Pentachloronaphthalene

(CAS reg no: 1321-64-8)

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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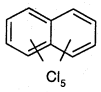
1 Introduction

The present document contains the assessment of the health hazard of pentachloronaphthalene 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 Ir M Busschers, M.Sc. and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of pentachloronaphthalene has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the online data bases Medline, Toxline, and Chemical Abstracts, covering the period 1966 to 26 April 1999 (19990416/UP), 1965 to 29 January 1999 (19990129/ED), 1967 to 24 April 1999 (19990424/ED; vol 130, iss 18), using the following key words: pentachloronaphthalene, the CAS registry number 1321-64-8 and a number of other registry numbers related to positional isomers*. HSDB and RTECS, data bases available from CD-ROM, were consulted as well (NIO99, NLM99). The final literature search has been carried out in April 1999.

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

2 Identity

name	:	pentachloronaphthalene
synonyms	:	-
molecular formula	:	$C_{10}H_3Cl_5$
structural formula	:	
CAS reg no	:	1321-64-8

Data from ACG99, Ada44.

* 55720-40-6, 55720-39-3, 55720-38-2, 55720-37-1, 55720-36-0, 55720-35-9, 55720-34-8, 55720-33-7, 51570-44-6, 51570-43-5, 50402-52-3, 50402-51-2, 2437-55-0, and 2437-54-9

The technical products of chloronaphthalenes are often called Halowaxes. These Halowaxes are graded according to their chlorine content and all are therefore mixtures of various isomers with one or two main derivatives predominating (Ben94, Cro70). Halowax 1013 was reported as a synonym for pentachloronaphthalene (ACG99, Ano85, NIO81), but also as a mixture of mainly tri- and tetrachloronaphthalene (Cro70) or hexa- and pentachloronaphthalene (Aho80). Halowax 1014 was an indication for pentachloronaphthalene (Ada44), and for a mixture of penta- and hexachloronaphthalene (She57) with traces of tri- and tetrachloronaphthalene (Cro70). However, Asplund et al (Asp86) analysed Halowax 1014 by gas chromatography and reported it as a mixture of tetra- to octachloronaphthalenes with penta- and hexachloronaphthalenes as the major ingredients.

3 Physical and chemical properties

molecular weight	:	300.4
boiling point	:	327-337°C
melting point	:	120°C
flash point	:	-
vapour pressure	:	at 20°C: <0.133 kPa
solubility in water	:	insoluble
log $P_{octanol/water}$	:	6.85
conversion factors (20°C, 101.3 kPa)	:	not applicable

Data from ACG99, Gre98.

Pentachloronaphthalene is a noncombustible, pale yellow solid with an aromatic odour.

4 Uses

Pentachloronaphthalene is used in lubricants and in the manufacture of insulation for electrical wire (ACG99).

5 Biotransformation and kinetics

A single oral dose (1 g) of pentachloronaphthalene to rabbits was not metabolised into the phenolic and conjugated urinary metabolites that are common for the lower chlorinated naphthalenes. Moreover, not more than 20 percent of unchanged pentachloronaphthalene was excreted via faeces and urine over the 4-day period following dosing (Cor58), indicating a possible bioaccumulation.

In another study, rats received a single oral dose of Halowax 1014, being a mixture of tetra- to octachloronaphthalenes, with mainly penta- and hexachloronaphthalene. After 1 day, all constituents could be found in the adipose tissue, but hexachloronaphthalene dominated after 10 and 30 days, and was the only detectable compound after 120 days. In the liver, hexachloronaphthalene was present at even higher concentrations than in adipose tissue and detected for up to 4 months. Bioaccumulation of the other chloronaphthalene constituents of Halowax 1014 was not reported (Asp86).

When dogs and rats on a low chlorine diet were fed with a mixture of penta- and hexachloronaphthalene, the chlorine concentration in the urine rose, indicating a detachment of chlorine from the compound (Dri39).

One week after a single intraperitoneal dose (100 mg/kg) of Halowax 1013 (consisting principally of penta- and tetrachloronaphthalene) and Halowax 1014, liver weights of the rats were increased by 19% and 21%, respectively. Halowax 1014 induced enzymes catalysing drug hydroxylation and glucuronidation, whereas Halowax 1013 had far less an effect on these enzymes (Aho80).

