Pentan-3-one

(CAS No: 96-22-0)

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 pentan-3-one 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).

In December 1997, literature was searched in the databases Medline and Chemical Abstracts (starting from 1966 and 1970, respectively), as well as Poltox (from 1994 backwards), HSELINE, CISDOC, MHIDAS, and NIOSHTIC (from 1997 backwards), and using the following key words: diethyl ketone, pentanone, dimethylacetone, and 96-22-0.

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 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 2003 did not result in information changing the committee's conclusions.

2 Identity

Name	:	pentan-3-one
synonyms	:	3-pentanone; pentanone-3; diethyl ketone; dimethylacetone; methacetone
molecular formula	:	$C_5H_{10}O$
Structure	:	CH_3-CH_2-CO-CH_2-CH_3
CAS number	:	96-22-0

3 Physical and chemical properties

molecular weight	:	86.1
boiling point	:	102°C
melting point	:	-42°C
flash point	:	13°C (open cup)
vapour pressure	:	at 25°C : 2.0 kPa
solubility in water	:	slightly soluble (at 20°C: 4.7 g/100 mL)
log $P_{octanol/water}$	:	0.99 (experimental); 0.75 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 mg/m^3 = 0.28 ppm 1 ppm = 3.59 mg/m^3

Data from NLM03, http://esc.syrres.com.

Pentan-3-one is a colourless, mobile liquid, with a acetone-like odour (ACG96). Odour thresholds of 7 (2 ppm) (Amo03) and ranging between 3 and 49 mg/m^3 (0.8 and 14 ppm) (Rut86) were reported.

4 Uses

Pentan-3-one is used as a solvent and in organic synthesis (ACG96).

5 Biotransformation and kinetics

The committee did not find data on the biotransformation and kinetics of pentan-3-one in humans or experimental animals

6 Effects and mechanism of action

Human data

Threshold concentrations for eye (subjectively) and lung (objectively by plethysmograph) response were determined by applying various concentrations of pentan-3-one to the eyes of (an unknown number of) subjects through close-fitting goggles and, in separate experiments, to the lungs via mouthpiece. No numbers were presented, but from a graph, the committee estimates that the thresholds for respiratory and eye irritation were roughly 400 and 800 ppm (ca. 1440 and 2870 mg/m^3), respectively (Dou87).

The committee did not find other human data on effects from (occupational) exposure to pentan-3-one.

Animal data

Irritation and sensitisation

Following instillation into the eyes of rabbits (n=5), pentan-3-one scored an injury grade of 4 (i.e., 0.02 mL of undiluted test substance gives injury up to 5.0 points, or 0.1 mL over 5 points) on a scale from 1 to 10 (Smy54; see also Car46). Moderate irritation was reported when 50 mg or 100 mg (for 24 hours) was instilled into the eyes of rabbits (no details presented) (NIO03).

Application of 0.01 mL undiluted pentan-3-one to the clipped skin of rabbits (n=5) caused an injury grade of 2 (i.e., 'the least visible capillary injection from undiluted compound') on a scale from 1 to 10 (Smy54; see also Smy62). Mild irritation was reported following application of 410 mg in an open irritation test or of 500 mg for 24 hours (no details presented) (NIO03).

Acute toxicity

Rats could tolerate exposure to a concentrated, probably saturated*, concentration of pentan-3-one without mortality occurring for a maximum of 15 minutes. When exposed to 28,700 mg/m^3 (8000 ppm) for 4 hours, 4/6 (male Carworth-Wistar) rats died within 14 days (Smy54). Dermal LD_{50} values were 20 mL/kg bw (i.e., 16,300 mg/kg bw) in rabbits (Smy54) and 2100 mgkg bw in rats (NIO03). Oral LD_{50} values in rats and mice were 2140 (95% confidence limits: 1540-2990 mg/kg bw; observation time: 14 days) (Smy54) and 3200 mg/kg bw (no details) (NIO03), respectively. Following intravenous injections into mice, LD_{50} and LD_{100} values of 514 and 1149 mg/kg bw, respectively, were estimated (Jep75).

In a study to explore the relationship between lipophilicity (log $P_{octanol/water}$) and biological activity (anaesthetic - AD_{100} - and lethal - LD_{50}, LD_{100} - doses) of classes of compounds (aliphatic hydrocarbons, ethers, ketones), continuous intravenous infusion of pentan-3-one into mice resulted in a mean AD_{100} (i.e., the dosis needed for complete loss of righting reflex) of 390 mg/kg bw (95% confidence limits: 338-445 mg/kg bw) (Jep75).

