Pentan-2-one

(CAS No: 107-87-9)

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 pentan-2-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 May 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: 2-pentanone, methyl propyl ketone, MPK, and 107-87-9. Current Contents and Poltox, HSELINE, CISDOC, MHIDAS, and NIOSHTIC, databases available on CD-ROM, were consulted as well.

In July 2000, the President of the Health Council released a draft of the document for public review. No comments were received.

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

2 Identity

name	:	pentan-2-one
synonyms	:	2-pentanone; methyl propyl ketone; ethyl acetone
molecular formula	:	$C_5H_{10}O$
structural formula	:	CH_3-CH_2-CH_2-CO-CH_3
CAS number	:	107-87-9

3 Physical and chemical properties

molecular weight	:	86.1
boiling point	:	102°C
melting point	:	-78°C
flash point	:	7°C (closed cup)
vapour pressure	:	at 25°C: 2.1 kPa
solubility in water	:	slightly soluble (at 25°C: 4 g/100 mL)
log $P_{octanol/water}$	:	0.91 (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 ACG98, NLM04, http://www.syrres.com/esc/est_kowdemo.htm.

Pentan-2-one is a colourless liquid with characteristic odour (ACG98). Odour thresholds between 28 and 46 mg/m^3 (8-13 ppm) (Amo83, Rut86) and of about 110 mg/m^3 (30 ppm) have been reported (Com95)*. In anosmic subjects (n=4), the nasal pungency threshold was about 11,100 mg/m^3 (3100 ppm) (Com95)*.

4 Uses

Pentan-2-one is used as a solvent, as a flavouring agent, and in organic synthesis (ACG98).

5 Biotransformation and kinetics

The respiratory uptake defined as $(C_{inhaled\ air} - C_{mixed\ exhaled\ air})/C_{inhaled\ air}$ x 100% for pentan-2-one was determined by exposing 4 resting, healthy male volunteers to a single concentration of 100 ppm (360 mg/m^3) for 10 minutes. The percentage solvent in end-exhaled air and in mixed-exhaled air increased after the start of the exposure and reached a quasi-steady-state level within a few minutes. The mean respiratory uptake for the last 5 minutes of pentan-2-one respiration was ca. 53% (Kum99).

Old data indicated that secondary ketones, such as pentan-2-one, were slowly oxidised and eliminated, and it was anticipated that considerable quantities would be found in the blood and expired air following exposure (Hag45).

* The committee estimated the data from figures in which Cometto-Muñiz et al. had plotted the thresholds on a logarithmic scale.

6 Effects and mechanism of action

Human data

In a brief review, Henson described that ketones are irritating to the mucous membranes of the eyes and nasal passages and have measurable toxicities and narcotic effects. Without documentation, he stated that concentrations of 2000 to 4000 ppm (7160-14,320 mg/m^3) pentan-2-one vapour were very irritating and that concentrations of 1500 ppm (5370 mg/m^3) had a strong odour and caused irritation of the eyes and nose. When applied to the skin, the solvent has a defatting activity, which may increase the skin's susceptibility to infections (Hen59). Besides the odour threshold (see Chapter 3), Cometto-Muñiz and Cain determined the eye irritation threshold of pentan-2-one in 10 subjects (6 males, 4 females, with ages between 19 and 30 years). They found an eye irritation threshold of about 10,000 ppm (35,900 mg/m^3) (see footnote previous page) (Com95).

The committee did not find information on systemic effects of pentan-2-one in humans.

Animal data

Irritation and sensitisation

Following instillation into the eyes of rabbits (n=5), pentan-2-one scored an injury grade of 3 (i.e., 0.1 mL of undiluted test substance gives injury up to 5.0 points, or 0.5 mL over 5 points) on a scale from 1 to 10 (Smy62; see also Car46). In guinea pigs, exposure to vapour concentrations of 2500 and 5000 ppm (i.e., ca. 9000 and 17,900 mg/m^3) immediately caused eye and nose irritation, while no such signs were seen at 1500 ppm (5370 mg/m^3) (Spe40, Yan36; see NIO78).

Application of 0.01 mL undiluted pentan-2-one to the clipped skin of rabbits (n=5) caused an injury grade of 1 (i.e., no irritation*) on a scale from 1 to 10 (Smy62).

