Propyl nitrate

(CAS No: 627-13-4)

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 propyl nitrate 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 A Wientjes, M.Sc. and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of propyl nitrate has been based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG98). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in April 1999, literature was searched in the on-line databases Medline, Toxline, Chemical Abstracts, and NIOSHTIC, starting from 1966, 1965, 1967, and 1973, respectively, and using the following key words: propyl nitrate and 627-13-4.

In February 2001, 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 February 2004 did not result in information changing the committee's conclusions.

2 Identity

name	:	propyl nitrate
synonyms	:	nitric acid *n*-propyl ester; *n*-propyl nitrate
molecular formula	:	$C_3H_7NO_3$
structural formula	:	$H_3C\text{-}CH_2\text{-}CH_2\text{-}ONO_2$
CAS number	:	627-13-4

3 Physical and chemical properties

molecular weight	:	105.09
boiling point	:	110°C
melting point	:	<-100°C
flash point	:	20°C (closed cup)
vapour pressure	:	at 20°C: 2.4 kPa
solubility in water	:	very slightly soluble
log $P_{octanol/water}$	:	1.74 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 ppm = 4.4 mg/m^3 1 mg/m^3 = 0.23 ppm

Data from ACG98, Dav93, Rin58, http://esc.syrres.com.

Propyl nitrate is a pale yellow liquid with a sweet, sickening odour (ACG98) and an odour threshold of 50 ppm (220 mg/m^3) (Amo83).

4 Uses

Propyl nitrate is used as a fuel ignition promoter, in rocket fuels, and as an intermediate in organic synthesis (ACG98).

5 Biotransformation and kinetics

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

6 Effects and mechanism of action

Human data

During an inhalation experiment on animals, one of the collaborators complained of a definite sweet sickening odour and a feeling of light-headedness at a concentration that was estimated to be approximately 220 mg/m^3 (50 ppm) (Rin58).

Animal data

Irritation and sensitisation

The committee did not find relevant data on the potential eye and skin irritation and sensitising potential of propyl nitrate. ACGIH cited an unpublished study from which it concluded that repeated dermal application of propyl nitrate may cause inflammation and thickening of the skin (ACG98).

Acute toxicity

Four-hour LC_{50} values of 9000 to 10,000 ppm (40,000-44,000 mg/m^3) and of 6000 to 7000 ppm (26,500-31,000 mg/m^3) were calculated for rats and mice, respectively (Rin58).

Citing an unpublished study, inhalation of propyl nitrate vapour by rats for 4 hours at 10,000 ppm (44,000 mg/m^3) was stated to produce cyanosis, methaemoglobinaemia, and death (ACG98).

Following dermal application of 11,000 or 17,000 mg/kg bw to rabbits, no effects were observed (no more details presented) (BIB88).

An oral dose of 5000 mg/kg bw was reported to be fatal to rats; 1000 mg/kg bw produced weakness, incoordination, and cyanosis. No further details are available (BIB88).

In unanaesthetised rabbits, an approximate intravenous LD_{50} of 200 to 250 mg/kg bw of the undiluted propyl nitrate was found; the animals usually died within 3 minutes after the injection. No attempt was made to establish the LD_{50} values for dogs and cats, but it was observed that intravenous doses of 200 mg/kg bw were always fatal to anaesthetised dogs and doses of 100 to 200 mg/kg bw were usually fatal to anaesthetised cats. Injections of 5 mg/kg bw or more caused a reduction in the blood pressure of dogs, whilst 30 mg/kg bw slowed the heart rate and 50 mg/kg bw reduced the contractile force of the heart and stopped the muscular contraction of the gut. At these doses, the dogs briefly stopped breathing and than started breathing at an abnormally fast rate, the latter effects being accompanied by cyanosis. Full recovery occurred within about 2 hours. Doses of 200 mg/kg bw or more produced an immediate drop in blood pressure and respiratory paralysis, and the dogs died within 1 minute of the injection. In cats, 6 out of 7 animals given an injection of 100 to 250 mg/kg bw died within
1 minute, one cat survived a dose of 150 mg/kg bw. All of an unspecified number of cats survived 25-75 mg/kg bw, but showed a drop in blood pressure and methaemoglobinaemia (Mur56).

Repeated-dose toxicity

Groups of rats, mice, guinea pigs, and hamsters were exposed to 14,000 mg/m^3 (3235 ppm) of propyl nitrate, 6 hours/day, 5 days/week, for 8 weeks. Rats had moderate cyanosis, lethargy, and, in the first week, weight loss; 5/20 animals died (no details given). In mice, signs of moderate cyanosis and excitement were seen; 6/29 died. In guinea pigs and hamsters, there were no signs of toxicity, and all 10 animals of each species survived the treatment (Rin58).

Exposure to 10,000 mg/m^3 (2110 ppm) for 26 weeks (6 hours/day, 5 days/week) caused lethargy and mortality (in 9/20) in rats, while all 10 guinea pigs were unaffected. At necropsy, examination showed a significant amount of increase in pigment in the liver, spleen, and, occasionally, the heart (Rin58).