6 Effects and mechanism of action

Human data

The skin of 6 white and 4 black male volunteers was exposed to Halowax 1014 (a mixture of penta- and hexachloronaphthalene) by daily application of 2 mL of a 3% solution, for 6 to 12 weeks. This resulted in dermal effects ranging from increased number of epidermal cells (day 5), follicular involvement without erythema (day 10), and follicular accentuation (day 14) to appearance of small (week 3-5) and large comedones (week 6-12). Topical application of a similar amount of hexachloronaphthalene to 4 volunteers resulted in an identical reaction pattern (Ham57).

Daily application of a mixture of penta- and hexachloronaphthalene (Halowax 1014) in a 50% mineral oil suspension, for 30 days, to the ear (auricle) of 3 male volunteers caused acne. Application of this suspension to 7 different body parts (n=3-5/part), for 35 days (biopsies taken at 60 days after the first application) caused acne (comedones) in all 31 volunteers. In a third experiment, the back of 5 male volunteers was treated for 2 months and biopsies were taken at 1, 2, 3, 4, 5,7, 12, and 16 weeks. An alarming fulmigant acne (indistinguishable from acne conglobata - grade IV acne) was seen in every subject. Even after dosing was ceased, the acne continued to develop in these experiments (She57).

Mono- and dichloronaphthalenes, used in a plant to shield coils, appeared to have no adverse effects on the workers. When these chloronaphthalenes were replaced by tetra- and pentachloronaphthalenes, 56 out of 59 examined workers exposed to the fumes of these chemicals, developed dermatoses consistent with chloracne, and complained of effects such as headache, fatigue, vertigo, and anorexia. No adequate data on liver damage were available (Kle72).

Crow (Cro70) investigated a paper capacitor plant, where exposure to a mixture of penta- and hexachloronaphthalenes produced chloracne in several workers. When this mixture was abandoned and replaced by a mixture of three parts of tri/tetrachloronaphthalene and one part of polystyrene, chloracne ceased.

Seven cases of poisoning from a manufacturing plant for wire cables in which pentachloronaphthalene was used for coating were described. All 7 workers showed signs of liver toxicity, and 2 of them died. Early symptoms included skin effects like rash or depigmentation. On prolonged exposure, the main target organ was the liver (Cot44). Although it was suggested that the exposure was mainly to pentachloronaphthalene, this is not stated clearly in the report. Therefore, the committee is of the opinion that the effects may also have been a result of exposure to other chemicals.

There are several other reports of hepatic injury, chloracne, and/or mortality among humans working in plants where chlorinated naphthalenes were used (Dri37, Pop97, Str44, War96). Although it was claimed that the main exposure was to chlorinated naphthalenes ('Halowax'), no details about the specific types of chlorinated naphthalenes or exposure to other chemicals were given. Therefore, the committee could not establish the causal role of trichloronaphthalene.

Animal data

Irritation

According to a summary report, a mixture of penta- and hexachloronaphthalene (Halowax 1014) is not corrosive to animal skin in a DOT (Department of Transport) corrosivity test. No details about the procedures and species were given (Car75).

The rabbit's ear canal skin was exposed to 1 mL of a 3% solution of Halowax 1014 (a mixture of penta- and hexachloronaphthalene) for 5 days. A mild dermatitis with striking follicular accentuation, thickening of the epidermis, and proliferation of the follicles and sebaceous gland ducts were observed. A gradual recovery of the effects occurred upon discontinuation of the applications (Ham57). Solutions of pentachloronaphthalene (Halowax 1014; chlorine content: 60%) in CCl_4 or olive oil were applied to the ear and abdomen of unknown experimental animals (n=1/experiment). No experimental details were presented; no (vehicle) controls were included. Single or repeated application of 5 or 10% solutions in CCl_4 or olive oil, generally induced erythema, follicle enlargement, exfoliation, hair loss, thickening, and keratosis. During the application and observation periods, the severity of these findings varied from very slight to moderate depending on the area, number of applications, and the time point of observation. Further, effects were persistent: in one case, very slight effects were still present 24 days after ending application (Ada44).