The committee did not find data from sensitisation studies on pentan-2-one.

With respect to the respiratory tract, de Ceaurriz et al. studied the sensory irritation of pentan-2-one in the upper part of the respiratory tract by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}).

* Grade 1 was also characterised as giving rise to 'the least visible capillary injection' (Smy54).

Using male Swiss OF1 mice, the RD_{50} for pentan-2-one was calculated to be 5915 ppm (i.e., 21,235 mg/m^3) (DeC84). Using male Ssc:CF1 mice, Hansen and Nielsen estimated the RD_{50} from a 10-minute period to be 12,832 ppm (ca. 46,100 mg/m^3); the RD_0 values, i.e., the mean threshold level causing a decrease in respiration rate, from the periods 0-2 and 11-20 minutes were 970 and 564 ppm (2405 and 2025 mg/m^3), respectively (Han94).

Acute toxicity

Rats could tolerate exposure to a concentrated, probably saturated*, concentration of pentan-2-one without mortality occurring for a maximum of 30 minutes. Exposure to 2000 or 4000 ppm (71,800 or 143,600 mg/m^3), for 4 hours, caused mortality in 1/6 and 6/6 (male Carworth-Wistar) rats, respectively (observation time: 14 days) (Smy62).

De Ceaurriz et al. examined the neurobehavioral properties of pentan-2-one in mice (male Swiss OF1) using the 'behavioural despair' swimming test. This bioassay is based on the finding that rodents that are forced to swim in a restricted space exhibit vigorous escape-directed activity during the first minute, then a transient period of swimming activity and mobility, and, after 3 minutes, a state of complete immobility. Exposure to concentrations of 976, 1180, 1549, and 1965 ppm (ca. 3500-7000 mg/m^3), for 4 hours, caused a dose-dependent decrease in the duration of immobility measured over a 3-minute period being statistically significant at 1180 ppm (ca. 4240 mg/m^3). The ID_{50}, i.e., the concentration responsible for a 50% decrease in immobility (compared to control values), was calculated to be 1348 ppm (ca. 4840 mg/m^3; 95% confidence interval: 1243-1454 ppm) (DeC84).

Yant et al. exposed guinea pigs to concentrations of pentan-2-one of 0, 1500, 5000, 13,000, or 50,000 ppm (0, 5370, 17,900, 46,540, or 179,000 mg/m^3)** for up to 13.5 hours. No abnormal signs or symptoms were observed in controls and animals exposed to 1500 ppm (5370 mg/m^3). At 5000 ppm (17,900 mg/m^3), nasal and eye irritation occurred within 3 minutes, lachrymation within 5 minutes, incoordination within 4.5 hours, and unconsciousness within about 8 to 12 hours, followed closely by dyspnoea, but all animals survived. The time of onset for all symptoms decreased rapidly with increasing pentan-2-one concentration, and mortality was observed at exposure to 13,000 and 50,000 ppm (46,540 and

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* Theoretically (at 25°C), the concentration in saturated atmosphere can amount to 21,000 ppm or 73,920 mg/m^3 (calculated from: vapour pressure in Pa/10^5 Pa x 10^6 ppm).

** Since the saturated concentration of pentan-2-one at 25°C is 21,000 ppm (73,920 mg/m^3), animals may have been exposed to aerosols/particulates at the higher levels.

17,9000 mg/m^3) for 300 and 50 minutes, respectively. Animals that died during exposure exhibited slight congestion of the brain and marked congestion of the systemic organs, including the lungs, which were also emphysematous and oedematous, while in the animals with marked incoordination, dyspnoea, and narcosis, only little or no and slight to moderate congestion were seen in the brain and in the lungs, liver, and kidneys, respectively, at post-mortem examinations immediately after the end of exposure. No gross abnormalities were found in animals exposed for 30 and 90 minutes and 4.5 hours to 5000 ppm (17,900 mg/m^3) or for 4.5 and ca. 8 hours to 1500 ppm (5370 mg/m^3) and killed for necropsy 4-8 days after ending exposure (Yan36; see NIO78).

