Hydrogen cyanide, potassium cyanide and sodium cyanide

MAK value (2001)	**2 mg/m³ I (inhalable fraction) as CN^-** **HCN: 1.9 ml/m³ (ppm) ≙ 2.1 mg/m³** **KCN: 5.0 mg/m³ I** **NaCN: 3.8 mg/m³ I**
Peak limitation (2001)	**Category II** **HCN: excursion factor 2** **KCN: excursion factor 1** **NaCN: excursion factor 1**
Absorption through the skin (2001)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2001)	**Pregnancy risk group C**
Germ cell mutagenicity	**–**
BAT	**–**

Chemical name (CAS)	Synonyms	CAS number	Formula	Molecular weight	Melting point (°C)	Boiling point (°C)	log P_{OW}
hydrogen cyanide	hydrocyanic acid	74-90-8	HCN	27.03	–13.24	25.70	0.66
potassium cyanide		151-50-8	KCN	65.11	634.5	1625	–0.44 (calculated)
sodium cyanide		143-33-9	NaCN	49.02	563.7	1496	no data

The MAK values which applied until 2001, 5 mg/m³ I for cyanides, 10 ml/m³ (11 mg/m³) for HCN were established, respectively, in 1958 on the basis of the then valid TLV and in 1971 (Henschler 1971). The present document is based in part on other reviews of the toxicological data for cyanides (Ballantyne and Marrs 1987, EPA 1992, NL Health Council 1999).

1 Toxic Effects and Mode of Action

Cyanide salts and HCN are very poisonous. The toxic effects include headaches, dizziness, nausea, a feeling of suffocation, metabolic acidosis, hyperventilation, oxygen saturation of the venous blood (pink skin colour), convulsions, loss of consciousness, respiratory arrest and dilated pupils. The cause of death is usually central respiratory paralysis caused by inhibition of cytochrome oxidase. The lethal oral dose of KCN and NaCN for humans is between 0.5 and 3.5 mg/kg body weight. Detoxification takes place mainly by reaction of cyanide with endogenous sulfur donors to yield thiocyanate, a reaction which is catalysed by the hepatic enzyme rhodanese. A small part of the dose is exhaled unchanged. Survivors of acute cyanide poisoning may later develop neurological damage. Unspecific CNS effects and enlarged thyroid glands have been found in chronically exposed workers. Cyanide concentrations above 5 mg/m^3 cause nasal irritation. Central and peripheral neurotoxicity is also observed in experimental animals given repeated doses just below the acutely toxic range. Cyanide is less toxic when administered in the feed or drinking water than when administered by gavage.

2 Mechanism of Action

The systemically active principle of the three compounds is the cyanide ion. It reacts with the trivalent iron in cytochrome oxidase to give a relatively stable complex. This inhibits the enzyme and blocks the last step in oxidative phosphorylation. The result is a deficiency of mitochondrial ATP and cell death (Szinicz 1996). Particularly sensitive tissues are those of the CNS and heart (EPA 1992).

Acute cyanide exposure leads to acidosis (increase in lactate concentrations), reduced carbon dioxide concentrations, and increase in the oxygen concentration, increasing catabolism via the pentose phosphate pathway, reduction in catabolism via the Embden-Meyerhof pathway and the citrate cycle, and an increase in glucose and inorganic phosphates in the blood (Ballantyne 1987, Isom *et al.* 1975, Katsumata *et al*. 1980, 1983).

Cyanide forms reversible complexes with metal ions and thus inhibits many other metalloenzymes (NTP 1993).

The thiocyanate produced from cyanide can reduce iodide uptake into the thyroid and therefore prolonged exposure, especially of persons with iodine deficiency, can increase the incidence of goitre. It is very probable that tropical ataxic neuropathy is a result of chronic intake of cyanide with a staple food, cyanide-containing cassava roots (manioc) (see Section 4.2.2).

3 Toxicokinetics and metabolism

3.1 Intake

The retention determined after exposure of volunteers breathing HCN (4–20 mg/m^3) via the mouth for 1 to 3 minutes was 39 % to 77 %. Nasal retention was 13 % to 19 %. It is unclear whether steady state was reached during these short exposure times. The data therefore probably represent maximum retention levels (NL Health Council 1999). For the salts, it must be assumed that intake via the respiratory tract occurs by inhalation of particles or droplets of aqueous solutions, and absorption is 100 % because any substance cleared from the respiratory tract may be swallowed.

Ingested cyanide salts react with the hydrochloric acid in the stomach to yield HCN which, because it is largely undissociated, is rapidly absorbed in the gastrointestinal tract. 94.7 % of the radioactivity ingested as $K^{14}CN$ by rats was recovered in the urine (collected for up to 14 days after dosing), which suggests complete absorption (see Section 3.4 Excretion).

The presence of moisture is a prerequisite for dermal absorption of the salts (Section 5.1). It has been shown with human skin *in vitro* that penetration of sodium cyanide in aqueous solution decreases with increasing pH (increasing dissociation). This means that undissociated HCN is absorbed more rapidly than is the cyanide ion: the permeability constant measured for the cyanide ion in aqueous solution was 3.5×10^{-4} cm/h, and that calculated for HCN was 1×10^{-2} cm/h (Dugard 1987). The level of absorption of gaseous HCN through the skin of volunteers was low (Schütze 1927, O'Donnell *et al.* 1940). Epicutaneous exposure of dogs to gaseous HCN (6500–16900 mg/m^3) for up to 180 minutes caused respiratory distress and even death (EPA 1992).

3.2 Distribution

After absorption, cyanide is distributed in all organs. After fatal poisonings, the highest concentrations were found in the liver, lungs, blood, spleen and brain (NL Health Council 1999). However, the administration route also affects the distribution pattern (EPA 1992).

3.3 Metabolism

Metabolic inactivation of cyanide takes place mainly (about 80 %) via formation of thiocyanate, which is catalysed by rhodanese in the liver. The reverse reaction can be brought about by peroxidases. In addition, 2-imino-4-thiazolidine carboxylic acid or the tautomer 2-aminothiazoline-4-carboxylic acid can be formed by reaction of cyanide with cystine, and cyanocobalamin by reaction with hydroxocobalamin (vitamin B_{12a}). Further minor metabolites are cyanate, nitrite, CO_2 and formate. The limiting factor is not the rhodanese

activity but the quantity of sulphanes available for sulphur transfer. Another crucial factor is transport of the sulphur compounds from the blood into the mitochondria. Binding of cyanide to methaemoglobin is used therapeutically (NL Health Council 1999). In humans (after i.v. injection), about 0.017 mg of cyanide per kg of body weight and minute (1.0 mg/kg body weight and hour) can be detoxified without therapeutic measures (EPA 1992). Another figure given in the literature for the detoxification capacity in man is 0.1 mg/kg body weight and hour (Dekant *et al.* 2001).

3.4 Excretion

Most cyanide is excreted in the urine as thiocyanate, but clear quantitative data are not available. After single doses (no further details), up to 95 % was excreted with the urine. In contrast, rats given KCN in the drinking water for 13 weeks in daily doses of 40, 80 or 160 mg/kg body weight excreted 11 % of the dose as thiocyanate each day. This is possibly a result of a decline in availability of thiosulphate during repeated exposure. A minor elimination route is exhalation of HCN (about 0.4–1.2 %) together with CO_2 (about 2.5–4 %) (NL Health Council 1999).

3.5 Endogenous formation

Cyanide is formed endogenously during vitamin B_{12} metabolism and is consumed in small quantities with food (e.g. soya beans) in the form of glycosidically bound cyanide (NL Health Council 1999).

