BG-Chemie 1997; HCN 2003).

Eyes

Severe eye irritation with corneal necrosis was reported in one study 18–24 hours after instillation of 5 % isoamyl alcohol solution into the rabbit eye. In another (unpublished) test, the compound (concentration not stated) was moderately irritating to the rabbit eye (reddening, swelling of the mucous membranes, corneal opacity) (BG-Chemie 1997, HCN 2003). Predicted and observed eye irritation of isopentanol (isoamyl alcohol) is stronger than for isopropanol or isobutanol as evidenced in a QSAR study (Barratt 1997).

Respiratory tract

The reported RD_{50} values (concentrations causing a 50 % depression of the respiratory rate due to sensory irritation of the respiratory tract) are 730 ppm (Swiss OF1 mice; Muller and Greff 1984) and 4 452 ppm (Swiss Webster mice; Kane *et al* 1980). The RD_{50} value of 2 588 ppm (9 499 mg/m^3) given by Alarie *et al* (1998, 2001) is approximately the mean of these two experimental data.

The RD_{50} values for aliphatic alcohols tend to decrease with increasing length of the carbon chain (Figure 2). This suggests that the irritation potency in mice, and possibly also in humans, tend to increase with increasing carbon chain length. Thus, isoamyl alcohol is expected to be more potent than for example *n*-butanol and less potent than *n*-octanol or 2-ethylhexanol with respect to irritation.

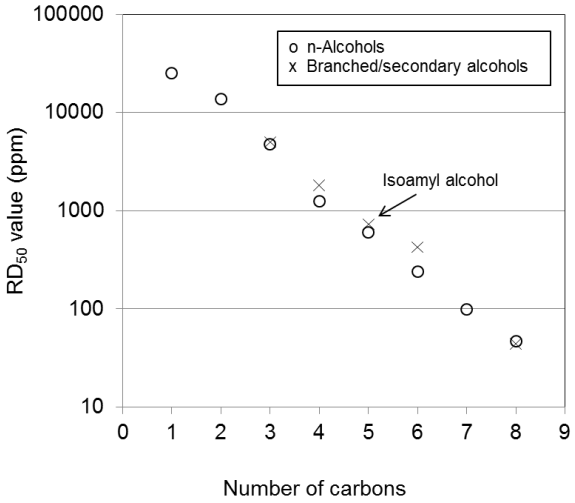


Figure 2. RD_{50} values (concentrations causing a 50 % depression of the respiratory rate) of aliphatic alcohols in mice versus number of carbon atoms. The circles (o) represent unbranched primary alcohols and the crosses (x) branched or secondary alcohols (calculated from Muller and Greff 1984)

Alarie (1981) found that health-based OELs for irritants correlate well with the experimental RD_{50} values, and suggested to use 0.03 of the RD_{50}, as it represents the logarithmic midpoint between 0.01 (no sensory irritation) and 0.1 (some sensory irritation). For isoamyl alcohol, the resulting OEL would be 0.03 × 730 = 22 ppm. This approach to set exposure limits has been questioned e.g. by Bos *et al* (2002) who pointed out that the finding of a correlation is not surprising as many OELs are based on animal data and that the lowest concentration inducing histopathological changes in the nose ranges from 0.3 x to 3 x RD_{50}. However, later on, Kuwabara *et al* (2007) reported a good correlation also between RD_{50} and LOAEC for irritation endpoints in humans (R^2 = 0.8).

7.4.3. . In vitro data

In vitro data were not available.

7.5. Sensitisation

7.5.1. Human data

No sensitisation was observed with 8 % isoamyl alcohol in petrolatum in a Kligman-maximisation test with 25 volunteers. In a patch test, three patients reacted positively to isoamyl alcohol as well as to other substances (BG-Chemie 1997, HCN 2003).

7.5.2. Animal data

Sensitisation tests in animals were not available.

7.5.3. In vitro data

In vitro data were not available.

7.6. Genotoxicity

7.6.1. Human data

Human data on genotoxic effects *in vivo* were not available.

