‘Iso-octyl’ alcohol (mixed isomers)

(CAS No: 26952-21-6)

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 isooctyl alcohol 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 AAE Wibowo, Ph.D. (Coronel Institute of the Academic Medical Centre, Amsterdam, the Netherlands).

In January 1998, literature was searched in the databases Medline, Embase, and Chemical Abstracts, starting from 1966, 1988, and 1970, respectively, and using the following key words: isooctyl alcohol, methylheptyl alcohol, and 26952-21-6. NIOSHTIC, HSELINE, CISDOC, MHIDAS (from 1997 backwards) and POLTOX (Toxline, Cambridge Scient Abstr and FSTA) (from 1986-December 1994), databases available from CD-ROM, were consulted as well. The final search was carried out in Toxline and Medline in November 2002.

In April 2003, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	'iso-octyl' alcohol
synonyms	:	isooctanol; isooctane-1-ol; 1-isooctanol; 6-methyl-1-heptanol
molecular formula	:	$C_8H_{18}O$
structural formula	:	$(CH_3)_2CH_2$-CH_2- CH_2-CH_2- CH_2-CH_2OH
CAS number	:	26952-21-6.

3 Physical and chemical properties

molecular weight	:	130.23
boiling point	:	184-191°C
melting point	:	-
flash point	:	82°C (open cup)
vapour pressure	:	at 25°C: 10 Pa (extrapolated value)
solubility in water	:	insoluble
log $P_{octanol/water}$	:	2.73 (estimated)
conversion factors	:	at 20°C, 101.3kPa: 1 mg/m^3 = 0.18 ppm 1 ppm = 5.41 mg/m^3

Data from ACG99, NLM01, http://esc.syres.com.

'Iso-octyl' alcohol is a mixture of closely related isomeric, primary alcohols with branched chains having the general formula R-CH_2OH in which R- represents heptyl radicals; these are mostly methyl groups usually located in the 3-, 4-, or 5-positions (ACG99). A typical 'iso-octyl' alcohol mixture was described to consist of 70-80% dimethyl-1-hexanols, 10-20% methyl-1-heptanols, and 5-10% other homologous primary alcohols (Sca73). 'Iso-octyl' alcohol is a colourless liquid with characteristic odour (ACG99). The odour threshold is not known.

4 Uses

'Iso-octyl' alcohol is used as a solvent and as a chemical intermediate in the production of plasticisers and other products, as an intermediate for non-ionic detergents and surfactants, in synthetic drying oils, cutting and lubricating oils, and hydraulic fluids, as a resin solvent, emulsifier, and antifoaming agent, and as a reagent for introducing the iso-octyl group into other compounds (ACG99).

5 Biotransformation and kinetics

The committee did not find quantitative data on the biotransformation and kinetics of 'iso-octyl' alcohol.

Based on systemic effects observed after occlusive applications of doses of 0.10-3.16 mL/kg (i.e., ca. 83 to 2630 mg/kg bw) to the clipped, intact abdominal skin of rabbits, percutaneous absorption is evident (Sca73).

6 Effects and mechanism of action

Human data

In an irritation/sensitisation test in which unreported amounts of undiluted 'iso-octyl' alcohol were applied to the skin of volunteers using 'standard patch testing procedures' (no details given), mild primary irritation reactions consisting of very mild erythema in 8/32 and erythema in 5/32 while no reactions were seen in the remaining 19 volunteers. Retesting 2 weeks later showed an intensification of reactions in 8 volunteers all showing very mild erythema while irritation was absent following the first application. The others had a similar reaction (n=12; no or very mild) or a less severe reaction (n=12) (Nel51). Contrary to Nelson who concluded that there was no evidence of sensitisation, the committee considers this test as inconclusive because of a slight intensification of irritation reactions in a number of the volunteers and the lack of experimental data.

Animal data

Irritation and sensitisation

In Wistar rats, Swiss mice, and English Short Hair guinea pigs (n=10/group; sex: not reported) exposed to nearly saturated vapours of 'iso-octyl' alcohol calculated to be 200 ppm (1082 mg/m^3), for 6 hours, slight to moderate irritation (on a 4-point grading scale of slight-moderate-marked-severe) of the mucous membranes of the eyes, nose, throat, and respiratory tract (blinking, lachrymation, preening, nasal discharge, salivation, gasping, chewing movements) were seen (Sca73) (see also '*Acute toxicity'*).