4 Effects in Man

4.1 Single exposures

The acute toxicity of KCN and NaCN in humans is well documented. A large number of deliberate poisonings (suicide, murder) or accidents has been described. The following symptoms have been reported for cyanide poisoning: rapid breathing, weakness, headaches (pulsation), feeling of pressure in the chest, facial flushing, dyspnoea, nausea, vomiting, diarrhoea, dizziness, drowsiness, confusion, convulsions, coma, irregular breathing and death. A very early characteristic feature is tachypnoea (rapid breathing) and hyperpnoea (increased depth of breathing) (Ballantyne 1987). In addition, the following complications of acute cyanide poisoning are possible: rhabdomyolysis, diffuse cerebral oedema, degenerative changes in the central nervous system and pulmonary oedema (Messing 1991).

4.1.1 Inhalation

Accidental occupational exposure may occur in particular during acidification of solutions containing cyanide, a process which liberates HCN.

Table 1 lists the acute toxic effects of HCN poisoning.

Table 1. Acute effects of HCN in humans (NL Health Council 1999)

Reaction	Concentration	
	mg/m^3	ml/m^3
immediate death	300	270
death after 10 min	200	181
death after 30 min	150	135
death after 0.5 to 1 h or later or risk of death	120–150	108–135
tolerable for 20 min to 1 h without immediate or later effects	50–60	45–54
slight symptoms after a few hours	20–40	18–36

It is evident from the table that the dose-response curve is rather steep. The 30-minute LC_{50} calculated for humans is 200 to 210 mg/m^3, taking detoxification into account (Ballantyne 1987).

4.1.2 Ingestion

It is difficult to estimate the lethal oral dose for humans from case reports because the doses in attempted suicides are often very high. Doses of 50 to 100 mg of NaCN and 150 to 250 mg of KCN were fatal.

Several reports indicate that survivors of acute cyanide poisoning can subsequently develop severe neurological problems: parkinsonism, slowing of movement, dystonia of the limbs, the trunk, the facial muscles and the eyelids, and speech disorders. A brain autopsy of a patient 19 months after the poisoning showed severe destructive changes in the *globus pallidus* and putamen. Changes detected instrumentally in survivors involved the putamen, the *substantia nigra*, the cerebellum and the pallidum. Reduced striatal dopa uptake and a diminished glucose metabolism in the putamen and cortex were found (Borgohain *et al.* 1995, Carella *et al.* 1988, Grandas *et al.* 1989, Messing 1991, Rosenberg *et al.* 1989, Uitti *et al.* 1985, Valenzuela *et al.* 1992).

4.1.3 Dermal absorption

There are no quantitative data for the acute dermal toxicity of cyanide in humans.

Cutaneous absorption was determined in an experiment carried out by the author on himself: 0.6% v/v (6000 ml/m^3) was tolerated for 50 minutes without symptoms; the exposure to 2.2% v/v (22000 ml/m^3) had to be discontinued after 27 minutes, that to

5.5% (55000 ml/m^3) after 22 minutes. Inhalation was prevented with appropriate measures (Schütze 1927). In another report it is claimed that absorption through the skin "begins above a concentration of 2 ounces per 1000 cubic feet" (about 1100 ml/m^3) "and proceeds quickly" at concentrations of 6 to 10 ounces per 1000 cubic feet (3000–5000 ml/m^3) (O'Donnell *et al.* 1940).

Effects as described in Section 4.1 occurred within 5 minutes after accidental exposure of a worker's hand to aqueous HCN solution while working with a gas mask (Ballantyne 1987). *In vitro* studies of human skin showed a high dermal permeability constant (3.5×10^{-4} cm/h). The dermal LD_{50} of HCN for humans has been reported to be 100 mg/kg body weight (no further details; EPA 1992).

4.2 Repeated exposure

4.2.1 Inhalation

Case reports

Case reports indicate that cyanide exposure at the workplace (no details of concentrations) leads to symptoms of neurotoxicity (visual disorders, convulsions, paresis) which disappear when the persons cease work with cyanide. There is controversy in the literature about whether these symptoms really are the consequences of chronic exposure or whether peak exposures are responsible. A few cases of goitre have been reported. There are also reports of gastrointestinal symptoms and skin changes which can probably be attributed to the irritant effects of cyanides (Ballantyne and Marrs 1987, Hardy *et al.* 1950, Sandberg 1967).

Epidemiological studies

36 male workers from the electroplating departments of three factories and 20 male workers not exposed to cyanide at work were investigated; 22 of the 36 exposed workers had been employed for more than 5 years in the factories. All those investigated were non-smokers, and there was no evidence of consumption of foods known to elevate the urine thiocyanate concentration. All those taking part in the study were asked about their current and past symptoms and their occupational history. The cyanide exposure levels (presumably in the inhalable fraction; no further details) were determined after sampling air in the breathing zone for 15 minutes. The main aim of the study was to detect any changes in the thyroid. Those taking part received $^{131}I^-$ on the Monday. The conventional blood parameters, the cyanomethaemoglobin concentration and the thiocyanate concentrations in the urine were determined. The cyanide concentrations measured for the three factories were 7.2 to 12.4 ml/m^3 (8.1–13.9 mg/m^3), 4.2 to 7.8 ml/m^3 (4.7–8.8 mg/m^3) and 5.9 to 8.6 ml/m^3 (6.6–9.7 mg/m^3). The respective average concentrations were 9.4, 6.4 and 8.0 ml/m^3 (10.6, 7.2 and 9.0 mg/m^3). 20 of the exposed workers had an enlarged thyroid, the thyroid was soft and smooth in 16, and hard and nodular in 4, "in two of whom it resembled lymphadenoid goitre". No information was provided about the control

subjects. No clinical signs of hyperthyroidism or hypothyroidism were found. Thyroid iodide uptake was significantly higher in the exposed workers (4 hours: 37.7 % versus 22.4 %; 24 hours: 48.3 % versus 40 %). The authors suggested that the increased iodide uptake was caused by reduction in thiocyanate concentrations over the work-free week-end and the subsequent increased deposition of iodide in the thyroid. No differences in the radioactivity in the blood of exposed and non-exposed workers were found. Cyano-methaemoglobin was also detected in the workers' blood (no data). Urinary thiocyanate excretion increased until the middle of the working week and then remained constant for the last three days. The average steady-state excretion showed a good correlation with the average cyanide concentration in the air in the second half of the week. The following linear relationship was found: $M = 0.65 \times C$, where M is the amount of thiocyanate in mg excreted in the urine in 24 hours; C is the cyanide concentration in the air in ml/m^3. This relationship indicates that the average amount of thiocyanate excreted in the urine in 24 hours by the exposed workers in the 3 factories was about 5 mg, whereas the average figure for the control group was 0.11 mg (maximum 0.4 mg).

Table 2. Symptoms with significantly increased incidences in persons exposed chronically to cyanide (El Ghawabi *et al.* 1975)

Symptoms	Exposed persons		Control group		p
	n	%	n	%	
headaches	29	81	6	30	< 0.001
weakness	28	78	4	20	< 0.001
changed sense of taste and smell	28	78	0	0	< 0.001
dizziness	20	56	3	15	0.008
throat irritation	16	44	1	5	0.006
vomiting	16	44	1	5	0.006
dyspnoea	16	44	2	10	0.02
lacrimation	9	25	0	0	0.02

It was observed that the various symptoms associated with cyanide exposure occurred distinctly more often in the exposed workers than in the control group (Table 2) (El Ghawabi *et al*. 1975). No distinction was made in the study between acute and past symptoms, so that it is not possible to relate the frequency of symptoms to the measured levels of exposure. No 8-hour average was determined. The number of enlarged thyroid glands in the exposed group suggests induction of goitre by the cyanide metabolite, thio-cyanate. The close correlation between the air concentrations and the biomonitoring parameters indicates that the results were not affected by dermal or oral exposure. The only possible conclusion from this study is that the cyanide exposure probably contrib-uted to the thyroid enlargement. This would also be biologically plausible. Thiocyanate was formerly used for treating hypertension but was prohibited because of the risk of goitre development. About 300 mg of potassium thiocyanate taken each day for 4 months led to goitre (Hardy *et al*. 1950). 300 mg potassium thiocyanate corresponds to 180 mg

thiocyanate ion. The amount of cyanide inhaled during exposure to a cyanide concentration of 10 ml/m^3 for 8 hours is about 66 mg, assuming a total inhaled air volume of 10 m^3 and 60 % retention. Of this inhaled cyanide, 80 % is metabolized to thiocyanate (117 mg). Hence the amount of thiocyanate produced is only slightly below the LOEL for goitre caused by thiocyanate.