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* Theoretically, the concentration in saturated atmosphere can amount to 20,000 ppm or 71,800 mg/m^3 (calculated from: vapour pressure in Pa/10^5 Pa x 10^6 ppm).

Repeated-dose toxicity

The committee did not find data from repeated inhalation studies on 3-pentanone in experimental animals.

Oral administration (gavage) of doses of 10 mg/kg bw/day of 3-pentanone to male Sprague-Dawley rats (n=8) for 16 days caused a decrease in body weight (by 7%; p=0.1) when compared to controls. Serum cholesterol values were 104, 81 (p=0.1), and 93% of control values measured at treatment days 4, 10, and 16, respectively (Car75).

In preliminary studies, pentan-3-one given to female Wistar rats (n=5/group) at concentrations of 1.0% (estimated by Homan and Weil to be equivalent to 634 mg/kg bw/day) for 7 days caused decreased body weight gains (by ca. 80%) accompanied by decreased food (by ca. 15%) and water (by ca. 30%) consumption. Gross post-mortem examination revealed pale or mottled kidneys in both treated and control animals. No effects were seen following administration of 0.5 % (estimated to be equivalent to 450 mg/kg bw) (Hom77). In the subsequent definitive study, 5 female Wistar rats were given oral (2.4% in drinking water) doses of pentan-3-one equivalent to 1860 mg/kg bw/day for 120 days. After exposure days 46, 57, 80, and 110, rats were submitted to 10 neurological tests examining balance, strength, coordination, and behaviour. Post-mortem examinations included liver and kidney weight determinations and gross, histopathological, and neuropathological evaluations. Results were compared with those from 2 control groups of 5 animals each, receiving tap water only. Pentan-3-one treatment caused a statistically significant decrease in body weight gain (by ca. 40%), accompanied by decreased food (by ca. 3-13%) and water (by ca. 30-40%) consumption. Performance in neurological testing was not impaired at any of the test days. Upon post-mortem examinations, livers were not affected, but there were statistically significant increases in relative and absolute kidney weights, which were not accompanied by gross or histological changes. There were no significant gross lesions in any of the other organs examined, and there was no evidence of sciatic nerve neuropathy or skeletal muscle atrophy (Hom77, Mar77).

Mutagenicity and genotoxicity

Pentan-3-one induced mitotic chromosomal malsegregation (aneuploidy), low levels of mitotic recombination, and, possibly, point mutations when tested in *S. cerevisiae* strain D61.M at concentrations of 0.99, 1.23, and 1.48% (Zim85).

Reproduction toxicity

Seven female CF1 mice were given daily intraperitoneal injections of 50 mg/kg bw of 3-pentanone for 28 days. From treatment day 10 onwards, they were mated with untreated males (2 females per male; males rotated every 5th day). At treatment day 28, females were sacrificed, and the number of pregnancies, viable fetuses, reabsorptions, and dead fetuses were recorded. In the 3-pentanone-treated animals, there were decreases in the number of pregnant animals (by 13%) and in the average number of fetuses per litter (by 14%) and an increase in the number of reabsorption sites per litter (5.4 fold) when compared with controls (n=62) (Car75; see also Hal74).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for pentan-3-one in the Netherlands is 705 mg/m^3 (200 ppm), 8-hour TWA

Existing occupational exposure limits for this substance 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 pentan-3-one in humans or experimental animals.

From a human volunteer study, the threshold concentrations for eye and respiratory irritation were roughly 1440 and 2870 mg/m^3 (400 and 800 ppm), respectively. The committee did not find other human data on effects from (occupational) exposure to pentan-3-one.

In experimental animals, pentan-3-one was moderately irritating to the eyes and mildly irritating to the skin of rabbits. A 4-hour exposure to 28,700 mg/m^3 (8000 ppm) was lethal to 4/6 male rats. Dermal LD_{50} values were 16,300 and 2100 mg/kg bw in rabbits and rats, respectively; oral LD_{50} values were 2140 and 3200 mg/kg bw in rats and mice, respectively.

When female rats were orally (2.4% in drinking water) exposed to doses of pentan-3-one equivalent to 1860 mg/kg bw/day – the only dose tested - for 120 days, there were decreases in body weights (by ca. 40%), which was accompanied by decreases in food and water consumption, and increases in relative and absolute kidney weights, which were not accompanied by gross or histological changes, while the livers were not affected. Performance in

neurological testing was not impaired and there was no evidence of sciatic nerve neuropathy or skeletal muscle atropy.