The chloracnegenic potential of pentachloronaphthalene was tested by applying 0.1 mL of a 0.005, 0.01, and 10% solution (vehicle: chloroform) to the inner surface of one ear of a rabbit (n=1/concentration), 5 days/week, for 4 weeks. No response was seen at the 2 lower concentrations while the 10% solution caused a questionable response. In a rerun using the 10% solution, a positive response was obtained (no more data/details were presented) (Cha71).

Single exposure

One out of 3 rabbits of a single oral dose of approximately 500 mg/kg bw, died within 7 days after administration (Cor58). A 100% survival dose and a 100% lethal dose after single oral administration were determined to be 5 mg/kg bw and 30 mg/kg bw, respectively, in guinea pigs, and 600 mg/kg bw and 1800 mg/kg bw, respectively, in rats (Ada44).

Repeated exposure

Inhalation studies on a mixture of penta- and hexachloronaphthalene (chlorine content of mixture: 62.6%; ratio not given) in rats (n=80/group) only showed

marked liver injury (liver cell swelling, granulation, hyaline droplet formation) after an average exposure to 1.16 mg/m^3 (range: 0.51-2.19 mg/m^3), 16 hours/day, 6 days/week, for up to 134 days (total exposure: 1864 hours), and after an average exposure to 1.44 mg/m^3 (range: 0.42-2.58 mg/m^3), 8 hours/day, 6 days/week, for up to 143 days (total exposure: 920 hours). Interim autopsies performed on groups of 3 to 15 animals showed abnormalities to increase slightly during the first half of the experiment while no further deterioration was seen in the second part of the study. However, the effects on the liver were persistent: in animals removed from exposure to 1.16 mg/m^3 after 105 days, lesions in animals sacrificed immediately after removal were generally similar to those seen in animals allowed to recover for 2 months. Exposure to an average concentration of 8.8 mg/m^3 (range: 5.75-14.0 mg/m^3), 16 hours/day, for 52 days (total exposure: 608 hours) caused loss of weight and appetite in all animals (n=80). Mortality was observed from day 8 onward. Fifty-five rats died during the exposure period, most of them markedly jaundiced, while only 8 rats survived the exposure period. The remaining 17 were killed for microscopic examination or by additional experiments (Ben38, Dri37). The committee noticed the absence of a control group.

During dietary exposure to a penta/hexachloronaphthalene mixture (see above) at 3000 mg/rat/day, all 10 rats lost weight and became ill from the beginning, and died within 33 days. At gross and microscopic postmortem examination, there were only effects on the liver (liver cell swelling, hypergranulation, hyaline inclusion and vacuolation, necrosis, fat accumulation). Daily doses of 1000 mg led to the death or moribund state of all 10 animals within 55 days. When rats (n=10) were fed a mixture of tetra- and pentachloronaphthalene (chlorine content: 56.4%; ratio not given) at 500 mg/rat/day, they all became ill and eventually died within 63 days. At necropsy, only liver injuries were observed. These lesions were comparable to but less severe than those in rats fed the penta/hexachloronaphthalene mixture (Ben38, Dri37). The committee noticed the absence of a control group.

Following 20 repeated feedings of Halowax 1014 (stated to be a 'pentachloronaphthalene' with a chlorine content of 60%) to rats, only effects on the liver were observed, varying from very slight to severe at 10 and 100 mg/kg, respectively.No effects were seen at doses of 1 mg/kg (no further data or details were given) (Ada44).

Daily oral doses of 2.5, 5, 10, or 20 mg/kg bw of 'technical' pentachloronaphthalene (purity unkown) in peanut oil (6 days/week, until death) to guinea pigs (n=1/dose) caused mortality within 7 (at 20 mg/kg) or 48 (at 2.5 mg/kg) days. Animals (n=1/dose) given doses of 15 and 20 mg/kg bw given for 8

and 4 days, respectively, died within 15 and 9 days, respectively. All animals showed significant body weight loss prior to death. Fatty degeneration of the liver was the most striking observation at macro- and microscopic examination (Ben66).