A further study is not informative because there are insufficient details of workplace exposure and the medical questionnaire was inadequate (Chandra *et al*. 1980).

36 former workers in a silver reclamation plant which had been closed 7 months previously because of elevated cyanide concentrations were asked to complete a questionnaire about symptoms during work, persistent symptoms and about the exposure conditions. The median time since the last exposure was 10.5 months (7–30 months). The median duration of exposure was 8.5 months. No control group was available. One day after closure of the plant, the measured HCN concentration averaged over 24 hours was 15 ml/m^3 (17 mg/m^3). No measurements of the concentrations in air while the plant was still in operation were available, but they were presumably higher. The prevalence of the reported symptoms during exposure (e.g. headaches, dizziness, nausea, taste disorders, eye irritation) was higher than the currently reported prevalence. The symptom index correlated inversely with the time since the last exposure and increased with the duration of exposure. No noteworthy changes in the thyroid or mucous membranes and no "neurological deficits" were found. The concentrations of vitamin B_{12} and folic acid in serum were significantly reduced, whereas a slight but significant increase in triiodothyronine (T_3) and thyrotropin was found, especially in workers whose exposure was classed as high. Although no data were available for the cyanide exposure levels at work, the authors concluded that the described effects are attributable to cyanide exposure. They were also of the opinion that the last-mentioned findings show that the consequences of previous cyanide exposure are still detectable after 7 months (Blanc *et al.* 1985). This study is flawed because no control group was included. Correlation of the symptoms with an exposure concentration is not possible. Compared with the persons studied by El Ghawabi *et al.* (1975), these workers were exposed for a much shorter time, and the last exposure was almost one year previously, so that any thyroid changes could have regressed.

In a study of 38 women employed in a cable factory and exposed to HCN concentrations up to a maximum of 7.5 mg/m^3 (time-weighted average not stated), the following enzymes were investigated: aspartate aminotransferase (AST), alanine aminotransferase, lactate dehydrogenase (LDH), α-hydroxybutyrate dehydrogenase, creatine phosphokinase and alkaline phosphatase. The control group comprised 20 female office workers. Whereas there was only a small increase in AST activity, there was a significant increase in the LDH activity in the serum of the exposed group. No differences were found between the exposed and control groups for the other enzymes (Hlynczak *et al.* 1980). No information is given about alcohol consumption, and so the results are not useful.

An important source of exposure for the general population is smoking. The normal levels of cyanide in the plasma are about 4 ng/ml for non-smokers and about 6 ng/ml for smokers. The corresponding levels in whole blood are 15 and 40 ng/ml (Szinicz 1996). Urine concentrations of the metabolite thiocyanate are about 0.3 to 3.8 µg/ml for non-smokers (n = 14) and 3 to 14 µg/ml for smokers (n = 22) (Maehly and Swensson 1970).

(The data for non-smokers are consistent, at least within an order of magnitude, with the maximum thiocyanate excretion of 0.4 mg/24 h mentioned above). This background exposure makes it difficult to quantify occupational exposure by biomonitoring.

In 35 cyanide-exposed non-smoking workers without thyroid disease, the serum thiocyanate concentration was significantly higher, 316 ± 15 µmol/l, than in control subjects matched for age and diet with the exposed workers (90.8 ± 9.02 µmol/l). The T_3 and T_4 (thyroxine) concentrations were significantly lower, and the TSH concentration was significantly higher than in the control subjects. Moreover, the T_4 concentration was correlated negatively, and the TSH concentration positively with the serum thiocyanate level. The levels of exposure are not given (Banerjee *et al.* 1997).

4.2.2 Ingestion

Various neuropathological disorders are attributed to chronic consumption of cyanide-containing foodstuffs. A very well known example is the tropical ataxic neuropathy of population groups using cassava as staple food. Cassava contains linamarin, a glycoside from which cyanide is liberated by hydrolysis after consumption. It is generally accepted (although not proved) that the neuropathological disorders are promoted by chronic cyanide exposure. An increased incidence of goitre and cretinism in the tropics, especially in the Democratic Republic of Congo (formerly Zaire), is regarded as the result of a low iodide intake combined with a high cyanide intake with cassava roots. However, it is not possible from the studies to plot quantitative relationships for the chronic toxicity of cyanide (NL Health Council 1999).

4.3 Effect on skin and mucous membranes

Skin contact with HCN solution or solutions of the cyanide salts led to dermatitis or rashes. No signs of eye irritation were found (EPA 1992).

Nasal irritation and septal ulceration were observed in electroplating workers exposed to cyanide concentrations of more than 5 mg/m^3 at work (ACGIH 1996).

5 Results of animal experiments and *in vitro* studies

5.1 Acute toxicity

Inhaled hydrogen cyanide is more toxic than the ingested salts because the latter can be detoxified in the liver (first-pass effect).

The LC_{50} and LD_{50} values for HCN, KCN and NaCN are listed in Tables 3 to 7 (Ballantyne 1983a, 1983b, 1987, 1988, Matijak-Schaper and Alarie 1982).

The lethal doses for female rabbits after exposure via the eye (Draize test) for HCN, NaCN and KCN are respectively 1.04, 5.06 and 7.87 mg/kg body weight (Ballantyne 1983b).

Table 3. Data from early studies of the acute toxicity of inhaled HCN

Species	Concentration (ml/m^3)	Exposure duration	Symptoms	References
mouse	1300	1–2 min	death	Flury and Zernik 1931
rat	1000	10 min	death	O'Donnell *et al.* 1940
guinea pig	725	14 min	no toxic effects	Schwab 1929
rat	500	10 min	not lethal	O'Donnell *et al.* 1940
cat	315		respiratory arrest after 2 min death after 5–10 min	Flury and Heubner 1919
dog	315		rapid death	Fassett 1962
guinea pig	315	n.s.	death	Flury and Zernik 1931 Dudley *et al.* 1942
guinea pig	200	1.5 h	tolerated without symptoms	Dudley *et al.* 1942
rabbit	150	33 min	death	Ahlmann 1905
rat	142	30 min	LC_{50}	Hofmann 1971
rabbit	135		dyspnoea	Dschang 1928
cat	125	6–7 min	markedly toxic	Dudley *et al.* 1942
rabbit	125	105 min	death	Ahlmann 1905
monkey	125	12 min	distinctly toxic	Dudley *et al.* 1942
rabbit	120		no marked toxic symptoms	Flury and Zernik 1931, Dudley *et al.* 1942
rat	118	12 h	minimum lethal dose	O'Donnell *et al.* 1940
dog	115	30 min	respiratory arrest	Flury and Zernik 1931
mouse	110	45 min	death	Flury and Zernik 1931
cat	110	30 min	respiratory arrest	Flury and Heubner 1919
rat	110	1.5 h	death	Flury and Zernik 1931, Dudley *et al.* 1942
cat	95	60 min	survived severe intoxication	Flury and Heubner 1919
dog	90		tolerated for hours, death after the end of exposure	Flury and Zernik 1931, Dudley *et al.* 1942
cat	56	60 min	tolerated but symptoms of intoxication still apparent	Flury and Heubner 1919
cat	54	110 min	convulsions then recovery	Wagschal 1903
cat	48	140 min	death	Wagschal 1903
guinea pig	45		respiration rate increased 15–23 %	Henschler 1965
mouse	45	2.5 h	death	Flury and Zernik 1931
mouse	40	7 h	tolerated without clinical symptoms	Dschang 1928
dog	35–65		vomiting, convulsions, recovery, sometimes fatal	Flury and Zernik 1931, Dudley *et al.* 1942
cat	27–36	4–6 h	tolerated without symptoms	Wagschal 1903
dog	30		tolerated	Flury and Zernik 1931, Dudley *et al.* 1942
guinea pig	7.5	2 h	no clinical symptoms	Henschler 1965

