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VOORGESTELD

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Probit function technical support document

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substance name	CAS number
Sodium cyanide	**143-33-9**

This draft document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

This document has been checked for completeness by the Netherlands' National Institute for Public Health and the Environment (RIVM) and has been assigned the status "voorgesteld" (proposed). The scientific expert panel on probit functions has approved this document for public discussion and comments. Interested parties are invited to submit comments and suggestions concerning this document within 6 weeks after the issue date to the email address mentioned above.

If the proposed probit function is approved by the expert panel on scientific grounds, after review and revisions following of public comments, the status of the document and probit function will be raised to "inhoudelijk vastgesteld" (approved content).

Detailed information on the procedures for the derivation, evaluation and formalization of probit functions is available at http://www.rivm.nl/en/Topics/P/Probit_functions.

Technical support document sodium cyanide

1. Substance identification[1]

CAS-number:	143-33-9
IUPAC name:	sodium cyanide
Synonyms:	Cyanogran; cyanide of sodium; cymag; hydrocyanic acid sodium salt; cyanobrik; white cyanide, sodium cyanide solution
Molecular formula:	NaCN
Molecular weight:	49 g/mol
Physical state:	solid (at 20°C and 101.3 kPa)
Boiling point:	ca. 1500°C (at 101.3 kPa)
Vapour pressure:	NA
Saturated vapor conc:	NA
Conversion factor:	1 mg/m^3 = 0.491 ppm (at 20°C and 101.3 kPa)
	1 ppm = 2.038 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H300-310-330

2. Mechanism of action and toxicological effects following acute exposure[2]

Specific substance information: The toxicity of sodium cyanide is related to its CN moiety. Hydrogen cyanide (HCN) is formed when in contact with moist in air or airways. Note that the dust from solid salts can also cause the same symptoms of toxicity. The text below is copied from the HCN TSD and applies also to sodium cyanide.

Acute effects:

The main target organs and tissues for inhalation exposure to hydrogen cyanide are the respiratory system, the central nervous system and the cardiovascular system. HCN inhibits cellular respiration. This is especially detrimental in tissues and organs with high energy demand, such as the brain. Exposure to HCN may cause neurological symptoms such as loss of consciousness and inhibition of the respiratory system. In addition, exposure to HCN may result in weakness, paralysis, and cardiac irregularities. Lethality caused by exposure to HCN is due to respiratory arrest.

Long-term effects: Although some neurological symptoms have been related to chronic exposure of workers to HCN, in none of the reports concomitant exposure to other chemicals could be ruled out. Reported symptoms, of which some increased with increasing number of years of work, included headache, fatigue, nausea, weakness, tremors and changes in taste and smell. Besides, chronic exposure to HCN has been associated with hypothyroidism. Information concerning possible long-term effects of acute exposure to toxic concentrations of HCN is limited, but shows that recovery may be uneventful without any permanent adverse health effects.

3. Human toxicity data

No informative reports on human toxicity following acute inhalation exposure were identified in which details about both health effects and the exposure have been documented in sufficient detail.

Please refer to the HCN technical support document (RIVM, 2017) describing human toxicity data for HCN.

[1] Chemiekaart C-0032 sodium cyanide is used as source for the data. Chemiekaart C-0789 describes sodium cyanide in solution (30%) and yields a boiling point of 110°C and a vapour pressure of 2 kPa.

[2] References for mechanism of action and toxicological effects following acute exposure.

4. Animal acute toxicity data

During the literature search the following technical support documents and databases were consulted:

1. AEGL final TSD on cyanide salts (2015), covering references before and including 1995. No ERPG document and EU RAR and reference database for sodium cyanide available.
2. An additional search covering publications from 1980 onwards was performed in HSDB, MEDline/PubMed, Toxcenter, IUCLID, ECHA database, RTECS, IRIS and ToxNet with the following search terms:
   - Substance name and synonyms
   - CAS number
   - lethal*
   - mortal*
   - fatal*
   - LC_{50}, LC
   - probit
3. Unpublished data were sought through networks of toxicological scientists.

No acute inhalation toxicity studies were identified with sodium cyanide.

Sensory irritation

No studies on sensory irritation were found.

5. Probit functions from individual studies

There are no acute inhalation toxicity studies with sodium cyanide.

