Oxalonitrile

(CAS No: 460-19-5)

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 oxalonitrile 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 M Busschers, M.Sc., and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of oxalonitrile has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG98). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the on-line databases Medline, Toxline, Chemical Abstracts, and NIOSHTIC covering the period 1966 to May 1999, 1965 to February 1999, 1967 to May 1999, and 1973 to April 1998, respectively, and using the following key words: dicyan, ethanedinitrile, carbon nitride, dicyanogen, nitriloacetonitrile, oxalic acid dinitrile, oxalonitrile, oxalyl cyanide, and 460-19-5. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO99, NLM99). The final literature search was carried out in April 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 search in May 2002 did not result in information changing the committee's conclusions.

2 Identity

name	:	oxalonitrile
synonyms	:	cyanogen*; carbon nitride; dicyan; dicyanogen; ethanedinitrile; nitriloacetonitrile; oxalic acid dinitrile; oxalyl cyanide; prussite
molecular formula	:	C_2N_2
molecular structure	:	N≡C-C≡N
CAS number	:	460-19-5

[a] name used in this document

Data from ACG98, Ric93.

3 Physical and chemical properties

molecular weight	:	52,04
boiling point	:	-21.2°C
melting point	:	-27.9°C
flash point	:	-
vapour pressure	:	at 20°C: 538 kPa
solubility in water	:	soluble
log $P_{octanol/water}$	:	0.07 (both experimental and estimated)
conversion factors (20°C, 101.3 kPa)	:	1 ppm = 2.2 mg/m^3 1 mg/m^3 = 0.46 ppm

Data from ACG98, Ano81, Har94, NLM99, http://esc.syrres.com.

Cyanogen is a colourless gas with a pungent, penetrating, almond-like odour. The odour threshold is reported as being about 500 mg/m^3 (230 ppm) (Rut86), while another study reports that humans did not detect any odour up to 550 mg/m^3 (250 ppm, the highest concentration tested) (McN60).

4 Uses

Cyanogen is primarily used in organic synthesis. It is, however, also used as a fuel gas for welding and cutting heat-resistant metals, as a rocket and missile propellant (with ozone or fluorine), and as a fumigant (ACG98). At one time, it was used in poison gas warfare (Ano81).

5 Biotransformation and kinetics

In cells, cyanogen combines with enzymes involved in the cellular oxygen transport and arrests oxidation in those cells (Lew84). The committee did not find further information on the biotransformation or kinetics of cyanogen.

Cyanogen hydrolyses to yield one molecule of hydrogen cyanide (HCN) and one of cyanate. The metabolism of cyanide has been reviewed in a criteria document on HCN, NaCN, and KCN by another committee of the Health Council, viz., the Dutch Expert Committee on Occupational Standards (DECOS). 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 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).

6 Effects and mechanism of action

Human data

Human volunteers experienced nasal and eye irritation when they were exposed to 35 mg/m^3 (16 ppm), for 6-8 minutes. A concentration of 18 mg/m^3 (8 ppm) for 6 minutes did not result in any irritation. Human subjects were unable to detect any odour from concentrations of cyanogen as high as 550 mg/m^3 (250 ppm) (McN60).

Generally, cyanogen possesses the same general type of toxicity and mode of action as hydrogen cyanide although cyanogen appears to be more irritating (Har94).

Animal data

Irritation and sensitisation

Dermal exposure of rabbits to cyanogen gas in an acute toxicity study indicates that cyanogen is not a skin irritant. Irritation of the eyes and upper respiratory tract was reported in an acute inhalation study, but a detailed description of the irritating effects on the different tissues was not available (McN60).

The committee did not find any data on the potential sensitising properties of cyanogen.

