Octane

(CAS No: 111-65-9)

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 octane 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, Academic Medical Centre, Amsterdam, the Netherlands).

The evaluation of the toxicity of octane has been based on the review by Low et al. (Low87). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in February 1998, literature was searched in the databases Medline, Current Contents, Embase, and Chemical Abstracts (starting from 1966, 1970, 1988, and 1970, respectively) and Poltox (from 1994 backwards), HSELINE, CISDOC, MHIDAS and NIOSHTIC, and using the following key words: n-octane, octane, and 111-65-9.

In March 2000, the President of the Health Council released a draft of the document for public review. The committee received comments by the following individuals and organisations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland), P de Kettenis (CEFIC, Brussels, Belgium), P Wardenbach, Ph.D. (Bundesanstalt für Arbeitsschutz and Arbeitsmedizin. Dortmund, FRG), and L Whitford (Health and Safety Executive, London, England). These comments were taken into account when deciding on the final version of the document.

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

2 Identity

name	: octane
synonyms	: n-octane
molecular formula	: C_8H_{18}
structure	: CH_3-$(CH_2)_6$-CH_3
CAS number	: 111-65-9

3 Physical and chemical properties

molecular weight	: 114.22
boiling point	: 125.7°C
melting point	: -56.8°C
flame point	: 13°C (closed cup); 22°C (open cup)
vapour pressure	: at 20°C: 1.4 kPa
solubility in water	: insoluble (at 25°C: 0.07 mg/100 mL)
log $P_{octanol/water}$	: 5.18 (experimental); 4.27 (estimated)
conversion factors	: at 20°C, 101.3 kPa: 1 ppm = 4.76 mg/m^3 1 mg/m^3 = 0.21 ppm

Data from ACG02, NLM04, http://www.syrres.com/esc/est_kowdemo.htm.

Octane is a colourless liquid with an odour of gasoline. Odour thresholds of ca. 230 (48 ppm) (Amo83) and from 725-1208 mg/m^3 (ca. 150-250 ppm) (Rut86) have been reported.

4 Uses

Octane is used as a solvent, in organic synthesis, and in azeotropic distillations. Octanes are present in gasoline and petroleum solvents such as VM&P naphta (ACG02).

5 Biotransformation and kinetics

In an occupational setting, the major route of exposure of octane is by inhalation. The extent of respiratory uptake in humans is not known, but Low et al. suggested that it is probably similar to that reported for hexane or heptane (Low87). The retention of hexane was estimated to lie between 6 and 34% (DEC87).

Dahl studied the fate of [^{14}C]-octane by nose-only exposure of male F344-rats to actual concentrations of ca. 11 or 1614 mg/m^3 (2.2 or 339 ppm) for 2 hours. Dahl found uptake rates of 6.1 and 3.4 nmol/kg/min/ppm, respectively (equivalent to 0.7 and 0.4 µg/kg/min/ppm octane) (Dah89).

Examining the absorption of various organic solvents through the skin of rats *in vitro*, Tsuruta calculated a skin penetration rate for octane of 8.2 x10^{-5} nmol/cm^2/min (i.e., 0.009 ng/cm^2/min), indicating very poor skin absorption (Tsu82).

Zahlsen et al. investigated the distribution of inhaled octane in male SD-rats exposed to ca. 480 mg/m^3 (100 ppm), 12 hours/day, for 3 days. The levels of octane were measured in blood, brain, liver, kidneys, and perirenal fat immediately after exposure at days 1 and 2 and immediately and 12 hours after exposure at day 3. Very low concentrations of octane were found in blood, relatively high concentrations in brain and kidneys, and the substance accumulated in fat tissues (Zah92). In mice exposed to concentrations varying between 48 and 47,600 mg/m^3 (10 and 10,000 ppm) for various exposure periods (between 0.5-24 hours), Holmberg et al. found approximately similar concentrations in kidneys and brain while those in the liver were usually somewhat higher. There was a relationship between the levels in blood and organs (Hol77).