When 0.1 mL of undiluted 'iso-octyl' alcohol was instilled into the left eye of rabbits (n=6), the compound was concluded to be severely irritating (on a 4-point grading scale of slight-moderate-marked-severe) observations at 1 and 4 hours, and 1, 2, 3, 4, and 7 days. Draize scores presented only for the observation points 1, 3, and 7 days were 24, 18, and 0, respectively (maximum score possible: 110) (Sca73).

'Iso-octyl' alcohol was concluded to be moderately irritating (on a 4-point grading scale of slight-moderate-marked-severe) following 24-hour occlusive application of doses of 0.10 to 3.16 mL/kg (i.e., ca. 83 to 2630 mg/kg bw) to the clipped intact abdominal skin of rabbits (n=4/dose). Signs of irritation observed included slight to moderate or severe erythema, slight to moderate oedema, as

well as atonia, blanching, desquamation, coriaceousness, necrosis, and eschar (Sca73). Application of unknown amounts of undiluted 'iso-octyl' alcohol to the skin of rabbits for 6 to 24 hours induced extensive erythema and oedema, and in several cases intracutaneous haemorrhages. The erythema disappeared within 2 or 3 days, the skin appeared dry and wrinkled, assuming a tanned and leathery appearance, and becoming very tough and rigid within 7 to 10 days. Thereafter, the leathery skin was completely sloughed (Nel51).

Acute toxicity

Scala and Burtis performed an inhalation study in which groups of Wistar rats, Swiss mice, and English Short Hair guinea pigs (n=10/species; sex: not reported) were exposed to atmospheres nearly saturated with 'iso-octyl' alcohol vapours, for 6 hours. Atmospheres were generated by passing all air entering the chamber through fritted-disk glass bubblers containing a measured amount of alcohol. No attempts to impact entrained droplets and no analytical determinations of the chamber concentrations were made. The nominal concentration, calculated from the net loss of alcohol from the bubblers and the total chamber airflow, was stated to be 200 ppm (1082 mg/m^3). Apart from slight to moderate irritation of the mucous membranes (see also '*Irritation and sensitisation*'), no effects were seen during the 24-hour observation period and at necropsy (Sca73).

Twenty-four-hour occlusive application of doses of 'iso-octyl' alcohol of 0.10 to 3.16 mL/kg (i.e., ca. 83 to 2630 mg/kg bw) to the clipped intact abdominal skin of rabbits (n=4/dose) resulted in the death of one animal in the highest dose group groups. Further, dermal irritation (see '*Irritation and sensitisation*') and central nervous system depression (laboured respiration, ataxia, sprawled limbs), disappearing 4 to 48 hours after exposure began, were seen. No information on dose-effect relationship, severity, or incidences was given (observation time: 7 days) (Sca73). All 3 rabbits survived dermal treatment with unknown amounts of undiluted 'iso-octyl' alcohol for 6 hours. All animals showed incoordination and unsteadiness. Treatment for 8.7, 12, or 24 hours caused mortality in 2/4 (at the end of the experiment), 3/3 (within 1-2 days), and 2/2 (within 1 day) animals, respectively. Systemic signs observed included incoordination, unsteadiness, very weak or absent corneal reflexes, and narcosis (observation period: 14 days) (Nel51).

An oral LD_{50} of 1480 mg/kg bw has been calculated for rats (Sprague-Dawley; n=5/dose) given doses of 0.032 to 10.0 mL/kg bw (i.e., ca. 27-8320 mg/kg bw). The principal effects included signs of central nervous system depression (such as inactivity, ataxia, limb sprawling, depressed righting and

placement reflexes, prostration, coma) and laboured respiration. At gross necropsy, there were no remarkable findings (Sca73). Nelson did not observe mortality or signs of toxicity in rats (n=2/dose) given single oral doses up to 3160 mg/kg bw or in rabbits (n=2) given 320 mg/kg bw. In rats, doses of 4220, 5620, and 10,000 mg/kg bw caused mortality (generally within 1 day) in 1/10, 10/10, and 2/2 animals, respectively. In rabbits, mortality (generally within 6 hours) incidences were 3/4, 3/4, and 2/2 at doses of 560, 1000, and 1780 mg/kg bw, respectively. Signs of toxicity such as incoordination, unsteadiness, weakened or absent corneal reflexes, and narcosis were observed. Upon histological examination, there were no remarkable findings (Nel51).