Acute toxicity

In an acute inhalation study, male rats (n=6/group) were exposed to cyanogen ranging from 540-8540 mg/m^3 (250-4000 ppm), for 7.5-120 minutes. Symptoms included eye and upper respiratory tract irritation, huddling together with inactivity, slow gasping, fluid from nose and mouth, poorly coordinated movements, bright pink colouration of the skin, laboured breathing, tremors, and, eventually, death. No macroscopic abnormalities were found. Mortality was dependent on dose and length of exposure: exposure to 850 mg/m^3 (400 ppm) for 45 minutes caused no mortality, whereas none of the animals survived a 1-hour exposure to the same concentration. The longest exposure (2 hours) to 540 mg/m^3 (250 ppm) resulted in the death of 2/6 rats during exposure and a further 2 rats died within 7 days after exposure. The 1-hour $LC5_0$ for cyanogen was 750 mg/m^3 (350 ppm) (McN60).

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

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

species[a]	concentration[b]		duration (min)	response
	mg/m3	ppm		
mouse	500	235	15	tolerated
	5 500	2 600	12	fatal
	31,5	15	<1	fatal
rabbit	210	100	240	practically no effects
	420	200	240	slight symptoms
	630	300	210	severe symptoms, delayed death
	840	400	105	fatal
cat	100	50	240	severe symptoms, recovery
	160	75	240	severe symptoms, fatal after 2 days
	210	100	120-180	fatal
	420	200	30	fatal
	4 260	2 000	13	fatal

[a] Sex and number not reported.
[b] Conversion by Flury and Zernik.

Dermal exposure of rabbits to 22,000 mg/m^3 (10,000 ppm), for 8 hours, did not result in any clinical observations or macroscopic effects (McN60).

Repeated-dose toxicity

Male rhesus monkeys (n=5/group) and male rats (n=30/group, including 4 interim kills per exposure level) were exposed to 25 mg/m^3 (11 ppm) or 56 mg/m^3 (25 ppm) cyanogen gas for 6 months (6 hours/day, 5 days/week). Body weights of rats exposed to 56 mg/m^3 for 6 months (n=6) were statistically significantly decreased; the mean body weights after 6 months of exposure were 543, 589, and 470 g for the control, the low- exposure group, and the high-exposure group, respectively. The total lung moisture content was lower in cyanogen-exposed monkeys than in control monkeys. The effect was not noted in rats and the biological relevance of this finding was considered unclear, also since no histological changes were observed. Moreover, no lung function parameters were studied, actual data on the (decrease in) moisture content were not reported and, hence, no information on a possible dose-response relationship was available. Behavioural testing was conducted in monkeys only. Although the response rate of all monkeys was reported to be slightly increased in the exposure period compared to baseline (pre-exposure) data, it was noted that the baseline response of the high-dose group was a factor 2 lower than that of the other groups. Furthermore, it should be noted that this effect was noted against a background of disturbingly low overall rates and high variability. No further abnormalities were noted in haematology or clinical biochemistry parameters, electrocardiograms (monkeys only), and macro- and microscopic examinations of heart, liver, kidney, cerebellum, cerebrum, lungs, thyroid, spleen, and bone marrow (upper respiratory tract was not examined). According to the authors, the findings suggested that inhaled cyanogen gas, under the conditions of this study, did not induce any organ specific or systemic toxicity but that 56 mg/m^3 (25 ppm) was likely to produce minor, untoward changes (Lew84). The committee considers the lung effects observed in the monkeys as non-adverse and 25 mg/m^3 (11 ppm) to be the NOAEL in this study. It should be kept in mind that the upper respiratory tract was not investigated in this study.