The committee did not find relevant data from other repeated-dose toxicity studies, including carcinogenicity and reproduction toxicity.

In an *in vitro* mutagenicity test, diethyl ketone caused chromosomal malsegregation (aneuploidy) and low levels of mitotic recombination and, possibly, point mutations. The committee did not find data from other genotoxicity studies on pentan-3-one.

The committee considers the toxicological database on pentan-3-one 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.

References

ACG96 American Conference of Governmental Industrial Hygienists (ACGIH). Diethyl ketone. In: TLVs and other occupational exposure values - 1996 [CD-ROM, version 1.7-s4 02/01/95]. Cincinnati OH, USA: ACGIH®, Inc, 1996.

ACG03a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, Inc, 2003: 47.

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: 27.

Amo83 Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 1983; 3: 272-90.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 34 (At-vejledning C.0.1).

Car46 Carpenter CP, Smyth HF Jr. Chemical burns of the rabbit cornea. Am J Ophthalmol 1946; 29: 1363-72.

Car75 Carlson GL, Hall IH, Piantadosi C. Cycloalkanones. 7. Hypocholesterolemic activity of aliphatic compound related to 2,8-dibenzylcyclooctanone. J Med Chem 1975; 18: 1024-6.

DFG03 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2003. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH Verlag GmbH & Co. KGaA, 2003; rep no 39.

Dou87 Douglas RB, Coe JE. The relative sensitivity of the human eye and lung to irritant gases. Ann Occup Hyg 1987; 31: 265-7.

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

Hal74 Hall IH, Carlson GL, Abernethy GS, et al. Cycloalkanones. 4. Antifertility activity. J Med Chem 1974; 17: 1253-7.

Hom77 Homan ER, Weil CS. Comparative toxicity to rats of methoxyacetone and five other aliphatic ketones in their drinking water. Pittsburgh PA, USA: Carnegie-Mellon University, Carnegie-Mellon Institute of Research, 1977; project report 40-37 (available from the National Technical Information Service, Springfield VA, USA; order no NTIS/OTS0206068).

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), UK: HSE Books, 2002: 23.

Jep75 Jeppsson R. Parabolic relationship between lipophilicity and biological activity of aliphatic hydrocarbons, ethers and ketones after intravenous injections of emulsion formulations into mice. Acta Pharmacol Toxicol 1975; 37: 56-64.

Mar77 Maronpot RR. Comparative pathology on rats given methoxyacetone and five other aliphatic ketones in drinking water (ketone neurotoxicity). Pittsburgh PA, USA: Carnegie-Mellon University, Carnegie-Mellon Institute of Research, 1977; project report 40-146 (available from the National Technical Information Service, Springfield VA, USA; order no NTIS/OTS0206068).

NIO03 US National Institute for Occupational Safety and Health (NIOSH), ed. 3-Pentanone. In: Registry of Toxic Effects of Chemical Substances (RTECS) (last update pentan-3-one file: October 2002); http://www.cdc.gov/niosh.

NLM03 US National Library of Medicine (NLM), ed. 3-Pentanone. In: Hazardous Substances Data Bank (HSDB) (last revision data pentan-3-one file: January 2003; last review date: September 1997); http://toxnet.nlm.nih.gov.

Rut86 Ruth JH. Odor thresholds and irritation levels of several chemical substances: a review. Am Ind Hyg Assoc J 1986; 47: A142-51.

Smy54 Smyth HF Jr, Carpenter CP, Weil CS, et al. Range-finding toxicity data. List V. Arch Ind Hyg Occup Med 1954; 10: 61-8.

Smy62 Smyth HF Jr, Carpenter CP, Weil CS, et al. Range-finding toxicity data: List VI. Am Ind Hyg Assoc J 1962; 23: 95-107.

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: 37.

TRG00 TRGS 900: Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

Zim85 Zimmermann FK, Mayer VW, Scheel I, et al. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in Saccharomyces cerevisiae. Mutat Res 1985; 149: 339-51.

Annex

Occupational exposure limits for pentan-3-one 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	200	705	8 h	administrative		SZW03
Germany						
- AGS	-	700	8 h			TRG00
- DFG MAK-Kommission	-	-				DFG03
Great-Britain						
- HSE	200	716	8 h	OES		HSE02
	250	895	15 min			
Sweden	-	-				Swe00
Denmark	200	700	8 h			Arb02
USA						
- ACGIH	200	-	8 h	TLV		ACG03b
	300	-	15 min	STEL		
- OSHA	-	-				ACG03a
- NIOSH	200	705	8 h	REL		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.