In dogs, exposure to 8800 mg/m^3 (2000 ppm), 6 hours/day, killed 3/3 animals within 2 days, animals showing vomiting, convulsions, cyanosis, and methaemoglobinaemia. Cyanosis, methaemoglobinaemia, haemolytic anaemia,

haemoglobinuria, and depression were observed at exposure levels of 3960 and 2465 mg/m^3 (900 and 560 ppm, respectively) that were lethal to 1/1 and 1/2 animals, respectively, following 6 exposures. The other animal exposed to 2465 mg/m^3 survived the 6-week exposure period (5 days/week). Exposure to 1145 mg/m^3 (260 ppm) for 26 weeks induced haemoglobinuria (disappearing after 2 weeks of the beginning of the exposure period), mild anaemia, and slight CNS depression (lasting for 2-3 weeks), but all 3 animals survived, and recovered completely. At necropsy, microscopic examinations showed a significant amount of pigment in the Kupffer cells of the liver and in the spleen. It was not mentioned whether a control group was used (Rin58).

Citing an unpublished study, rats orally administered with 1500 mg/kg bw/day, 5 days/week, for 2 weeks, showed signs of temporary weakness, cyanosis, weight loss, methaemoglobinaemia, and spleen swelling. These effects became less severe over the 10-day treatment, and the rats gained weight 10 days after treatment had ended (BIB88).

Intravenous injections of 40 mg/kg bw into a dog for 8 days or of 90 mg/kg bw into rabbits for 6-12 days did not produce any lesions in the intestine, spleen, pancreas, kidney, liver, lungs, or heart on microscopic examination (Mur56).

Mutagenicity and genotoxicity

Referring to an abstract, propyl nitrate was stated to be slightly mutagenic in the bacteriophage T4B, a virus that attacks *E. coli* (BIB88).

The committee did no find data on propyl nitrate concerning the carcinogenicity and reproduction toxicity or on the mutagenicity or genotoxicity in mammalian cell systems or intact animals.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for propyl nitrate in the Netherlands is 110 mg/m^3 (25 ppm), 8-hour TWA.

Existing occupational exposure limits for propyl nitrate 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 biotransformation and kinetics of propyl nitrate.

The committee did not find data on effects in humans due to occupational exposure to propyl nitrate. One of the collaborators in an experimental animal study complained of a sickening odour and light-headedness at a concentration estimated to be approximately 220 mg/m^3 (50 ppm).

The committee did not find data from which conclusions on the potential eye and skin irritating and sensitising properties of propyl nitrate can be drawn.

Based on acute lethality data (4-hour LC_{50} rat: ca. 40,000 mg/m^3 or 9000 ppm; no effects in rabbits following dermal application up to 17,000 mg/kg bw), the committee concludes that propyl nitrate is of low toxicity following acute exposure by inhalation and by dermal contact.

Data from inhalation experiments in rodents and dogs indicate that methaemoglobinaemia, cyanosis, hypotension, and CNS depression are the main signs of toxicity following acute and repeated exposure to propyl nitrate (Rin58). The dog seems to be the most sensitive species: exposure to 1145 mg/m^3 (260 ppm), for 26 weeks, induced slight effects. However, the committee concludes that due to the limited design of these studies, they cannot serve as a starting point for deriving a health-based occupational exposure limit.

The committee did not find valid data on the mutagenicity or genotoxicity, carcinogenicity, or reproduction toxicology of propyl nitrate.

The committee considers the toxicological database on propyl nitrate 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

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ACG03 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, 2003: 114.

ACG04 American Conference of Governmental Industrial Hygienists (ACGIH). 2004 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®, 2004: 48.

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.

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BIB88 British Industrial Biological Research Association (BIBRA). Toxicity profile of n-propyl nitrate. Carshalton (Surrey), England: BIBRA, 1988.

Dav93 Davis RA. Aliphatic nitro, nitrate, and nitrite compounds. In: Clayton GD, Clayton FE, eds. Toxicology. 4th ed. New York: John Wiley & Sons, 1993: 634-6. (Patty's industrial hygiene and toxicology; Vol II, Pt A).

DFG03 Deutsche Forschungsgemeinschaft (DFG): Commisson 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 & Co. KGaA, 2003: 99 (rep no 39).

EC04 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.

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

Mur56 Murtha EF, Stabile DE, Wills JH. Some pharmacological effects of n-propyl nitrate. J Pharmacol Exp Ther 1956; 118: 77-83.

Rin58 Rinehart WE, Garbers RC, Greene EA, Stouper RM. Studies on the toxicity of n-propyl nitrate vapor. Am Ind Hyg Assoc J 1985; 19: 80-3.

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.

SZW04 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2004. The Hague, the Netherlands: Sdu Uitgevers, 2004: 39.

TRG03 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArBl 2003; (9).

Annex

Occupational exposure limits for propyl nitrate 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	25	110	8 h	administrative		SZW04
Germany						
- AGS	25	110	8 h			TRG03
- DFG MAK-Kommission	25	110	8 h			DFG03
	50	220	15 min[c]			
Great-Britain						
- HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	25	110	8 h			Arb02
USA						
- ACGIH	25	-	8 h	TLV		ACG04
	40	-	15 min	STEL		
- OSHA	25	110	8 h	PEL		ACG03
- NIOSH	25	105	10 h	REL		ACG03
	40	170	15 min	STEL		
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] Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.