7.6.2. Animal data

Rats were treated orally once with one-fifth of the LD_{50} and bone marrow cells were analysed 48 hours later with respect to cytogenetic effects. There was a slight increase in the number of cells with chromosomal aberrations (2.6 % vs. 0 % in controls), but no changes in the numbers of cells with polyploidy or chromosome gaps (Barilyak and Kozachuk 1988).

7.6.3. In vitro

Isoamyl alcohol was not mutagenic when tested in *Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537) with or without metabolic activation (HCN 2003).

Isoamyl alcohol was negative in a *umu* light absorption test with the *S. typhimurium* TA1535/pSK1002 strain but positive in a *umu* luminescence test with the TA1535/pTL210 strain (Nakajima 2006).

A spot test in *Escherichia coli* K12 showed no effects on gene transposition. The substance did not induce gene mutations in mammalian cells (HPRT-assay in V79 hamster fibroblasts with or without metabolic activation) or DNA damage in a Comet assay with human blood cells (BG-Chemie 1997; HCN 2003; Kreja and Seidel 2002).

7.7. Carcinogenicity

7.7.1. Human data

Human data on carcinogenic effects were not available.

7.7.2. Animal data

There is only one older report on the potential carcinogenic effects of isoamyl alcohol (double-distilled) in rats following oral and subcutaneous administration (Gibel *et al* 1974 , 1975). Fifteen rats (male or female) were given the compound by gavage in doses of 0.1 ml/kg bw (81 mg/kg bw) twice a week until the animals died naturally. Twenty-four additional animals were treated subcutaneously with 0.04 ml/kg bw (32 mg/kg bw) once weekly for their entire lifespan. Two control groups of 25 animals each received saline in the same way. After oral exposure, 4 malignant tumours (liver, forestomach and myeloid leukaemia) and 3 benign tumours (details not given) were detected. Three animals of the concurrent control group had 3 benign tumours. Subcutaneous exposure induced 10 malignant tumours (liver, spleen, glandular stomach, myeloid leukaemia) and 5 benign tumours (details not given). The concurrent controls developed 2 benign tumours. Nearly all exposed rats showed non-carcinogenic effects (hyperplasia of bone marrow, liver damage, splenic metaplasia). Similar increases in tumour frequencies were seen for all tested alcohols, namely isoamyl alcohol (3-methyl-1-butanol), 2-methyl-1-butanol and 1-propanol (Gibel *et al* 1974, 1975). Due to limitations of the experimental design (only one dose tested, small group sizes, uncommon pattern of exposure) and insufficient reporting (no details and no statistical analysis provided), no definite conclusions can be drawn from these results.

7.8. Reproductive toxicity

7.8.1. Human data

Human data on reproductive or developmental effects were not available.

7.8.2. Animal data

Fertility
Data on fertility effects in animals were not available.

Developmental toxicity
Pregnant rats or rabbits were exposed to concentrations of 500, 2 500 and 10 000 mg/m^3 of isoamyl alcohol (136, 681 and 2 725 ppm), 6 hours/day, on gestational days 6–15 or 7–19 (Klimisch and Hellwig 1995) according to OECD guideline 414. In the high-concentration groups of both species, maternal toxicity was seen (retarded body weight gain in both species). There were no other effects including haematological alterations. There were no signs of embryotoxicity or teratogenicity even at the highest exposure level. Rabbits exhibited a significant increase in foetal soft tissue variations. As the incidence for this endpoint was unusually low in the concurrent control group and the incidences of the treated group were within the range of biological variation, the authors considered these findings not toxicologically relevant. Therefore, NOAECs in rats and rabbits are 10 000 mg/m^3 for developmental effects and 2 500 mg/m^3 for maternal effects.

7.9. Lack of specific scientific information

In general, Isoamyl alcohol is a well-investigated compound experimentally. There is no specific lack of information.

8. GROUPS AT EXTRA RISK

There is no specific information on population groups at extra risk from Isoamyl alcohol.

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