Daily subcutaneous injection (approximately 15 mg/kg bw) of a mixture of tetra- and pentachloronaphthalene resulted in the death of all 5 rabbits between days 12 and 15. Injection of a penta- and hexachloronaphthalene mixture and of the sublimate of that mixture given off at 172°C into rabbits (n=5/group) killed all animals between day 12 and 26 and day 9 and 14, respectively. The livers of all these rabbits showed signs of yellow atrophy. The sublimate of the tetra- and pentachloronaphthalene mixture given off at 192°C did not result in any effect (Fli36).

The committee did not find data on the potential mutagenicity, genotoxicity, carcinogenicity, or reproduction toxicity of pentachloronaphthalene.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for pentachloronaphthalene in the Netherlands is 0.5 mg/m^3, 8-hour TWA.

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

8 Assessment of health hazard

Data from occupational exposure (Cro70, Kle72) and experimental dermal studies in humans (Ham57, She57) and rabbits (Ada44, Ham57) indicated that pentachloronaphthalene causes chloracne. Occupational exposure to pentachloronaphthalene was also associated with liver injury and fatalities (Cot44). However, the workers were most probably exposed to a variety of chloronaphthalenes and other chemicals.

A single oral dose of 500 mg/kg bw was lethal to 1 out of 3 rabbits (Cor58), whereas single doses of 30 and 1800 mg/kg bw were lethal to all guinea pigs and rats, respectively. No animals died at oral doses of 5 mg/kg bw (guinea pigs) or 600 mg/kg bw (rats) (Ada44).

Following exposure by inhalation or oral administration, the target organ for toxicity is the liver.

Liver injury was noted in rats after inhalation of a mixture of penta- and hexachloronaphthalene at average concentrations of *ca*. 1.3 mg/m^3, 8 or 16 hours/day, for *ca*. 140 days, whereas exposure to 8.8 mg/m^3 (16 hours/day, 52 days) resulted in mortality and severe liver injury (Ben38, Dri37). Due to the mentioned shortcomings (no control group, wide range in exposure concentration, uncertainties in the composition of the exposure mixture), the committee considers this study not suitable as a starting point for deriving an occupational exposure limit.

After oral exposure (diet), all rats died within about 30 to 60 days and showed marked to severe liver injury when given a mixture of penta- and hexachloronaphthalene (3000 mg/rat/day) and of tetra- and pentachloronaphthalene (500 mg/rat/day) (Ben38, Dri37, Ben66). Twenty repeated doses of 10 or 100 mg/kg bw/day of pentachloronaphthalene (Halowax 1014) produced very slight to severe liver lesions, but no mortality; no effects were seen at 1 mg/kg bw/day (Ada44). In guinea pigs, repeated oral doses of 2.5 mg/kg bw caused mortality within 48 days (Ben38, Dri37, Ben66).

Daily subcutaneous injection (15 mg/kg bw) of a tetra- and pentachloronaphthalene mixture, a penta- and hexachloronaphthalene mixture or the sublimate of the latter mixture, resulted in the death of all exposed rabbits and signs of yellow atrophy in the liver (Fli36).

The committee considers the toxicological data base on pentachloronaphthalene too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that, based on the effects found in the inhalation studies in rats, the present MAC value of 0.5 mg/m^3 is too high.

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Annex

Occupational exposure limits for pentachloronaphthalene in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	lit ref[b]
	ppm	mg/m^3				
the Netherlands						
-Ministry	-	0.5	8 h	administrative		SZW01
Germany						
-AGS	-	0.5[c]	8 h		S	TRG00
		2	15 min			
-DFG MAK-Kom.	-	-[d]			S	DFG01
Great-Britain						
-HSE	-	-				HSE01
Sweden	-	-				Arb00b
Denmark	-	0.5	8 h		S	Arb00a
USA						
-ACGIH	-	0.5	8 h	TLV	S	ACG01
-OSHA	-	0.5	8 h	PEL	S	ACG00
-NIOSH	-	0.5	10 h	REL	S	ACG00
European Union						
-SCOEL	-	-				CEC00

[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] Inhalable dust

[d] As chlorinated naphthalenes, these compounds are listed among substances for which studies of the effects in man or in experimental animals had yielded insufficient information for the establisment of a MAK value