Table 4. LC_{50} values for inhaled HCN

Species	Sex	Duration of exposure	LC_{50} in mg/m^3 (ml/m^3)
rat	♀	10 sec	3778 (3362)
rat	♀	1 min	1129 (1004)
rat	♀	5 min	493 (439)
rat	♀	30 min	173 (154)
rat	♀	60 min	158 (140)
rat	♀	30 min	151 (134)
rat	n.s.	5 min	553 (492)
mouse	♂	30 min	176 (156)
mouse	n.s.	5 min	363 (323)
rabbit	♀	45 sec	2432 (2165)
rabbit	♀	5 min	409 (364)
rabbit	♀	35 min	208 (185)
cat	n.s.	30 min	204 (182)
goat	n.s.	30 min	461 (410)

Table 5. Data from early studies of the acute toxicity of HCN and its salts

Species	Administration route	Salt	Dose	Symptoms	References
dog	intravenous	KCN	0.08 mg/kg/min	average survival time 28 ± 1.2 min	Mercker *et al.* 1958
dog	subcutaneous	NaCN	5.36 ± 0.28 mg/kg	LD_{50}	Chen and Rose 1952
cat	intravenous	KCN	4 or 8 mg/kg/2 min	respiratory paralysis	Offterdinger and Weger 1969
cat	subcutaneous		1.1 mg/kg	death	Hunt 1923
guinea pig	intravenous	NaCN	0.2 mg/kg/min	respiratory failure after 23.6 ± 1.0 min	Friedberg and Schwarzkopf 1969
rat	intravenous	HCN in oil	1.8 mg/kg	lethal dose (expressed as free HCN)	Forst 1928
rat	subcutaneous	HCN in oil	3.5 mg/kg	lethal dose (expressed as free HCN)	Forst 1928
rat	oral	HCN in oil	4.5 mg/kg	lethal dose (expressed as free HCN)	Forst 1928
mouse	subcutaneous	HCN in oil, KCN NaCN	4 mg/kg	median lethal dose (expressed as free HCN)	Forst 1928
mouse	subcutaneous	KCN	8.5 mg/kg	LD_{50}	Way *et al.* 1966
mouse	oral	KCN	4 mg/kg	median lethal dose (expressed as free HCN)	Forst 1928
mouse	oral	KCN	8.5 mg/kg	LD_{50}	Sheehy and Way 1968

Table 6. Acute toxicity of the three cyanide compounds after ingestion

Compound	Species	Sex	LD_{50} (mg/kg body weight)
HCN	rabbit	♀	2.49
HCN	rat	♀	3.62 *
HCN	rat	♀	4.21
NaCN	rabbit	♀	5.11
NaCN	rat	♀	5.09
NaCN	rat	♀	5.72
KCN	mouse	♂	8.50
KCN	rabbit	♀	5.82
KCN	rat	♀	9.69 *
KCN	rat	♀	7.48
KCN	rat	♂	10.00

* fasted animals

Table 7. Acute dermal toxicity of the cyanides for rabbits (exposure via an occlusive chamber) (Ballantyne 1994)

Compound	State of skin	LD_{50} (mg/kg body weight)
HCN	healthy	6.90
NaCN	healthy	14.63
KCN	healthy	22.33
HCN	abraded	2.34
NaCN	abraded	11.28
KCN	abraded	14.29
NaCN	healthy, dry	> 200
NaCN	healthy, moist	11.83
NaCN	abraded	7.35

5.1.1 Clinical effects

Irrespective of the mode of exposure, the following clinical effects were observed in experimental animals exposed to a lethal cyanide dose: dyspnoea, irregular, shallow and gasping breathing, ataxia, tremor, tonic convulsions, loss of consciousness, muscle spasms and attacks of choking (Ballantyne 1983b, 1994, EPA 1992). The dose-response curve for acute cyanide poisoning is steep above a threshold concentration e:

$$(c - e) \times t = \text{constant}.$$

The lethal dose is very close to the highest dose which has no evident effects.

5.1.2 Neurotoxic effects

Single doses of cyanide close to the lethal dose cause disturbances of the neurochemical processes in the brain which result in changed neurotransmitter levels (e.g. γ-amino-

butyric acid and dopamine) and the levels of their precursors or metabolites (amino acids such as tyrosine and glutamic acid, L-dihydroxyphenylalanine, dihydroxyphenylacetic acid, hydroxyindoleacetic acid and homovanillic acid). Changes in the levels of cyclic guanosine monophosphate and intracellular calcium have also been found. Lipid peroxidation in the brain is regarded as clear evidence of the acute effects of cyanide. In addition, antioxidant enzymes in the brain are inhibited by cyanide. Cyanide treatment may cause an increase in the adrenaline and noradrenaline levels in the plasma. Changes in the electroencephalogram have been observed after acute cyanide exposure. Acute cyanide exposure leads to clear irreversible changes in the concentration of high-energy phosphate components in the rat brain, including a decrease in the ATP level. An increase in lactate and ADP and a large decrease in glycogen concentrations were observed in the brain of cyanide-exposed rats. The reaction of the cytochrome c oxidase in the brain is more pronounced than that of the cytochrome c oxidase in other tissues. Near lethal single doses of cyanide cause various histological changes in the brain. Acute exposure to cyanide may have adverse effects on movement and possibly on memory functions (NL Health Council 1999).

CNS depression was detected in mice exposed to HCN concentrations of 20 to 100 ml/m^3 (22–112 mg/m^3). The calculated DC_{50} was 63 ml/m^3 (Matijak-Schaper and Alarie 1982).

5.1.3 Cardiovascular effects

Acute cyanide exposure leads to changes in cardiac function, e.g. in heartbeat and ECG, to histological changes in the myocardium and to an increase in cardiospecific creatine phosphokinase in the blood (NL Health Council 1999).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

No studies which can be used to establish a no observed adverse effect level (NOAEL) are available.

Histological changes were studied in the brains of dogs exposed for 30 minutes to an HCN concentration of 50 mg/m^3. Three of the dogs died during the study. Severe histological damage in the brain was found (Valade 1952). The study is inadequately documented.

In rabbits exposed to an HCN concentration of 0.5 mg/m^3 continuously for 4 weeks, no histopathological changes were found in the heart, lung or adjoining arteries (Hugod 1979). No other endpoints were investigated in this study.

5.2.2 Oral intake

The results of studies with histopathological examination and examination of the thyroid after repeated oral administration are listed in Table 8.

