Valeraldehyde

(CAS No: 110-62-3)

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 valeraldehyde 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 MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

Literature was retrieved from the databases Medline, Toxline, and Chemical Abstracts, covering the periods 1966 to May 1999, 1981 to April 1999, and 1937 to April 1999, respectively, and using the following key words: valeraldehyde, pentanal, pentaldehyde, hexanal, caproaldehyde, butanal, butyraldehyde, butylaldehyde, 110-62-3, 66-25-1, and 123-72-8. Data considered to be critical were evaluated by reviewing the original publications. The final literature search was carried out in May 1999.

In September 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

An additional literature search in May 2002 did not result in information changing the committee's conclusions.

2 Identity

name	:	valeraldehyde
synonyms	:	amyl aldehyde; butyl formal; pentanal; *n*-pentanal; valeric aldehyde; valeral; *n*-valeraldehyde; valerianic aldehyd; valeric acid aldehyde; *n*-valeric aldehyde; valeryl aldehyde
molecular formula	:	$C_5H_{10}O$
structural formula	:	$O{=}CH\text{-}CH_2\text{-}CH_2\text{-}CH_3$
CAS number	:	110-62-3

Data from How92.

3 Physical and chemical properties

molecular weight	:	86.13
boiling point	:	103°C
melting point	:	-91.5°C
flash point	:	open cup: 12.2° C; closed cup: 6°C
vapour pressure	:	at 20°C: 3.46 kPa
solubility in water	:	slightly soluble
Log $P_{octanol/water}$	:	1.31 (estimated)
conversion factors (20°C, 101.3 kPa)	:	1 mg/m^3 = 0.28 ppm 1 ppm = 3.59 mg/m^3

Data from ACG99, Möl93, Rou86, http://esc.syrres.com.

Valeraldehyde is a colourless liquid with a strong, pungent odour. Because of its low flash point, it is a dangerous fire hazard (ACG99). Its vapour mixes well with air, forming explosive mixtures. Valeraldehyde can polymerise violently under the influence of inorganic acids and bases, ammonia, and amines. It reacts vigorously with oxidants (Che99). Odour thresholds of 0.10 and 0.36 mg/m^3 (0.028, 0.10 ppm) were reported (Amo83, Joh73)

4 Uses

Valeraldehyde is used in flavouring compounds, in resin chemistry, and as a rubber accelerator (ACG99).

Valeraldehyde occurs naturally in a large number of food products (Bec96, Mar94, Opd79).

5 Biotransformation and kinetics

The committee did not find data on the biotransformation and kinetics of valeraldehyde.

Apart from inhalation of valeraldehyde in occupational settings, exposure can also take place by inhaling the volatile compounds of wood and by ingestion. It can also be generated by lipid peroxidation processes in the liver (Bec96, Mar94, Opd79).

6 Effects and mechanism of action

Human data

Tested at a concentration of 2% in petrolatum, valeraldehyde did not cause irritation in a 48-hour closed-patch test in (an unknown number of) human subjects or sensitisation in a maximisation test carried out on 25 volunteers (Opd79).

The committee did not find other data on the effects of valeraldehyde in humans.

Animal data

Following application of 0.01 mL of undiluted aldehyde to the uncovered clipped abdomen of 5 albino rabbits, valeraldehyde scored an injury grade of 2 (i.e., giving rise to 'an average reaction equivalent to a trace of a capillary injection') on a scale from 1 to 10 (Smy69; see also Smy49). In another (unpublished) study, undiluted compound was found moderately irritating after 24-hour covered application to the intact or abraded skin of rabbits (Opd79). In guinea pigs, it was reported to be severely skin irritating (Fas63).

When instilled into the eyes of rabbits, valeraldehyde scored an injury grade of 5 on a scale of 1 to 10, which was defined as producing an injury of up to 5.0 points (out of a maximum of 20) 18 to 24 hours after instillation of 0.005 mL of undiluted test substance (0.02 mL gives over 5.0 points) (Smy69; see also Car46)*. According to unpublished information, it was severely irritating to the skin of rabbits (Fas63).

The sensory irritation potential of inhaled valeraldehyde was investigated in $B6C3F_1$ and Swiss-Webster mice. Groups of 3 or 4 mice were exposed in a head-only exposure chamber for 10 minutes. Sensory irritation was quantified by measuring respiratory rate depression during these exposures. Five concentrations of valeraldehyde were used to construct a concentration-response curve from which the RD_{50} value was determined. These RD_{50} values (the concentrations eliciting a 50 % decrease in respiratory rate) were 4284 and 4036 mg/m^3 for $B6C3F_1$ and Swiss-Webster mice, respectively (Ste84).

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* Grade 5 was also characterised as a 'severe burn from 0.005 mL' (Smy54).