A dermal LD_{50} of 8 mL/kg bw (6,472 mg/kg bw) was estimated in rabbits (Smy62). Oral LD_{50} values of 3730 and 3018 mg/kg bw were reported in rats (Hen59, Smy62).

Repeated-dose toxicity

The committee did not find data on the toxic effects (including carcinogenicity and reproduction toxicity) of pentan-2-one following repeated inhalation or oral exposure.

In rats subcutaneously injected with pentan-2-one doses of 344 mg/kg bw/day and equimolar doses of hexan-2-one, 5 days/week, for 20 weeks, decreases in body weight were greater, weakness of the hind legs more severe, and alertness and resistance on handling less than in a group treated with hexan-2-one only. The maximum motor fibre conduction velocity and the motor distal latency period, measured in the tail nerves every 2 weeks, were increased and decreased, respectively, to a statistically significantly greater extent than in the hexan-2-one group (Mis85). This experiment indicated that combined exposure of pentan-2-one and hexan-2-one may induce aggravation of the effects on the peripheral nervous system and probably also on the central nervous system.

Mutagenicity and genotoxicity

Pentan-2-one induced mitotic chromosomal malsegregation (aneuploidy), but no mitotic recombination or point mutations when tested in *S. cerevisiae* strain D61.M (Zim85, Zim89).

The committee did not find data from other *in vitro* or *in vivo* mutagenicity or genotoxicity assays.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for pentan-2-one in the Netherlands is 700 mg/m^3 (200 ppm), 8-hour TWA.

Existing occupational exposure limits for pentan-2-one in various countries are summarised the annex.

8 Assessment of health hazard

In human volunteers, the threshold for eye irritation was about 35,900 mg/m^3 (10,000 ppm). The committee did not find information on systemic effects of pentan-2-one in humans.

In rabbits, pentan-2-one was slightly irritating to the eyes and not irritating to the skin. In mice, mean threshold levels causing decreases in respiration rate (RD_0), from the periods 0-2 and 11-20 minutes, were 970 and 564 ppm (2405 and 2025 mg/m^3), respectively. Exposure to 2000 or 4000 ppm (71,800 or 143,600 mg/m^3), for 4 hours, caused mortality in 1/6 and 6/6 male rats, respectively (observation time: 14 days). When mice were exposed to concentrations of 976, 1180, 1549, and 1965 ppm (ca. 3500-7000 mg/m^3), for 4 hours, there was a dose-dependent effect in the 'behavioural despair' swimming test being statistically significant at 1180 ppm (ca. 4240 mg/m^3) and higher. No effects were reported in guinea pigs exposed to 5000 ppm (5370 mg/m^3) for up to 13.5 hours. Exposure to 5000 ppm (17,900 mg/m^3) caused nasal and eye irritation (within 3 minutes), incoordination (within 4.5 hours), and unconsciousness and dyspnoea (after 8 hours); concentrations of 13,000 ppm (46,540 mg/m^3) were lethal. The dermal LD_{50} was 6472 mg/kg bw for rabbits; the oral LD_{50} values 3018 and 3730 mg/kg bw for rats.

The committee did not find data on the toxic effects (including carcinogenicity and reproduction toxicity) of pentan-2-one following repeated inhalation or oral exposure.

Pentan-2-one induced mitotic chromosomal malsegregation (aneuploidy), but no mitotic recombination or point mutations when tested in *S. cerevisiae*. The committee did not find data from other *in vitro* or *in vivo* mutagenicity or genotoxicity assays.

The committee considers the toxicological database on pentan-2-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 present MAC-value.

References

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Annex

Occupational exposure limits for pentan-2-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	700	8 h	administrative		SZW04
Germany						
- AGS	200	710	8 h			TRG04
	800	2840	15 min			
- DFG MAK-Kommission	-[c]	-[c]				DFG04
Great-Britain						
- HSE	200	716	8 h	OES		HSE02
	250	895	15 min			
Sweden	-	-				Swe00
Denmark	200	700	8 h	OEL		Arb02
USA						
- ACGIH	200	-	8 h	TLV		ACG04b
	250	-	15 min	STEL		
- OSHA	200	700	8 h	PEL		ACG04a
- NIOSH	150	530	10 h	REL		ACG04a
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] Listed among compounds for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values.