Table 8. Toxicity of cyanides after repeated oral exposure

Species number	Exposure	CN^- dose: effects	References
rat 6 ♂ 2 ♀	KCN: 2500 mg/kg feed (CN^-: about 36 mg/kg body weight and day) 84 days	**36 mg/kg body weight:** decreased feed consumption and weight gain; histopathology of liver, kidneys, thyroid and spleen unaffected	EPA 1992
rat F344/N 10 ♂ 10 ♀	NaCN: 3, 10, 30, 100, 300 mg/l drinking water, (CN^-: 0.16, 0.5, 1.6, 4.2, 12.5 mg/kg body weight per day) 13 weeks	**≥ 1.6 mg/kg body weight:** ♀: NOAEL ♂: dose-dependent, significant reduction in the weight of the cauda epididymis (7 %) **≥ 4.2 mg/kg body weight:** ♂/♀: decreased water consumption ♀: prooestrus and dioestrus longer and metoestrus and oestrus shorter ♂: NOAEL **about 12.5 mg/kg body weight:** ♂: decreased body weights (5 %), decreased spermatid head counts and spermatid counts (13 % each), decreased absolute testis weight (7 %) and absolute weight of *cauda epididymis* (13 %)	NTP 1993
rat 10 ♀	KCN: 50000, 100000 mg/kg feed (CN^-: about 500 and 1000 mg/kg body weight) [1] 14 weeks	**≥ 500 mg/kg body weight:** hair loss, apathy, decreased body weights, decreased haemoglobin, cell volumes, total serum protein, serum T4, relative spleen weights; increased relative thyroid weight; thymus atrophy, centrilobular liver cell necrosis	Olusi *et al.* 1979
rat 10 ♂	KCN: 1500 mg/kg feed (CN^-: about 30 mg/kg body weight and day) [2] feed with or without reduced levels of iodide, vitamin B_{12} and DL-methionine 11.5 months	**30 mg/kg body weight:** decreased body weights and plasma T4 levels after 4 months; slight primary myelin degeneration in the white matter of the spinal cord (more marked in rats with diets deficient in methionine and vitamin B_{12})	Philbrick *et al.* 1979
rat 10 ♂ 10 ♀	feed exposed to HCN gas (CN^-: about 1 or 3.5 mg/kg body weight) [3] 2 years	**3.5 mg/kg body weight:** NOAEL histopathology of 11 organs/tissues, haematology, mortality, feed consumption, body weights unaffected.	Howard and Hanzal 1955, NL Health Council 1999

Table 8. continued

Species number	Exposure	CN^- dose: effects	References
mouse $B6C3F_1$ 10 ♂ 10 ♀	NaCN: 3, 10, 30, 100, 300 mg/l drinking water, (CN^-: 0.3, 1, 3, 9, 26 mg/kg body weight and day) 13 weeks	**≥ 9 mg/kg body weight:** ♂/♀: decreased water intake; NOAEL **about 26 mg/kg body weight:** ♀: decreased body weight gain; menstrual cycle unchanged ♂: decreased absolute epididymis weight (10 %) and absolute weight of *cauda epididymis* (18 %); spermatid head density and sperm motility unchanged, decreased body weights (5 %) (not significant)	NTP 1993
dog 3 ♂ 2 ♀	NaCN: 2500 mg/kg feed (NaCN: 6 mg/kg body weight and day)[4] (CN^-: 3 mg/kg body weight) 32 days	**3 mg/kg body weight:** NOAEL feed consumption, haematology; autopsy, comprehensive histopathology (no further details)	EPA 1992
dog 3 (sex not specified)	NaCN: 0.5, 1–2 × 2 mg/kg body weight and day (CN^-: 0.27, 0.53–2 × 1.06 mg/kg body weight), (in capsules) 15 months	**≥ 0.27 mg/kg body weight:** degenerative changes in gangliocytes **> 0.53 mg/kg body weight:** acute toxicity	EPA 1992
pig 3 ♂ + ♀	CN^-: 0.4, 0.7, 1.2 mg/kg body weight and day, by gavage 24 weeks	**≥ 0.4 mg/kg body weight:** dose-dependent increase in T3 and T4, increased blood glucose levels in all treated groups, various behavioural parameters changed, prolonged narcosis **1.2 mg/kg body weight:** increased limping and stiffness, increased convulsions and trembling	Jackson 1988
rabbit 6 ♂	KCN: 1 755 mg/kg feed (CN^-: 702 mg/kg feed, about 15 mg/kg body weight and day) 10 months	**about 15 mg/kg body weight:** decreased body weight gain; LDH and AP increased in serum, kidney, liver; SDH, GPT and AP decreased in liver, increased in serum; AP in lung decreased; focal necrosis in liver, tubular and glomerular necrosis in kidney, pulmonary oedema and necrosis; pancreas and heart unaffected.	Okolie and Osagie 1999, 2000

[1] assumed feed consumption 25 g/kg body weight (normal 50 g/kg), since body weight loss up to 25 %
[2] assumed feed consumption 50 g/kg body weight
[3] according to NL Health Council 1999
[4] according to EPA 1992

Effects were found on the thyroid (Jackson 1988, Philbrick *et al.* 1979), the central nervous system and behaviour (EPA 1992, Jackson 1988, Philbrick *et al.* 1979), glucose metabolism (Jackson 1988), lungs, liver, kidneys (Okolie and Osagie 1999, 2000), the male reproductive organs (but without reduction in the sperm count) and the menstrual cycle of female rats (NTP 1993). In the NTP (1993) study, described in detail in Section

5.5, no changes in the thyroid were detected. The NOAEL for CN^- found in this study is 1.6 mg/kg body weight and day for rats and 9 mg/kg body weight for mice. The authors point out that the absence of effects on the CNS and the thyroid in the animal experiments is not consistent with the findings of human epidemiological studies but that this is possibly a result of a difference in the sensitivity of humans and rodents (NTP 1993).

The studies with administration of bolus doses to pigs (Jackson 1988) and of capsules to dogs (EPA 1992) are not used for the present assessment because the sudden rise in the cyanide level caused by these modes of administration is not equivalent to protracted workplace exposures. This difference is significant because of the steep dose-response curve for acute toxic effects. This is shown by the fact that on administration via the feed or drinking water a multiple of the acute oral LD_{50} is tolerated each day.

5.3 Effects on skin and mucous membranes

There are no studies of dermal irritation. Clear signs of eye irritation were observed on exposure of the animals' eyes to HCN, NaCN or KCN (Ballantyne 1983b, 1988).

Allergenic effects of cyanides have not been studied.

5.4 Reproductive and developmental toxicity

Pregnant golden hamsters (5–7 animals/dose group) received infusions of NaCN delivered in constant volumes by osmotic minipumps implanted subcutaneously in the neck. The pumps were implanted on day 6 of gestation and delivered calculated doses of 0, 0.126, 0.1275 or 0.1295 mmol/kg body weight and hour, equivalent to 6.17, 6.25 and 6.35 mg/kg body weight and hour. The calculation assumed a minipump delivery rate of 0.85 µl/hour. Preliminary tests had shown that ≤ 0.125 mmol/kg body weight and hour (6.12 mg/kg body weight and hour) had no teratogenic effects in 3 pregnant hamsters but that 0.133 mmol/kg body weight and hour (6.52 mg/kg body weight and hour) led to resorption of all the embryos and to high maternal toxicity. The tests were accordingly carried out in an extremely narrow dose range. The minipumps were removed 3 days after implantation on day 9 after conception, the hamsters were killed on day 10. More or less pronounced signs of maternal toxicity were found in the animals in all three cyanide-exposed groups: loss of weight, hypothermia, ataxia, salivation, dyspnoea. The animals recovered rapidly after removal of the minipumps. The cyanide doses were highly embryotoxic, producing early resorption rates of 63 %, 72 % and 83 % (control: 10 %). Except in the highest dose group, sufficient foetuses were still present, despite the high embryotoxicity, and 16/26 and 10/23 (control 4/75) showed malformations. The commonest anomalies were an open neural tube, exencephaly and encephalocele. The doses were thus also highly teratogenic, although, according to the authors, the malformations did not correlate with the intensity of maternal toxicity. It was possible to prevent both the maternal toxicity and the embryotoxic and teratogenic effects by simultaneous administration of sufficiently high thiosulphate doses (6.3 mg/kg body weight and hour). This indicates that the teratogenic effect is attributable to the cyanide itself and not to the