In male F344 rats nose-only exposed to actual concentrations of [^{14}C]-labelled octane of ca. 11 or 1614 mg/m^3 (2.2 or 339 ppm) for 2 hours, the major route of elimination during the 2-hour exposure and 70-hour post-exposure period was by exhalation of hydrocarbon and carbon dioxide, accounting for ca. 76 (ca. 69.5 and 6.5% during and after exposure, respectively) and ca. 15% (ca. 8 and 7% during and after exposure, respectively) of the radioactivity inhaled, respectively, at the low concentration and for ca. 89 (ca. 84.5 and 4.5% during and after exposure) and 5% (ca. 2 and 3% during and after exposure, respectively), respectively, at the high concentration. Radioactivity excreted in urine and faeces amounted to ca. 15 and 0.5% of the radioactivity inhaled, respectively, at the low concentration and to ca. 4 and 0.3%, respectively, at the high concentration. At 2.2 ppm, nearly 5% of the total concentration inhaled radiolabel remained in the rat body 70 hours post-exposure vs. ca. 2% at 339 ppm. Fifty percent of the radioactivity that was retained at the end of the 2-hour exposure period was eliminated 5-10 hours later. Elimination of radioactivity stopped after 30 hours, when 75 to 85% of the activity had been eliminated (Dah89).

Olson et al. studied the biotransformation of octane in male and female F344 rats given oral (gavage) doses of octane (purity: 99%) of 1400 mg/kg bw on alternate days for 2 weeks. The authors identified the metabolites 2-octanol, 3-octanol, 5-oxohexanoic acid, and 6-oxoheptanoic acid in the urine, collected for the first 48 hours following initial dosing, but no ketone, (γ-)diketone, or diol derivatives. The relative amounts of these metabolites differed between males and females, 2-octanol and 5-oxohexanoic acid being the major metabolite in female and male rats, respectively (Ols86).

6 Effects and mechanism of action

Human data

According to publications published around 1930, concentrations of ca. 38,000-48,000 (8,000-10,000 ppm) and 64,000 mg/m^3 (13,500 ppm) should be narcotic and lethal, respectively, to humans (ACG02). In their review, Low et al. reported that octane has not been shown to cause the type of peripheral neuropathy associated with hexane. The health effects of octane should be similar to those of heptane, except that octane is about 1.2-2 times more toxic. Citing a paper from 1936, Low et al. stated that application of liquid octane to the forearm (for 1 hour) and to the thigh (for 5 hours) of human volunteers was found to cause erythema, hyperaemia, inflammation, and pigmentation as well as a burning and itching sensation at the application site. Some blister formation with the pain subsiding 3 hours after discontinuation of contact with octane occurred after the 5-hour exposure (Low87).

Animal data

The committee did not find data from studies on the eye- and skin-irritating and skin-sensitising potential of octane.

With respect to the respiratory tract, Kristiansen and Nielsen studied the sensory irritation of octane in the upper part of the respiratory tract by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}) in male Ssc:CF1 mice. An RD_{50} could not be established since the decrease in respiratory rate did not exceed 40% at the concentration range tested (up to 11,693 ppm or ca. 55,700 mg/m^3) when compared to controls (Kri88). Schaper listed an RD_{50} of 84,600 mg/m^3 (18,500 ppm), which was indicated to be an extrapolated value (probably from the data from Kristiansen and Nielsen) (Sch93).

A 4-hour LC_{50} of 118,000 mg/m^3 (24,780 ppm) has been reported for rats (NIO04). Referring to studies performed in mice in the 1920s, Low et al. stated that no narcotic effects were seen until exposure concentrations were between 33,200 and 47,600 mg/m^3 (7000 and 10,000 ppm). Loss of righting reflexes was seen in mice exposed to 33,200 mg/m^3 (7000 ppm) for ca. 90 minutes. Complete loss of reflexes and anaesthesia was reported after exposure to 51,170 mg/m^3 (10,750 ppm) for 30 minutes and 120 minutes, respectively (Low87).

