Cyanogen chloride

(CAS No: 506-77-4)

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 cyanogen chloride 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 RN Hooftman, M.Sc. and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of cyanogen chloride has been based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in October 1997, literature was searched in the on-line databases Medline, Toxline, and Chemical Abstracts, starting from 1965, 1965, and 1967, respectively, and using the following key words: cyanogen chloride and 506-77-4.

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

2 Identity

name	:	cyanogen chloride
synonyms	:	chlorcyan; chlorine cyanide; chlorocyan; chlorocyanide; chlorocyanogen
molecular formula	:	CClN
structural formula	:	Cl-CN
CAS number	:	506-77-4

3 Physical and chemical properties

molecular weight	:	61.5
boiling point	:	13.8°C
melting point	:	-6°C
flash point	:	not available
vapour pressure	:	at 25°C: 164 kPa
solubility in water	:	soluble (at 20°C: 2500 mL in 100 mL water)
log $P_{octanol/water}$	:	-0.39 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 ppm = 2.56 mg/m^3 1 mg/m^3 = 0.39 ppm

Data from ACG91, NLM03, http://esc.syrres.com.

Cyanogen chloride is a colourless liquid or gas with a pungent odour (ACG91). An odour threshold of 2 mg/m^3 (0.8 ppm) has been reported (Rut86).

It tends to form polymers upon storage.

4 Uses

Cyanogen chloride is used in organic synthesis, as a poison (tear) gas by the military, and as a warning agent in fumigant gases and pesticides (ACG91, NLM03).

According to the database of the Dutch Pesticide Authorisation Board (CTB)*, cyanogen chloride is at present not permitted in the Netherlands for use in pesticides.

5 Biotransformation and kinetics

Based on its physico-chemical properties, it can be expected that cyanogen chloride will be readily absorbed after respiratory, dermal, and oral exposure.

Cyanogen chloride reacts with haemoglobin and glutathione eventually liberating the CN ion. A two-step mechanism was postulated. In the first step, cyanogen chloride should react with a compound having vicinal amino and sulphydryl groups (e.g., glutathione, *N*-acetylcysteine, haemoglobin, carboxyhaemoglobin) to a cyclic compound. In the second step, reaction with glutathione should release HCN. Both *in vitro* and *in vivo* experiments showed that cyanogen chloride is very rapidly converted into HCN although not quantitatively. The fate of the remaining fraction has not been determined (Ald46, Ald51).

Another committee of the Health Council, viz., the Dutch Expert Committee on Occupational Standards (DECOS), has reviewed the metabolism of cyanide in a criteria document on HCN, NaCN, and KCN. In summary, cyanide is distributed to many organs and the blood. At lethal or nearly lethal doses of these cyanides, relatively high concentrations were found in the liver, lungs, kidneys, brain, and blood. Various biotransformation pathways have been identified for cyanide. The most important way is the formation of thiocyanate by the acceptance of a sulphane-sulphur of thiosulphate or other sulphane-sulphur-containing compounds (transsulphurisation), the key enzyme being rhodanese. The rate-limiting factor of this pathway is the lack of sulphane-sulphur sources in the body. Cyanide is largely eliminated from the body via the urinary excretion

* At: http://www.ctb-wageningen.nl.

of thiocyanates in the case of high exposure levels. Other minor elimination routes include the exhalation of carbon dioxide and traces of hydrogen cyanide. The relative importance of various biotransformation and elimination routes is unknown for lower, clearly sublethal exposure levels (Hea02).

Cyanogen chloride was stated to be detoxified at rates of 0.03-0.06 and 0.02-0.04 mg/kg/min by rabbits and dogs, respectively depending on the injection rate. For man, the detoxification rate should be 0.02-0.1 mg/kg/min (Moo46).

6 Effects and mechanism of action

Human data

Limited data on human exposure are reported. They mostly originate from its use as a poison gas during World War I.

The lowest irritant concentration to man was reported to be 1 ppm (2.6 mg/m^3) for a 10-minute exposure period. Exposures to 2 ppm (5.2 mg/m^3) for 10 minutes and to 20 ppm (52 mg/m^3) for 1 minute were reported to be unbearable. Exposure to 40 ppm (104 mg/m^3) should immediately induce irritation of the eyes and respiratory tract with blepharospasms, strong lachrymation, and tickling cough. Levels of 48 ppm (125 mg/m^3) and 159 ppm (410 mg/m^3) were stated to be fatal after 10 and 30 minutes exposure, respectively (cited by ACG91, Gre97, Har94 from probably poorly documented literature from the 1920s and 1930s; see e.g., Flu31).