metabolite thiocyanate. The authors of the study point out that no dose-effect relationships can be derived from the results because the delivery rate from the minipumps is very variable and the calculated delivery rates cannot be confirmed *in vivo*. Assuming an acute subcutaneous LD_{50} of 7.4 mg/kg body weight, the pregnant hamsters received from the minipumps in this study about 30 to 40 times the LD_{50} after bolus injection (Doherty *et al.* 1982). All these considerations must be taken into account in interpreting the study results. Accordingly, the study shows only that if highly maternally toxic cyanide doses are given during organogenesis they may cause malformations in hamsters like those produced by other cyanogenic substances such as acetonitrile (see "Acetonitrile" in the present volume). The available comparable investigations of the effects of cyanides or cyanogenic aliphatic nitriles on other species such as rats and rabbits suggest that the prenatal neural tube damage is probably specific to hamsters and is not a malformation seen in other species too (see "Acetonitrile" in the present volume).

Groups of 10 female rats were given KCN in concentrations of 50000 mg/kg diet or 100000 mg/kg diet for 13 weeks. None of the cyanide-treated rats, but 9 of 10 control animals, became pregnant (Olusi *et al.* 1979).

Female rats received a diet based on cassava meal (contains HCN in a concentration of 12 mg/kg meal) and containing 1250 mg of KCN per kg of feed, equivalent to about 125 mg of KCN per kg body weight. The animals were treated during mating (for up to 19 days), pregnancy, lactation and after weaning. Cyanide had no effect on the following parameters: body weight, weight gain during pregnancy, lactation and delivery, litter size, mortality of the pups during delivery, body weights of the pups at birth, weight gain of the pups during lactation, liver and kidney weights of the dams. Treatment of the pups after weaning resulted in a significant reduction in growth and feed consumption. There was likewise a reduction in the protein efficiency ratio (body weight gain/protein intake) for the treated pups (Tewe and Maner 1981a).

Groups of 6 pregnant sows received fresh cassava containing cyanide in a concentration of 277 and 521 mg/kg. The pigs were exposed from the day after mating until farrowing. No significant effects were found on reproduction parameters such as size of the piglets, size of the piglets during weaning, birth weights of the piglets, daily food intake of the sows and piglets, and body weight gain during pregnancy. Histopathological examination of the sows (n = 2/dose) revealed increased kidney cell hyperplasia. Histopathological changes were also found in the thyroid glands of the animals in the high-dose group (follicular cell hypoplasia) and increased relative thyroid weights. The foetuses in the high dose group showed reduced relative heart and spleen weights, whereas those in the low dose group were found to have reduced relative thyroid weights (Tewe and Maner 1981b).

In the 13-week study described in Section 5.2.2 (NTP 1993), sodium cyanide in the drinking water led to changes in some reproductive parameters in male rats and mice. In rats, the weight of the *cauda epididymis* was significantly reduced after CN^- doses of 1.6 mg/kg body weight and above, and after 12.5 mg/kg body weight there were significant reductions in the weights of the whole epididymis and of the testes, and in the number of (late) spermatids in the testes, together with reduced body weights. In male mice the weights of the whole epididymis and the *cauda epididymis* were significantly reduced only in the highest dose group. In both species there was no change relative to the control

values in the sperm concentration in the epididymis after exposure. The authors therefore regard the observed reductions as not biologically relevant for the rodent species, but point out that humans are relatively more sensitive to such changes in reproductive parameters. In the female rats of the two higher dose groups there were merely slight shifts in the stages of the menstrual cycle, that is, prooestrus was longer and oestrus was shorter (see Table 8).

5.5 Genotoxicity

Tests with NaCN and KCN carried out in various *Salmonella typhimurium* strains (TA1535, TA1538, TA1537, TA98, TA100, TA97, TA102) and in the presence and absence of S9 mix yielded negative results. However, in one study positive results were obtained with HCN and the strain TA100 in the absence of metabolic activation. Negative results were obtained in tests for DNA damage with repair-competent and repair-deficient *Escherichia coli* strains WP67, CM871 and WP2, and in a test with the *Bacillus subtilis* strain N45. KCN did not inhibit DNA synthesis in the mouse testis (no further details; NL Health Council 1999, NTP 1993). NaCN did not cause DNA strand breaks in mouse lymphoma cells without metabolic activation (Garberg *et al.* 1988). KCN caused DNA double strand breaks in human lung epithelial cells only at concentrations which were cytotoxic, reducing cell survival by more than 40 % (Vock *et al.* 1998).

5.6 Carcinogenicity

There have been no studies of the carcinogenicity of HCN, KCN or NaCN. In a 14-week study with excessive doses, benign tumours of the coecum and colon were found in 5 of 10 rats in the 50 g/kg group and 7 of 10 rats in the 100 g/kg group. However, the MTD was clearly exceeded in these dose groups (25 % decrease in weight) (Olusi *et al.* 1979; Table 8). This study is unsuitable for assessment of carcinogenicity of these substances.

6 Manifesto (MAK value, classification)

Data available for human exposures show that long-term exposure to cyanide in concentrations of 4.7 to 13.9 mg/m^3 may lead to symptoms such as headaches, weakness, dizziness, throat irritation, dyspnoea, thyroid enlargement and an increase in thiocyanate excretion in the urine (El Ghawabi *et al.* 1975). No NOAEL was found in this study. Thiocyanate is the main metabolite of cyanide, and there is a causal association between exposure to thiocyanate and development of goitre. As stated in Section 4.2.1, occupational exposure to HCN in concentrations of 10 ml/m^3 for 8 hours must be expected to produce amounts of thiocyanate which are in the region of the LOEL for development of goitre. However, in the 13-week study on rats and mice, no effect on the thyroid was

found with far higher doses. It is unclear whether or not humans are more sensitive to development of goitre caused by thiocyanate than are rats and mice. Irritant effects were seen in workers exposed to cyanide (alkali metal cyanides) in concentrations above 5 mg/m^3 (ACGIH 1996). In the 13-week study there were dose-dependent reductions in the weights of the reproductive organs of male rats and, in animals with reduced body weights, also a reduction in the spermatid concentration, which had, however, no effect on the sperm concentration. The NOAEL for cyanide in male rats is thus 4.6 mg/kg body weight. Changes in the phases of the menstrual cycle were found in female rats exposed at and above 4.6 mg/kg body weight. The NOAEL is 1.6 mg/kg body weight.

The cyanide detoxification capacity of humans is given as 0.1 to 1.0 mg/kg body weight and hour. On the basis of the lower figure, the amount of cyanide which can be detoxified per shift is calculated to be 56 mg, or 0.8 mg/kg body weight and day.

On the basis of the findings described above it was concluded that the MAK value of 10 ml/m^3 (11 mg/m^3) which was valid until 2001 was too high. A worker exposed to cyanide at a concentration of 2 mg/m^3 takes up a dose of 20 mg (worker weighing 70 kg, inhaling 10 m^3 in 8 hours, 100 % absorption). This is equivalent to 0.28 mg/kg body weight and day. Keeping the exposure concentration at this level or below would be sufficient to preclude all the effects mentioned above.

The MAK value for HCN, KCN and NaCN was therefore fixed uniformly in 2001 at 2 mg/m^3 (expressed as cyanide).