Glowa studied the effects of acute inhalation exposure to octane concentrations of 2380-33,320 mg/m^3 (500-7000 ppm) on behaviour, i.e., schedule-controlled responding (maintained under a fixed interval, 60-second schedule of milk presentation), of male Charles River CD-1 mice. Animals received cumulative exposures with incrementally increased concentrations at 40-minute intervals until the responding stopped or 4-hour exposures to single concentrations. At the cumulative exposure scenario, concentrations less than 4760 mg/m^3 (1000 ppm) did not greatly affect the responding, while exposure to ca. 14,300 (3000 ppm), 26,660 (5600 ppm), and 33,320 mg/m^3 (7000 ppm) reduced responding by approximately 50, 90, and 100%, respectively. At the 4-hour exposure scenarios, there was a slight decrease (by 23%) at 2380 mg/m^3 (500 ppm) and an increase (by 47%) at 9520 mg/m^3 (2000 ppm), while concentrations of ca. 19,000 and 33,320 mg/m^3 (4000 and 7000 ppm) resulted in decreases by 85 and 99% (Glo84). In their sensory irritation studies, Kristiansen and Nielsen observed no conspicuous CNS effects (indicator: 'series of body movements') in male CF-1 mice during 30-minute exposures to octane concentrations up to 9640 ppm (ca. 46,000 mg/m^3) (10,000 ppm). At exposure to 11,693 ppm (ca. 55,700 mg/m^3), these series of movements were seen during the first 24 minutes of exposure after which they were followed by single movements (Kri88).

Nessel et al. reported that octane did not cause any significant effect upon daily examination of motor activity (using an automated video image analysis system), functional observation measures, and learned performance of a visual discrimination task (depression of a lever under an illuminated light in order to receive a water award) in male rats (WAG/RijCrlBR) exposures to 1400, 4200, or 14,000 mg/m^3 (294, 882, or 2940 ppm), 8 hours/day, for 3 days (no more data available) (Nes00a, Nes00b).

Contrary to its branched-chain isomers, e.g., 2,2,4-trimethylpentane, 2,3,4-trimethylpentane, and 2-methylheptane, which are known to cause proximal tubular nephropathy in male rats (Loc90, Ser92), octane did not induce histological changes in the kidneys of male and female rats after oral (gavage) administration of doses of 1400 mg/kg bw/day on alternate days for 2 weeks (Ols86).

An Indian research group published several reports on the effects on the activities of enzyme systems after intraperitoneal administration of octane. In female albino rats intraperitoneally injected with 710 mg/kg bw/day for 2 or 7 days, Khan and Pandya found significant increases in relative liver wet weights (7-day treatment) and decreased activities of aniline hydroxylase (7-day treatment), aminopyrine-*N*-demethylase (2- and 7-day treatment), and glucose-6-

phosphatase (7-day treatment) in the supernatant of liver homogenate. A significant increase of phenobarbital-induced sleeping time (2- and 7-day treatment) was also noted. The authors concluded that the mode and site of action of octane are a depression of drug-metabolising enzyme activities in the smooth endoplasmic reticulum of the liver (Kha80a). Further, this treatment induced significant reductions (at both treatments) in the specific activities of benzo[*a*]pyrene hydroxylase, benzphetamine-*N*-demethylase, *p*-nitroanisole-*O*-demethylase, and glutathione-*S*-transferase. Cytochrome P450 (measured only at the 7-day treatment) and total and free sulphydryl contents of the liver were also decreased significantly after the 7-day treatment; liver lipid peroxidation was significantly increased (Kha80b). Alkaline phosphatase activities of the liver, spleen, and bone marrow were significantly increased after 2 and 7 treatment days. However, there were no changes in brain alkaline phosphatase activities (Pan82). Effects on hepatic and serum enzymes included decreased activities of serum acetylcholine esterase and carboxylesterase and increased aldolase activity after 2 and 7 days of treatment. Total protein, albumin, total and free cholesterol levels were significantly decreased after 7 treatment days (Kha85).

Rabovsky et al. examined the effects of octane on cytochrome P450 enzyme activities *in vitro* in induced rat liver and lung microsomes. Octane (at 2mM) inhibited the activity of benzo[a]pyrene hydroxylase in rat liver but not in lung microsomes and the activity of 7-ethoxycoumarin deethylase in both microsomal preparations. Octane did not affect the NADPH generation system (Rab86). In further *in vitro* studies using lung microsomes, octane also inhibited the activity of the cytochrome P450-dependent enzyme benzyloxyphenoxazone dealkylase (Rab89).

The committee did not find data on repeated-dose toxicity, including carcinogenicity and reproduction toxicity, mutagenicity and genotoxicity of octane.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for octane in the Netherlands is 1450 mg/m^3 (300 ppm), 8-hour TWA.