Unpublished information submitted to the ACGIH TLV Committee (in 1977) said that under occupational conditions, people had to leave work because of severe eye and nose irritation at concentrations of 0.7 ppm (1.8 mg/m^3) (ACG91). From a case of chronic exposure (daily for 8 months to an unknown concentration), it is known that cyanogen chloride causes muscular weakness, lung congestion, skin irritation, hoarseness, conjunctivitis, oedema of the eyelids, significant weight loss, and burning urine. In a group of 10 workers with long-term occupational exposure to unknown levels, there were complaints of chronic vomiting, diarrhoea, cough, cold sensation, chronic headache, and weight loss (cited by ACG91 and Gre97 from a report published in 1920).

Generally, cyanogen chloride possesses the same general type of toxicity and mode of action as hydrogen cyanide, but it is more irritating (Har94).

Animal data

Cyanogen chloride was stated to cause marked irritation of the respiratory tract with haemorrhagic exudate from the bronchi and trachea and pulmonary oedema, but no exposure levels were presented (ACG91).

Concentrations of approximately 260 mg/m^3 (100 ppm) were reported to be lethal to dogs, rats, and mice after 20, 37, and 60 minutes, respectively (Gre97). These data suggested that dogs are more sensitive than rats or mice.

Some toxicity data concerning acute exposure by inhalation are presented in Table 1.

Table 1 Summary of effects of cyanogen chloride following single exposure by inhalation (data from Flu31).

species[a]	concentration[b]		duration (min)	response	species	concentration		duration (min)	response
	mg/m^3	ppm				mg/m^3	ppm		
mouse	200	80	5	tolerated by some animals	cat	1000	400	[c]	fatal
	300	120	3.5	fatal to some animals	dog	50	20	20	tolerated
	1000	400	3	fatal		120	48	360	fatal
rabbit	3000	1200	2	fatal		300	120	8	severe injury, recovery
cat	100	40	18	fatal after 9 days		800	320	7.5	fatal
	300	120	3.5	fatal	goat	2500	1000	3	fatal after 70 hours

[a] Sex and number not reported.
[b] Conversion by Flury and Zernik.
[c] A 'few inhalations'.

For rabbits and dogs, intravenous LD_{50} values of 3.15 and 3.30 mg/kg bw, respectively, have been reported. Based on comparison with hydrogen cyanide, Moore and Gates felt that cyanogen chloride was as toxic by inhalation as by intravenous injection (Moo46).

The oral LD_{50} was 6 mg/kg for cats, with deaths occurring at about 30 minutes (Moo46).

Subcutaneous doses of 5 and 20 mg/kg bw were reported to be lethal to dogs and rabbits, respectively (NIO03).

Daily exposure of dogs and swine (0.5-2 hours/day, for 2 weeks) to unspecified, sublethal concentrations resulted in vomiting, diarrhoea, irritation of eyes and upper respiratory tract, tachycardia, polypnoea, and weight loss. Severe lung congestion was observed (Gre97).

Since it is reasonable to ascribe the (possible) systemic toxicity due to exposure to cyanogen chloride to cyanide, the findings as presented in the aforementioned criteria document on HCN, NaCN, and KCN will be summarised here. In humans, exposure to lethal or nearly lethal doses leads to a series of respiratory, cardiovascular, and neurological symptoms. Death is preceded by coma, and is caused by respiratory failure or cardiac arrest. Acute toxicity is characterised by a rather steep dose-response/effect relationship: exposure to 20 mg/m^3 for several hours may lead to slight effects only, while exposure to 120 mg/m^3 may be fatal. Survival of serious acute poisoning may be followed by severe neurotoxicological sequelae. Some case studies suggested that human cyanide toxicity is not restricted to acute effects and their sequelae, but that effects may gradually develop upon repeated exposure, in particular neurotoxicity and goitre. However, it was not possible to link these effects to exposure levels.

In one epidemiological study in which exposure levels were 5.9 to 12.4 ppm (6.5-13.8 mg CN/m^3), higher incidences of a number of symptoms (headache; weakness; changes in taste, smell; giddiness; throat irritation; vomiting, dyspnoea; lachrymation; precordial pain; salivation; disturbances of accommodation; psychosis) were reported in occupationally exposed workers when compared to not-exposed controls, as well as enlarged thyroids, pointing to goitre, in most of the exposed workers. In experimental animals, similar respiratory, cardiovascular, and neurological effects are observed following single exposures.