Because of the rapid onset of systemic effects, HCN is classified in Peak limitation category II. An excursion factor of 2 is appropriate because brief peaks at acutely toxic concentrations can be detoxified (see above: human detoxification capacity is given as 0.1 to 1.0 mg/kg body weight and hour). In the case of the salts it is not possible to decide whether the systemic or the local action is more important. As there are no data for the NOEL for local action of the substance, for safety the excursion factor is set at 1.

Scarcely any useful developmental toxicity studies are available; even the well-documented infusion study with pregnant hamsters showed only that the teratogenic effect of infused maternal-toxic to maternal-fatal doses can be prevented by thiosulphate treatment. This means that the cyanide ion is responsible for the teratogenic effects. The detoxification capacity mentioned above suggests that no prenatal toxicity is to be expected if the MAK value is observed, especially since it has been shown that the product of detoxification, thiocyanate, does not cause prenatal toxicity (Doherty *et al.* 1982). HCN, KCN and NaCN are classified in Pregnancy risk group C. This classification is also supported by data for the reproductive toxicity of acetonitrile, which is metabolized to cyanide and is likewise classified in Pregnancy risk group C with a far higher MAK value (see "Acetonitrile" in the present volume).

In an *in vitro* study, the permeability constant of human skin for aqueous solutions of cyanides was found to be 3.5×10^{-4} cm/hour. The permeability for an aqueous solution of HCN is almost 30 times higher, 10^{-2} cm/hour. A further study showed that toxic effects occur within 5 minutes after accidental exposure of a worker's hand to aqueous HCN solution. The designation "H" is therefore retained. The low dermal LD_{50} of HCN and cyanide salts also supports this designation.

No data are available for potential allergenic effects. Likewise, there are no useful studies of germ cell mutagenicity.

7 References

ACGIH (American Conference of Governmental Industrial Hygienists) (1996) Hydrogen cyanide and cyanide salts. in: *Documentation of TLVs and BEIs.* ACGIH, Cincinatti, OH, USA

Ahlmann H (1905) *Weitere Untersuchungen über die Giftigkeit der Blausäure* (Further studies of the toxicity of hydrogen cyanide) (German). Doctoral thesis, Bayerische Julius-Maximilians-Universität Würzburg

Ballantyne B (1983a) The influence of exposure route and species on the acute lethal toxicity and tissue concentrations of cyanide. in: Hayes AW, Schnell RC, Miya TS (Eds) *Developments in the Science and Practice of Toxicology*, New York, Elseviers Science Publishers BV

Ballantyne B (1983b) Acute systemic toxicity of cyanides by topical application to the eye. *J Toxicol Cut Ocular Toxicol 2*: 119–129

Ballantyne B (1987) Toxicology of cyanides. in: Ballantyne B, Marrs TC (Eds) *Clinical and Experimental Toxicology of Cyanides*, Wright, Bristol, UK, 41–126

Ballantyne B, Marrs TC (Eds) (1987) *Clinical and experimental toxicology of cyanides*, Wright, Bristol, UK

Ballantyne B (1988) Toxicology and hazard evaluation of cyanide fumigation powders. *J Toxicol Clin Toxicol 26*: 325–335

Ballantyne B (1994) Acute percutaneous systemic toxicity of cyanides. *J Toxicol Cut Ocular Toxicol 13*: 249–262

Banerjee KK, Bishayee A, Marimuthu P (1997) Evaluation of cyanide exposure and its effect on thyroid function in workers in a cable industry. *J Occup Environ Med 39*: 258–260

Blanc P, Hogan M, Mallin K, Hryhorczuk D, Hessl S, Bernard B (1985) Cyanide intoxication among silver-reclaiming workers. *J Am Med Assoc 253*: 367–371

Borgohain R, Singh AK, Radhakrishna H, Rao C, Mohandas S (1995) Delayed onset generalised dystonia after cyanide poisoning. *Clin Neurol Neurosurg 97*: 213–215

Carella F, Grassi MP, Savoiardo M, Contri P, Rapuzzi B, Mangoni A (1988) Dystonic-parkinsonian syndrome after cyanide poisoning: clinical and MRI findings. *J Neurol Neurosurg Psychiatry 51*: 1345–1348

Chandra H, Gupta BN, Bhargava SK, Clerk SH, Mahendra PN (1980) Chronic cyanide exposure, a biochemical and industrial hygiene study. *J Anal Toxicol 4*: 161–165

Chen KK, Rose CL (1952) Nitrite and thiosulfate therapy in cyanide poisoning. *J Am Med Assoc 149*: 113–119

Dekant W, Vamvakas S, Henschler D (2001) Wichtige Gifte und Vergiftungen (Prominent poisons and poisonings) (German). in: Forth W, Henschler D, Rummel W, Förstermann U, Starke K (Eds) *Allgemeine und spezielle Pharmakologie und Toxikologie*, Urban & Fischer, München, 1034

Doherty PA, Ferm VH, Smith RP (1982) Congenital malformations induced by infusion of sodium cyanide in the golden hamster. *Toxicol Appl Pharmacol 64*: 456–464

Dschang KY (1928) *Entgiftung eingeatmeter Blausäure durch Schwefelpräparate* (Detoxification of inhaled hydrogen cyanide by sulfur compounds) (German). Doctoral thesis, Bayerische Julius-Maximilians-Universität Würzburg

Dudley HC, Sweeny TR, Miller JW (1942) Toxicology of acrylonitrile (vinyl cyanide) II. Studies of effects of daily inhalation. *J Ind Hyg 24*: 255–258

Dugard PH (1987) The absorption of cyanide through human skin *in vitro* from solutions of sodium cyanide and gaseous HCN. in: Ballantyne B, Marrs TC (Eds) (1987) *Clinical and Experimental Toxicology of Cyanides, Wright*, Bristol, UK, 127–137

El Ghawabi SH, Gaafar MA, El Saharti AA, Ahmed SH, Malash KK, Fares R (1975) Chronic cyanide exposure: a clinical, radioisotope, and laboratory study. *Br J Ind Med 32*: 215–219

EPA (US Environmental Protection Agency) (1992) *Drinking water criteria document for cyanide*. prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinatti, OH, for US EPA, Washington DC, External Review Draft

Fassett DW (1962) Cyanides and Nitriles. in Patty FA (Ed.) *Industrial Hygiene and Toxicology Vol. II*, 2nd revised edition, Interscience Publishers, John Wiley & Sons, New York, London, p 1996

Flury F, Heubner W (1919) Über Wirkung und Entgiftung eingeatmeter Blausäure (Action and detoxification of inhaled hydrogen cyanide) (German). *Biochem Z 95*: 249–256

Flury F, Zernik F (1931) *Schädliche Gase* (Hazardous gases) (German). Springer, Berlin, p 400

Forst JA (1928) Zur Entgiftung der Blausäure (Detoxification of hydrogen cyanide) (German). *Naunyn-Schmiedebergs Arch Pharmakol 128*: 1–66

Friedberg KD, Schwarzkopf HA (1969) Blausäureexhalation bei der Cyanidvergiftung (Exhalation of hydrogen cyanide in cyanide poisoning) (German). *Arch Toxikol 24*: 235–248

Garberg P, Akerblom E-L, Bolcsfoldi G (1988) Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. *Mutat Res 203*: 155–176

Grandas F, Artieda J, Obeso JA (1989) Clinical and CT scan findings in a case of cyanide intoxication. *Mov Disord 4*: 188–193

Hardy HL, Jeffries WMcK, Wasserman MM, Wadell WR (1950) Thiocyanate effect following industrial cyanide exposure. Report of two cases. *N Engl J Med 242*: 968–972

Henschler D (1965) unpublished data from the Department of Toxicology, University of Würzburg

Henschler D (Ed.) (1971) Cyanwasserstoff (Hydrogen cyanide) (German). in: *Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten*, 1st issue, 1972. VCH-Verlagsgesellschaft, Weinheim