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

Systemic effects due to cyanide exposure

Since cyanogen hydrolyses to yield cyanate and cyanide systemic effects may arise which are due to the cyanide formed. Therefore, 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 HCN/m^3 for several hours may lead to slight effects only, while exposure to 120 mg HCN/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 4.2 to 12.4 ppm (4.7-13.9 mg CN^-/m^3), higher incidences of a number of symptoms (headache; weakness; changes in taste and 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 ½ h, 1 exposure per 8 days, or 14 or 19 exposures of ½ h, 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 behaviour, the CNS, and the male reproduction, were reported from short-term oral experiments in experimental animals at daily doses of 0.4 mg KCN, 0.5 mg NaCN, and 3.5 mg NaCN/kg bw. No effects were seen in rats orally exposed to about 3.5 mg HCN/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 in the Netherlands is 20 mg/m^3 (10 ppm), 8-hour TWA.

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

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

8 Assessment of health hazard

Data on humans and rats indicate that cyanogen can cause nasal and/or eye irritation. In human volunteers, no irritation was observed during a 6-minute exposure to 18 mg/m^3 (8 ppm) while eye and nasal irritation were experienced at 35 mg/m^3 (16 ppm) (McN60).

No data were found on the potential sensitising properties of cyanogen.

An inverse correlation was noted between concentration and exposure-time in an acute inhalation study, in which rats were exposed to cyanogen concentrations ranging from 540-8540 mg/m^3 (250-4000 ppm) for 7.5-120 minutes. The symptoms included asphyxiation, lachrymation, poorly coordinated movements, pink colouration of the noticeable skin, and, eventually, death. A 2-hour exposure to 540 mg/m^3 (250 ppm) caused the death of 4/6 rats. The 1-hour LC_{50} was 750 mg/m^3 (350 ppm) (McN60).

Other acute inhalation data indicate that cyanogen is toxic by inhalation to various species. Exposures to 210 mg/m^3 (100 ppm), for 2-3 hours, and to 840 mg/m^3 (400 ppm), for less than 2 hours, were lethal to cats and rabbits, respectively (Har94).

Acute dermal exposure of rabbits to 22,000 mg/m^3 (10,000 ppm), for 8 hours, did not result in any clinical observations or macroscopic effects (McN60).

Repeated exposure of monkeys and rats to 25 mg/m^3 (11 ppm) or 56 mg/m^3 (25 ppm) cyanogen gas, for 6 months, did not result in mortality or other severe effects. Effects noted were a decreased body weight of rats exposed to 56 mg/m^3 and a reduced moisture content of the lungs in both groups of cyanogen-treated monkeys (Lew84). However, potential upper respiratory tract irritation was not addressed in this study.

No data were found on the potential genotoxicity, carcinogenicity, or reproduction toxicity of cyanogen.

The committee takes the NOAEL of 25 mg/m^3 found in the 6-month inhalation study in rats and monkeys as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall assessment factor of 9 is established. This factor covers the following aspects: the intra- and interspecies variation. Thus, applying this factor of 9 and the preferred value approach, a health-based occupational exposure limit of 2 mg/m^3 is recommended for oxalonitrile. In view of the NOAEL and LOAEL for irritation of 18 and 35 mg/m^3 (8 and 16 ppm), respectively, found in human volunteers exposed for 6-8 minutes, the committee is of the opinion that this HBROEL will be sufficiently low to offer protection against irritation as well. Furthermore, since one molecule of cyanogen yields 2 CN^- ions, the HBROEL of 2 mg/m^3 is very well in line with the HBROEL for CN^- of 1 mg/m^3.

The committee recommends a health-based occupational limit for oxalonitrile of 2 mg/m^3, as an 8-hour time-weighted average.

References

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Annex

Occupational exposure limits for cyanogen 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	10	20	8 h	administrative		SZW02
Germany						
- AGS	10	22	8 h		S	TRG00
	40	88	15 min			
- DFG MAK-Kommission	10	22	8 h			DFG02
	20	44	15 min[c]			
Great Britain						
- HSE	10	22	8 h	OES		HSE02
Sweden	-	-				Swe00
Denmark	10	20	8 h			Arb02
USA						
- ACGIH	10	-	8 h	TLV		ACG02b
- OSHA	-	-				ACG02a
- NIOSH	10	20	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.
[c] Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.