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

Uptake rates of 6.1 and 3.4 nmol/kg/min/ppm, respectively (equivalent to 0.7 and 0.4 μg/kg/min/ppm octane) were estimated in male F344 rats exposed to concentrations of [^{14}C-]octane of ca. 11 or 1614 mg/m^3 (2.2 or 339 ppm) for 2 hours. The major route of elimination during and after exposure was exhalation of unchanged parent compound (ca. 76 and 89%, respectively) and CO_2 (ca. 15 and 5%, respectively). Only minor amounts were excreted in the urine (ca. 3 and 4%, respectively) and faeces (ca. 0.5 and 0.3%, respectively) or remained in the carcass (ca. 5 and 1%, respectively). *In vitro* experiments using rat skin, resulting in a skin penetration rate of 0.009 ng/cm^2/min suggested a poor skin absorption potential. Following administration of oral (gavage) doses of 1400 mg/kg bw/day (on alternate days for 2 weeks) to male and female F344 rats, metabolites identified in the first 48-hour urine, included 2-octanol, 3-octanol, 5-oxohexanoic acid, and 6-oxoheptanoic acid. The relative amount of metabolites was sex dependent, 2-octanol and 5-oxohexanoic acid being the major metabolite in female and male rats, respectively. There was no evidence of formation of metabolites such as γ-diketones, which is considered the first of a series of steps leading to peripheral neuropathy.

Human data from publications from the 1930s indicate that liquid octane is irritating to the skin; concentrations of 38,000-48,000 (8000-10,000 ppm) and 68,000 mg/m^3 (13,500 ppm) were thought to be narcotic and lethal, respectively.

The 4-hour LC_{50} in rats was 118.000 mg/m^3 (24,780 ppm). In mice, loss of righting reflexes was seen at exposure to 33,200 mg/m^3 (7000 ppm) for ca. 90 minutes and complete loss of reflexes and anaesthesia at exposure to 51,170 mg/m^3 (10,750 ppm) for 30 minutes and 120 minutes, respectively. In mice exposed to concentrations incrementally increasing at 40-minute intervals or to single concentrations for 4 hours, no effect on scheduled-controlled responding was observed at concentrations up to 4760 mg/m^3 (1000 ppm) while performance was affected at levels of 9520 mg/m^3 (2000 ppm) and higher. In (male) rats exposed to concentrations up to 14,000 mg/m^3 (2940 ppm), 8 hours/day, for 3 days, no significant effects were seen upon daily examination of motor activity, functional observation measures, and learned performance of a visual discrimination task. No kidney effects were observed in male and female rats given oral (gavage) doses of 1400 mg/kg bw/day on alternate days for 2 weeks. Data from rats intraperitoneally injected with doses of 710 mg/kg bw/day for 2 or 7 days and from *in vitro* experiments in which octane (at 2 mM) was incubated

with rat liver or lung microsomes showed that octane can affect the activity of metabolic enzymes.

The committee did not find data from experimental animal studies on the potential eye and skin irritation, skin sensitisation, repeated-dose (longer than 1 week) toxicity (including carcinogenicity), reproduction toxicity, mutagenicity, and genotoxicity of octane.

The committee considers the toxicological database on octane 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 octane 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	300	1450	8 h	administrative	-	SZW05
Germany						
- AGS	500	2350	8 h		[d]	TRG04
	2000	9400	15 min			
- DFG MAK-Kommission	500	2400	8 h			DFG05
	1000	4800	15 min[c]		[e, f]	
Great-Britain						
- HSE	-	-				HSE02
Sweden	200	900	8 h		[d]	Swe00
	300	1400	15 min			
Denmark	200	935	8 h	OEL	-	Arb02
USA						
- ACGIH	300	-	8 h	TLV	[d]	ACG05
- OSHA	500	2350	8 h	PEL		
- NIOSH	75	350	8 h	REL		ACG04
	385	1800	ceiling-15 min			ACG04
European Union						
- SCOEL	-	-				EC05

[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.
[d] For all octane isomers.
[e] For all isomers, except 2,2,4-trimethylpentane.
[f] Listed among substances with MAK values but no pregnancy risk group classification.