Henschler D (Ed.) (1981) Stickstoffwasserstoffsäure, Natriumazid. in: *Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten*, 8th issue. VCH-Verlagsgesellschaft, Weinheim

Hlynczak JA, Kersten E, Wysocki K, Stamm E, Fokt M, Raczynski A (1980) Untersuchungen zur Aktivität einiger Enzyme im Serum HCN-exponierter Frauen. *Z Aerztl Fortbild 74*: 591–593

Hofmann HTh (1971) personal communication of data from the toxicology laboratory of the BASF AG, Ludwigshafen

Howard JW, Hanzal RF (1955) Chronic toxicity for rats of food treated with hydrogen cyanide. *Agric Food Chem 3*: 325–329

Hugod C (1979) Effect of exposure to 0.5 ml/m^3 hydrogen cyanide singly or combined with 200 ml/m^3 carbon monoxide and/or 5 ml/m^3 nitric oxide on coronary arteries, aorta, pulmonary artery, and lungs in the rabbit. *Int Arch Occup Environ Health 44*: 13–23

Hunt R (1923) Cyanwasserstoff, Nitrilglukoside, Nitrile, Rhodanwasserstoff, Isocyanide (Hydrogen cyanide, nitrile glycosides, nitriles, thiocyanate, isocyanides) (German). in Heffter A (Ed.) *Handbuch der experimentellen Pharmakologie, Vol. 1*, Springer, Berlin, 771–774

Isom GE, Liu DHW, Way JL (1975) Effect of sublethal doses of cyanide on glucose catabolism. *Biochem Pharmacol 24*: 871–875

Jackson LC (1988) Behavioral effects of chronic sublethal dietary cyanide in an animal model: Implications for humans consuming cassava (*Manihot esculenta*). *Hum Biol 60*: 597–614

Katsumata Y, Sato K, Oya M, Suzuki O, Yoshino M (1980) Kinetic analysis of the shift of aerobic to anaerobic metabolism in rats during acute cyanide poisoning. *Life Sci 27*: 1509–1512

Katsumata Y, Sato K, Yada S, Suzuki O, Yoshino M (1983) Kinetic analysis of anaerobic metabolism in rats during acute cyanide poisoning. *Life Sci 33*: 151–155

Maehly AC, Swensson A (1970) Cyanide and thiocyanate levels in blood and urine of workers with low-grade exposure to cyanide. *Int Arch Arbeitsmed 27*: 195–209

Matijak-Schaper M, Alarie Y (1982) Toxicity of carbon monoxide, hydrogen cyanide and low oxygen. *J Combustion Toxicol 9*: 21–61

Mercker H, Lochner W, Gestenberg E (1958) Untersuchungen über das Verhalten des Kreislaufes, der Atmung und der Sauerstoffsättigung des Blutes bei Cyanidvergiftung (Effects of cyanide poisoning on circulation, respiration and oxygen saturation of the blood) (German). *Naunyn-Schmiedebergs Arch Pharmakol 232*: 459–469

Messing B (1991) Extrapyramidal disturbances after cyanide poisoning (first MRT-investigation of the brain). *J Neural Transm 33, Suppl*: 141–147

NL Health Council (1999) *Hydrogen cyanide, sodium cyanide, and potassium cyanide, Draft*. Dutch Expert Committee on Occupational Standards, Health Council of the Netherlands, Den Haag

NTP (1993) *Technical report on toxicity studies of sodium cyanide, 37, NIH Publication 94-3386*, US Department of Health and Human Services, National Institutes of Health, Bethesda, MD, USA

O'Donnell JE, Mundt HW, Knudsen WN, Delano PH (1940) Hydrogen cyanide gas fumigation. *J Ind Hyg 22*: 253–275

Offterdinger H, Weger N (1969) Kreislauf und Atmung bei Blausäurevergiftung und Therapie mit Ferrihämoglobinbildnern und Kobaltverbindungen (Circulation and respiration in cyanide poisoning and therapy with ferrihemoglobin-forming and cobalt compounds) (German). *Naunyn-Schmiedebergs Arch Pharmakol 264*: 289

Okolie NP, Osagie AU (1999) Liver and kidney lesions and associated enzyme changes induced in rabbits by chronic cyanide exposure. *Food Chem Toxicol 37*: 745–750

Okolie NP, Osagie AU (2000) Differential effect of chronic cyanide intoxication on heart, lung and pancreatic tissue. *Food Chem Toxicol 38*: 543–548

Olusi SO, Oke OL, Odusote A (1979) Effects of cyanogenic agents on reproduction and neonatal development in rats. *Biol Neonat 36*: 233–243

Philbrick DJ, Hopkins JB, Hill DC, Alexander JC, Thomson RG (1979) Effects of prolonged cyanide and thiocyanate feeding in rats. *J Toxicol Environ Health 5*: 579–592

Rosenberg NL, Myers JA, Martin WRW (1989) Cyanide-induced parkinsonism: clinical, MRI, and 6 fluorodopa (PET) studies. *Neurology 39*: 142–144.

Sandberg CG (1967) A case of chronic poisoning with potassium cyanide? *Acta Med Scand 181*: 233–236

Sheehy M, Way JL (1968) Effect of oxygen on cyanide intoxication. 3. Mithridate. *J Pharm Exp Ther 161*: 163–168

Schütze W (1927) Über die Gefährdung von Mensch und Tier durch große Konzentrationen einiger giftiger Gase von der Haut aus (Danger from exposure of the skin of man and animals to high concentrations of poisonous gases) (German). *Arch Hyg 98*: 70–83

Schwab R (1929) Der Einfluß von Traubenzucker auf den Verlauf von Giftwirkungen (The effect of glucose on the course of intoxication) (German). *Z Ges Exp Med 67*: 513–537

Szinicz L (1996) Toxische Gase. in: Greim H, Deml E (Eds) *Toxikologie: Eine Einführung für Naturwissenschaftler und Mediziner*, VCH-Verlagsgesellschaft, Weinheim

Tewe OO, Maner JH (1981a) Long-term and carry-over effect of dietary inorganic cyanide (KCN) in the life cycle performance and metabolism of rats. *Toxicol Appl Pharmacol 58*: 1–7

Tewe OO, Maner JH (1981b) Performance and pathophysiological changes in pregnant pigs fed cassava diets containing different levels of cyanide. *Res Vet Sci 30*: 147–151

Uitti RJ, Rajput AH, Ashenhurst EM, Rozdilsky B (1985) Cyanide-induced parkinsonism: a clinicopathological report. *Neurology 35*: 921–925

Valade MP (1952) Lésions du système nerveux central dans le intoxications chroniques expérimentales par l'acide cyanhydrique gazeuse. *Bull Acad Natl Med, Paris 136*: 280–285

Valenzuela R, Court J, Godoy J (1992) Delayed cyanide induced dystonia. *J Neurol Neurosurg Psychiatry 55*: 198–199

Vock EH, Lutz WK, Hormes P, Hoffmann HD, Vamvakas S (1998) Discrimination between genotoxicity and cytotoxicity in the induction of DNA double-strand breaks in cells treated with etoposide, melphalan, cisplatin, potassium cyanide, Triton X-100, and gamma-irradiation. *Mutat Res 413*: 83–94

Wagschal F (1903) *Quantitative Studien über die Giftigkeit der Blausäure-Dämpfe* (Quantitative studies of the toxicity of hydrogen cyanide) (German). Doctoral thesis, Bayerische Julius-Maximilians-Universität Würzburg

Way JL, Gibbon SL, Sheehy M (1966) Effect of oxygen on cyanide intoxication I. Prophylactic protection. *J Pharm Exp Ther 153*: 381–385

completed 01.03.2001