Repeated-dose toxicity

Male rats (Crl:CD®(SD)BR; n=10/group) were exposed nose-only to 0, 110, 600, or 3100 mg/m^3 of 'isooctanol' consisting of C_8 isomers, predominantly primary dimethylhexanols and methylheptanols, 6 hours/day, 5 days/week, for 2 weeks. Half of the animals were killed after the 10th exposure, the remaining animals after a 14-day recovery period. Clinical observations and body weight recordings were made regularly. Post-mortem examinations included analysis of urine and blood samples, organ and body weights, gross and microscopic evaluations of amongst others nasal cavity and trachea. There was no treatment-related mortality. Clinical signs observed included lung noise in 3/20 rats of the 2 lower exposure groups and frequent instances of lung noise, eye and nose irritation, red-stained perineum, inactivity, impaired balance, ruffled fur, and alopecia in the animals exposed to 3100 mg/m^3. None of these signs were seen during the recovery period in any of the groups. There were no effects on the body weights of the animals of the 2 lower exposure groups, but those of the animals of the high-exposure group were significantly lower from day 2 onwards when compared to controls. Statistically significant organ weight changes observed in the animals sacrificed after the 10th exposure included increased absolute kidney weights in the low- and mid-concentration group, increased relative kidney weights in the mid- and high-concentration group, decreased absolute and relative spleen weights, decreased absolute lung and thymus weights, and increased relative liver weights in the high-concentration group. After the 14-day recovery period, there were statistically significant decreases in absolute and relative spleen weights in all treated groups and increases in relative kidney weights in the high-concentration group. Upon macroscopic and microscopic examination only nasal effects were found. In the animals sacrificed after the 10th exposure, dermatitis of the nasal area and acute rhinitis with respiratory

nasal epithelial necrosis and squamous metaplasia were seen in 5/5 animals of the high-concentration group (all with severity degree 'moderate') and respiratory nasal epithelial squamous metaplasia in 4/4 animals of the mid-concentration group (severity: 'moderate' in 3, 'slight' in 1; no tissue present on slide of remaining animal). After a 14-day exposure-free period, there were still 'slight' rhinitis and 'slight' squamous metaplasia in 2/5 animals of the high-concentration group and 'slight' squamous metaplasia in 1/5 animals of the mid-concentration group. No lesions were observed in the animals exposed to 110 mg/m^3. Upon urine and blood analysis, the only effects considered to be test substance-related were significant increases in red blood cell parameters indicative of polycythaemia found in animals immediately sacrificed after the final exposure to 600 or 3100 mg/m^3 (DuP85). From this study, the committee could not establish a no-observed-adverse-effect level, since decreased absolute and relative spleen weights were found in animals sacrificed 14 days after receiving a final exposure to 110 mg/m^3, the lowest concentration tested. *[the committee notes the relatively wide ranges in concentrations at the exposure levels (18-180, 230-900, and 1600-4600 mg/m^3) and further that it could not be assessed whether the aerosols were adequately generated since the appendix presenting the results of these measurements was not present in the copy made available to the committee although particle size was determined at 2 occasions]*.

No mortality or any other effects were reported in rats (n=5) exposed to air saturated with 'iso-octyl' alcohol vapour at 20°C for 150 hours (no further data available) (Nel51).

In a study to examine whether and to what extent 'plasticiser alcohols' had similar effects as industrial plasticisers, such as di-(2-ethylhexyl) phthalate and adipate, daily oral (gavage) administration of 130 mg/kg bw of 'iso-octyl' alcohol to male rats (Alderley Park Wistar derived ; n=5), for 14 subsequent days, did not induce testicular atrophy, hepatomegaly, peroxisome proliferation, or hypolipidaemia (Rho84).