Depending on species, compound, and exposure duration, the respiratory LC_{50} ranged between 134 and 410 ppm (149-455 mg/m^3). Repeated exposures (12 exposures of 1/2 hour, 1 exposure per 8 days or 14 or 19 exposures of 1/2 hour, 1 exposure per 2 days) to 50 mg HCN/m^3 resulted in severe histological brain lesions in dogs; no histological effects were observed in hearts, lungs, and adjacent arteries of rabbits continuously exposed to 0.5 mg HCN/m^3 for 4 weeks. A wide variety of effects, among others on the CNS and the male reproduction, were reported from short-term oral experiments in experimental animals at daily doses of about 0.5 mg/kg bw. No effects were seen in rats orally exposed to about 3.5 mg/kg bw/day, for 2 years. No indications for a carcinogenic or genotoxic potential were found. However, because of flaws in design of the long-term studies and the limited number of genotoxicity endpoints examined, no definitive conclusions could be drawn.

Cyanides were embryotoxic and teratogenic at maternally toxic doses. Since lower doses were not tested, a definitive conclusion concerning reproduction toxicity cannot be drawn either. Finally, DECOS concluded that the most important primary effect of cyanide is the inhibition of the enzyme cytochrome C

oxidase in the respiratory chain, thus blocking the utilisation of oxygen and the production of ATP by oxidative phosphorylation. Cyanides can inhibit other metallo enzymes as well; however, the effects of this inhibition are assumed to be overshadowed by the effects of the inhibition of cytochrome C oxidase, at least at the high doses investigated (Hea02).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for cyanogen chloride in the Netherlands is 0.6 mg/m^3 (0.3 ppm), which is a ceiling value.

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

In its criteria document on HCN, NaCN, and KCN, DECOS recommended a health-based occupational exposure limit of 1 mg/m^3, 8-hour TWA, and a ceiling limit of 10 mg/m^3 as CN^- from any combination of these 3 compounds (Hea02).

8 Assessment of health hazard

Cyanogen chloride has the same general type of toxicity and mode of action as hydrogen cyanide, but it is considered to be much more irritating to the respiratory tract and the eyes, even at very low concentrations. According to data from the 1920's and 1930's, the lowest concentration inducing irritation in humans should be 1 ppm (2.6 mg/m^3) at a 10-minute exposure period. Other symptoms observed in humans exposed to unknown concentrations include muscular weakness, lung congestion, skin irritation, hoarseness, conjunctivitis, oedema of the eyelids, cold sensation, weight loss, chronic headache, and burning urine.

Inhalation data for experimental animals are limited to acute exposures, from which it is clear that cyanogen chloride should be classified as very toxic by inhalation.

The committee did not find data on toxicity following repeated exposure (including those on carcinogenicity and reproduction toxicity) and mutagenicity.

The committee considers the toxicological database on cyanogen chloride 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: 36.

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: 22.

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Har94 Hartung, R. Cyanides and nitriles. In: Clayton GD, Clayton, FE. Toxicology. 4th ed. New York, USA: John Wiley & Sons, Inc, 1994: 3132-34 (Patty's industrial hygiene and toxicology; Vol 2, Part D).

Hea02 Health Council: Dutch Expert Committee on Occupational Standards. Hydrogen cyanide, sodium cyanide, and potassium cyanide. Health-based recommended occupational exposure limits. The Hague, the Netherlands: Health Council of the Netherlands, 2002; publ no 2002/15OSH.

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Committee, 1946: 7-16 (Vol 1) (available from National Technical Information Service, Springfield VA, USA; rep no PB158508).

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

NLM03 US National Library of Medicine (NLM), ed. Cyanogen chloride. In: The Hazardous Substances Data Bank (HSDB) (last revision date cyanogen chloride file: February 2003; last review date: January 1997); http://toxnet.nlm.nih.gov.

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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: 30 (Ordinance AFS 2000:3).

SZW04 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2004. The Hague, the Netherlands: Sdu Uitgevers, 2004: 22.

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

Annex

Occupational exposure limits for cyanogen chloride 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	0.3	0.6	ceiling	administrative		SZW04
Germany						
- AGS	-	0.75	8 h			TRG03
- DFG MAK-Kommission	-[c]	-[c]				DFG03
Great-Britain						
- HSE	0.3	0.77	15 min	OES		HSE02
Sweden	0.1	0.3	8 h			Swe00
	0.3	0.8	15 min			
Denmark	0.10	0.30	8 h			Arb02
USA						
- ACGIH	0.3	-	ceiling	TLV		ACG04
- OSHA	-	-	-			ACG03
- NIOSH	0.03	0.06	ceiling	REL		ACG03
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.