Rats could tolerate exposure to a concentrated, probably saturated* level of valeraldehyde without mortality occurring for a maximum of 15 minutes while a 4-hour exposure to 14,400 mg/m^3 (4000 ppm) caused mortality in 3/6 rats (Smy69). In other, unpublished studies, 3 rats exposed to approximately 172,000 mg/m^3 (48,000 ppm) all died within 1.2 hours while 6/6 rats survived a 6-hour exposure to approximately 5000 mg/m^3 (1400 ppm (Fas63). In a study on the inhalation toxicity of a series of aldehydes, groups of 50 mice, 20 guinea pigs, and 5 rabbits were exposed to a concentration of 2359 mg/m^3 valeraldehyde aerosol. The animals were exposed for periods up to 10 hours, or until death intervened. Exposure to the aldehydes caused an initial increase in activity in all of the animals used. The animals blinked, closed their eyes, and rubbed their faces with their paws. After the initial irritation, the animals settled down and respiration became slow and deep. This was observed until the animals convulsed just prior to death. Of the animals exposed to valeraldehyde aerosol, 2 mice died during the period of exposure, and 5 guinea pigs and 2 mice died on subsequent days. No rabbits died during or after exposure. At autopsy, all animals were observed to have expanded, oedematous, and haemorrhagic lungs. Fluid was observed in the pleural cavity. The animals showed consolidated lungs, distended alveoli, and ruptured alveolar septa. The livers appeared enlarged and fluid was observed in the peritoneal cavity. Most of the lung sections showed dilated and engorged blood vessels (Sal60).

The dermal LD_{50} for male rabbits (albino New Zealand; n=4/group) was 4857 mg/kg bw (exposure time: 24 hours; observation time: 14 days) (Smy69; see also Smy62). For guinea pigs, a dermal LD_{50} of >20,000 mg/kg bw has been reported (Fas63).

The oral LD_{50} determined in non-fasted male rats (Carworth-Wistar; n=5/group) was 4580 mg/kg bw (observation time: 14 days) (Smy69; see also Smy62). Oral LD_{50} values for rats and mice of 3200-6400 and 6400-12,800 mg/kg bw, respectively, were reported (Fas63).

No data on repeated-dose toxicity, potential carcinogenicity, or reproduction toxicity of valeraldehyde were found.

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* Theoretically, the concentration in saturated vapour (at 20°C) can amount to 35,000 ppm; calculated from: (vapour pressure in Pa/10^5 Pa) x 10^6 ppm.

Mutagenicity and genotoxicity

Valeraldehyde was negative in:
- a bacterial mutation assay using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without rat liver metabolic activation (Flo80)
- a sister chromatid exchange (SCE) assay in human lymphocytes without metabolic activation (Obe79)
- a DNA repair test in *B. subtilis* (rec-assay), with and without metabolic activation (Mat89)
- a DNA-repair test (the *umu*-test) using *S. typhimurium* strain TA1535, with and without rat liver metabolic activation (Ono91)
- a test on the induction of DNA double and single strand breaks in bacteriophage PM2 DNA (Bec96)
- an unscheduled DNA synthesis (UDS) assay in human hepatocytes (Mar94).

Valeraldehyde was positive in:
- a forward mutation assay using V79 Chinese hamster lung cells in the absence of a metabolic system (Bra89).
- a test on the induction of DNA double and single strand breaks in bacteriophage PM2 DNA in the presence of $CuCl_2$ (Bec96)
- a test on the induction of DNA single strand breaks in Chinese hamster ovary (CHO) cells (Mar84)
- an unscheduled DNA synthesis (UDS) assay in rat hepatocytes (Mar94).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) in the Netherlands for valeraldehyde is 175 mg/m^3, 8-hour TWA.

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

8 Assessment of health hazard

The committee did not find human data on the toxicity of valeraldehyde.

Valeraldehyde was irritating to eyes of rabbits and to the skin of rabbits and guinea pigs (Fas63, Opd79, Smy69). Inhalation exposure for 10 minutes induced sensory irritation and a decrease of the respiratory rate in mice. The

RD_{50} was approximately 4150 mg/m^3 (Ste84). The acute toxicity after oral or dermal administration was found to be low in all tested species (Fas63, Smy69). The acute inhalation toxicity of a series of aldehydes were studied by Salem and Cullumbine (Sal60). Valeraldehyde and iso-valeraldehyde were by far the least toxic substances: only a few of the experimental animals died after being exposed for 10 hours to a concentration of 2359 mg/m^3. At autopsy, the animals were observed to have severe lung damage.

No data on repeated-dose toxicity, carcinogenicity, or reproduction toxicity of valeraldehyde have been found.

The committee considers the toxicological database on valeraldehyde 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-level.

References

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Bra89 Brambilla G, Cajelli E, Canonero R. Mutagenicity in V79 Chinese hamster cells of *n*-alkanals produced by lipid peroxidation. Mutagenesis 1989; 4: 277-9

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Smy69 Smyth HF Jr, Carpenter CP, Weil CS, *et al.* Range-finding toxicity data: List VII. Am Ind Hyg Assoc J 1969; 30: 470-6.

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Annex

Occupational exposure limits for valeraldehyde 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	175	8 h	administrative		SZW02
Germany						
- AGS	-	175	8 h			TRG00
- DFG MAK-Kommission	-	-				DFG02
Great Britain						
- HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	50	175	8 h			Arb02
USA						
- ACGIH	50	-	8 h	TLV		ACG02b
- OSHA	-	-				ACG02a
- NIOSH	50	175	10 h	REL		ACG02a
European Union						
- SCOEL	-	-				EC02

[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.