The committee did not find data on the potential long-term toxicity, carcinogenicity, mutagenicity/genotoxicity, or reproduction toxicity of 'iso-octyl' alcohol.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for ‘iso-octyl’ alcohol in the Netherlands is 270 mg/m^3 (50 ppm), 8-hour TWA.

Existing occupational exposure limits for ‘iso-octyl’ alcohol in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find data on the toxicokinetics of ‘iso-octyl’ alcohol, but from acute dermal toxicity data in experimental animals, percutaneous absorption was evident.

Upon testing in human volunteers, mild skin irritation was found while results were negative or inconclusive regarding sensitisation. In experimental animals, ‘iso-octyl’ alcohol was irritating to eyes and skin.

Exposure to nearly saturated vapours (probably 1082 mg/m^3 or 200 ppm), for 6 hours, caused eye, nose, throat, and respiratory tract irritation but no other effects in several animal species. Dermal occlusive application of unknown amounts to rabbits induced effects on the nervous system (laboured respiration, ataxia, incoordination, unsteadiness, narcosis) and mortality. Following oral administration, a LD_{50} of 1480 mg/kg bw was found in rats. Effects observed were similar to those seen after dermal exposure.

In a 14-day inhalation study using male rats (DuP85), exposure to aerosol concentrations of 110, 600, and 3100 mg/m^3 caused, amongst others, clinical signs, decreased body weight, relative organ weight changes (increase: kidney, liver; decrease: spleen), changes indicative of polycythaemia, and acute rhinitis with respiratory epithelial necrosis and squamous metaplasia in animals sacrificed immediately after the last exposure to 3100 mg/m^3 and increased relative kidney weights, changes indicative of polycythaemia, and respiratory nasal epithelial squamous metaplasia in animals sacrificed after the last exposure to 600 mg/m^3. After a 14-day recovery period, the only effects observed were, amongst others, decreased absolute and relative spleen weights in all groups and nasal lesions in 2/5 and 1/5 animals of the high- and mid-concentration group, respectively. Because of the effects on spleen weights found in the recovery group at all concentration levels, the committee could not set a NOAEL in this study. In view of the limited number of animals (n=5/group/sacrifice), the short duration, and the lack of data on particle size and particle size distribution, the

committee is of the opinion that this study cannot be used to derive a health-based occupational exposure limit.

The committee did not find data on the potential long-term toxicity, carcinogenicty, mutagenicity/genotoxicity, or reproduction toxicity of 'iso-octyl' alcohol.

The committee considers the toxicological database on 'iso-octyl' alcohol too poor to recommend a health-based occupational exposure limit.

Considering the effects found in a 14-day (male) rat inhalation study (organ weight changes at 110 mg/m^3 and the nasal lesions at 600 mg/m^3), the committee concludes that the present MAC value for 'iso-octyl' alcohol of 270 mg/m^3 (50 ppm), 8-hour TWA, may be too high.

References

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ACG03a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, Inc, 2003: 74.

ACG03b American Conference of Governmental Industrial Hygienists (ACGIH). 2003 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2003: 36.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 28 (At-vejledning C.0.1).

DFG02 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2002. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH, 2002; rep no 38.

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EC03 European Commission: Directorate General of Employment and Social Affairs. Occupational exposure limits (OELs). http://europe.eu.int/comm/employment_social/h&s/areas/oels_en.htm.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 20.

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Sca73 Scala RA, Burtis EG. Acute toxicity of a homologous series of branched-chain primary alcohols. Am Ind Hyg Ass J 1973; 34: 493-9.

Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.

SZW03 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2003. The Hague, The Netherlands: Sdu, Servicecentrum Uitgevers, 2003: 31.

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Annex

Occupational exposure limits for ‘iso-octyl’ alcohol 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	50	270	8 h	administrative		SZW03
Germany						
- AGS	-	270			S	TRG00
- DFG MAK-Kommission	-	-				DFG02
Great Britain						
- HSE	50	271	8 h	OES		HSE02
Sweden	-	-				Swe00
Denmark	50	270	8 h		S	Arb02
USA						
- ACGIH	50	-	8 h	TLV	S	ACG03b
- OSHA	-	-				ACG03a
- NIOSH	50	270	10 h	REL	S	ACG03a
European Union						
- SCOEL	-	-				EC03

[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.