6. Derivation of the human probit function

To derive the human probit function for sodium cyanide the points of departure for HCN have been used. The toxicity of sodium cyanide is best predicted by its hydrolysis product HCN. Upon contact with moist in air or in airways one mole of sodium cyanide hydrolysis to one mole of HCN. It is noted that sodium cyanide as salt is relatively stable, the AEGL document (2015) mentions a half-live of 7.7 hours at 25 °C (unknown humid conditions), therefore making the assumption of complete hydrolysis conservative. The assumption is less conservative for sodium cyanide used in aqueous or acidic solutions where hydrolysis occurs more rapidly.

The points of departure for HCN are a 30-min geometic mean animal LC_{50} value of 181 mg/m^3 (equal to 6.7 mmol/m^3 (MW HCN = 27 mg/mmol HCN)) and an arithmetic mean n-value of 1.71 (for details see the HCN TSD; RIVM, 2017).

The estimated 30-minute animal LC_{50} value for sodium cyanide can be derived based on the assumption that one mole of sodium cyanide hydrolyses to one mole of HCN. Hence, 6.7 mmol/m^3 of sodium cyanide corresponds to 6.7 mmol/m^3 HCN. The 30-min animal LC_{50} value of sodium cyanide is therefore 6.7 mmol/m^3 equalling 328 mg/m^3 (MW NaCN = 49 mg/mmol).

The human equivalent LC_{50} was calculated by applying the following assessment factors:

Table 1 *Rationale for the applied assessment factors.*

Assessment factor for:	Factor	Rationale

Animal to human extrapolation:	1	The AF is set to 1 based on the data on HCN that indicated that there is no significant difference in toxicity between the test animals and humans that would require an AF larger than 1.
Nominal concentration	1	Based on analytical data in the studies with HCN.
Adequacy of database:	1	Despite the fact that there are no acute lethal studies with sodium cyanide itself, it is well-known that the toxicity of cyanide salts is caused by the formation of HCN. Since the hydrolysis process of sodium cyanide is conservatively considered as rapid and complete there is no need for an uncertainty factor that would further lower the human equivalent of the LC_{50}.

The estimated human equivalent 30-min LC_{50} value is 328 / 1 = 328 mg/m^3.

The experimentally determined n-value was **1.71** for HCN which is adopted for sodium cyanide. Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.17**.

The human probit function is then calculated on the human equivalent 30-min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1.17 \times \ln(328^{1.71} \times 30)$ resulting in the a-value of **-10.56**.

$Pr = -10.56 + 1.17 \times \ln(C^{1.71} \times t)$ with C in mg/m^3 and t in min.

The derived human probit function has a scientifically acceptable basis. The probit function is based on the lethality data for hydrogen cyanide, including three studies in the rat with A quality, where in total 84 C x t combinations are included, including durations ranging from 2.5 to 60 minutes and lethality in the range of 0-100%.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 46 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 68 mg/m^3.

Table 2 *LC-values calculated with the derived probit function compared with existing acute inhalation exposure guidelines.*

Estimated level	30 min (mg/m^3)	60 min (mg/m^3)
0.1% lethality, this probit	70	46
1% lethality, this probit	102	68
AEGL-3[3] (2015, final)	42	30
ERPG-3		NA
LBW	NA	NA

Compared with equivalent (inter)national guideline levels as presented in the table above, the lethal levels derived with this probit function are higher.

[3] AEGL and ERPG values were converted from ppm to mg/m^3 with the conversion factor calculated in section 1. Therefore, the AEGL and ERPG values in mg/m^3 can deviate slightly from those reported in the AEGL and ERPG TSDs.

Appendix 1 Reference list

AEGL, 2015. National Research Council. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 19. Washington, DC. The National Academies Press, 2015.

Chemiekaarten. Natriumcyanide. Ed 32. Den Haag. TNO/SDU uitgevers, 2023.

Chemiekaarten. Natriumcyanide (30% in water). Ed 32. Den Haag. TNO/SDU uitgevers, 2023.

Ruijten M.W.M.M., J.H.E. Arts, P.J. Boogaard *et al*. Methods for the derivation of probit functions to predict acute lethality following inhalation of toxic substances. RIVM report 2015-0102. Bilthoven, RIVM, 2015.

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